

Public Comments Received in Response to Request for Information (RFI): ClinicalTrials.gov Modernization

Guide Notice Number: NOT-LM-20-003

December 30, 2019–March 14, 2020

The National Library of Medicine (NLM) launched an effort to modernize ClinicalTrials.gov to improve the user experience by updating the platform to accommodate growth and enhance efficiency. To obtain detailed and actionable input, NLM issued a [request for information](#) (RFI), NOT-LM-20-003, on December 30, 2019, with comments due by March 14, 2020. The RFI's purpose was to solicit comments on the ClinicalTrials.gov website's functionality, information submission processes, and use of data standards. NLM received 268 responses, listed in the Contents in the order in which they were received. As indicated in the RFI, the comments received, including the name and affiliation of the submitter, are being posted publicly without change. For more information about the modernization effort, please see the ClinicalTrials.gov Modernization [webpage](#).

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1. Anonymous¹
2. Tyrone Quarterman; UPENN
3. Anonymous
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7. Michael Hoffman; University of Toronto
8. Anonymous
9. Liza Rovniak; Penn State College of Medicine
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11. Richard diMonda; Medical Device Consultant
12. Anonymous
13. Jordan Elm; Medical University of South Carolina
14. Anonymous
15. Anonymous
16. Anonymous
17. Rodrigo Garcia; Source Healthcare
18. Anonymous
19. Vinod; GSK
20. Michael Sutton; Urgent Research
21. Anonymous
22. Vidushi Khurana; Cource5 Intelligence
23. Anonymous
24. Tom Crocker; Bradford Teaching Hospitals
25. Anonymous
26. Anonymous
27. Anonymous
28. David Shapiro
29. Elizabeth Molnar; Seaforth Medical, Brisbane
30. Michael Copeman; Copeman Clinic, Palm Beach, Sydney, Australia
31. Timothy Fortin; ICI Research
32. Anonymous
33. Anonymous
34. Rahul Ganatra; VA Boston Healthcare System
35. Anonymous
36. Anonymous
37. Abdul Rahman; Freelance
38. Alistair Sinclair; n/a
39. Anonymous
40. Anonymous

¹ No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

41. Anonymous
42. Anonymous
43. Anonymous
44. Melissa Cliver; Wondros
45. Anonymous
46. Mark Tedford; Parkinson's
47. Christian Capitini; University of Wisconsin
48. Scott Lofgren; Source One PC
49. Anonymous
50. Granio; Potentiel d'action - France
51. Anonymous
52. Anonymous
53. Ahmed Elwakeel; Cairo University, Egypt
54. Anonymous
55. Joe Risser, MD, MPH; San Diego Family Care (FQHC)
56. Virginia Guptill; NIH CC ORSC
57. Stacy Smith; Coastal Clinical Research
58. Alexey Strygin; Cryno Biotech
59. Aurélien Marabelle; Gustave Roussy
60. Sarah Morgan; BIDMC Harvard University
61. Lara Fournier; OHSU Knight Cancer Institute
62. Ed Croom; Pfeiffer University
63. Gregory Sizikov; NA
64. Alicia Leung; Insmed
65. Anonymous
66. Anonymous
67. Anonymous
68. Dr. Ola Landgren; Memorial Sloan Kettering Cancer Center, New York
69. Laura
70. Corey Polen; ALS patient and advocate
71. Lisa King; NCI/CCR/OCD
72. Anonymous
73. Anonymous
74. Anonymous
75. Anonymous
76. Dr. Jonathan D. Berman
77. Carmen Gonzalez
78. Samantha Spear; TrialSpark
79. Bettina Ryll; Melanoma Patient Network Europe
80. Megan von Isenburg; Duke Medical Center Library & Archives
81. Anonymous
82. Jordan Wilkinson, CRA; Tufts University
83. Alyssa Bartoshevich, MPH; Gulf South NCORP
84. Anonymous

85. Michael FitzGerald; Submittable
86. Michelle Jenkerson; Washington University School of Medicine
87. Joyce Hauze
88. Ian Lock
89. Anonymous
90. Carol Smith
91. Anonymous
92. Joyce Hauze; Mallinckrodt
93. Lindsay Satterwhite Mayberry; Vanderbilt University Medical Center
94. Anonymous
95. Thomas Kirby; DES
96. Anonymous
97. Brian Lenescar; N/A
98. Paul Hession; Philip Morris International
99. Zucker Chad
100. Anonymous
101. Grant Bakewell; Eskaton Senior Programs and Services
102. Anonymous
103. Anonymous
104. Rob Wudlick; GUSU2Cure Paralysis
105. Allan Konrad
106. Anonymous
107. Anonymous
108. Anonymous
109. Reena; Indian muscular dystrophy²
110. Huntington's Disease Society of America
111. Amanda Haddock; Dragon Master Foundation
112. Eric Braverman, MD; PATH Foundation NY
113. Fabian Pla; FCS-Blanquerna Ramon Llull University³
114. Leslie Norins, MD, PhD, FIDSA; Alzheimer's Germ Quest
115. IQVIA Biotech CRO
116. Sean Rinehart; PFS Clinical
117. Greg Bauer
118. Sara Bernstein; National MS Society
119. Cynthia Rajan; NeolimmuneTech
120. Thomas Newman; UCSF
121. Anonymous
122. Maher Ghalmoush; Tufts Medical Center
123. Anonymous
124. Paul O'Regan; Cancer Research UK

² No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

³ No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

125. Ian Kleckner; University of Rochester Medical Center
126. Kathleen McNaughton, Mayo Clinic
127. Scott Weinberg; American Medical Informatics Association (AMIA)
128. Charlene Liggins; NIH
129. Dr. Jonathan D. Berman; self
130. Anonymous
131. Lisa Gallatin; BRIGHT Research Partners
132. Katie Goodman; Florida Cancer Specialists
133. Anonymous
134. Trial Transparency; Sanofi
135. Anonymous
136. Jessica Yingling; Mosaic Life Care/Heartland Regional Medical Center
137. Anastasiya Shor
138. Robert Morgan⁴
139. Anonymous
140. Stephan Schwebke; Nonesuch
141. Anonymous
142. Anonymous
143. Katja Theobald; Edwards Lifesciences
144. Anonymous
145. Jennifer Brown; Medical College of Wisconsin
146. C. Marc Taylor; ISRCTN registry
147. Joseph Stacey; Self
148. Darren Taichman; ICMJE
149. Kerry
150. Anonymous⁵
151. Anonymous
152. ResMed
153. Jimmy Wah; Common
154. Dr. Arturo Loaiza-Bonilla, MD, MSED and Selin Kurnaz, PhD; Massive Bio
155. Vilmantas Navickas; Boehringer Ingelheim
156. Amber Hicks; UT Southwestern Medical Center, Dallas, TX
157. Karen Creekmore; purpleangel-global.com
158. The ChEMBL Team; EMBL-EBI (European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, UK)
159. American Society of Hematology
160. Joy Rusthoven; SURVIVEiT
161. Jennifer; Cleveland Clinic
162. Anonymous
163. Ellen Ciesielski; UConn Health

⁴ No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

⁵ No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

164. Nate Root; PHUSE and Ionis Pharmaceuticals
165. Anonymous
166. Zach Weingarden; TrialAssure (MMS Holdings)
167. Anonymous
168. Neha Tickoo; Kinapse
169. Ivan Zipancic; Synteract
170. Anonymous
171. Joseph M. Betz, PhD; NIH Office of Dietary Supplements
172. Sarah Brookhart; Association of Psychological Science
173. Rachel Bent; Dana Farber Cancer Institute
174. Novartis
175. Anonymous
176. Ashley McKhann; Center for Biostatistics in AIDS Research
177. Jennifer Dexter; National Health Council
178. Dr. Ting-Chao Chou; MSKCC/PD Science LLC
179. Dr. Jesse Berlin; Johnson & Johnson
180. Anonymous⁶
181. Elke Hausner; IQWiG
182. Sarah Johnston; IQVIA
183. Smita Shukla; GSK
184. Anonymous
185. Kristin West; Council on Government Relations
186. Joshua D. Wallach; Yale School of Public Health
187. Eleanor Dehoney; Research!America
188. Memorial Sloan Kettering Cancer Center
189. MIRACUM (Part of the Medical Informatics Initiative)
190. Jessica Cohen; Vertex Pharmaceuticals Inc.
191. Christine Hodgdon; Storm Riders Network
192. Melanie Chladny; University of Michigan Medical School
193. Michael Vaughn; TransCelerate BioPharma Inc.
194. Ravi Thadhani; Partners HealthCare
195. Sarah White; Brigham and Women's Hospital
196. Anonymous
197. Maathuri; The Hospital for Sick Children
198. Anonymous
199. Eric Anthony; International Society for Stem Cell Research
200. Christine Gleave; Geisinger
201. Max Narovlyansky; FlowCell
202. Mary M. Langman; Medical Library Association & Association of Academic Health Sciences Libraries
203. Saad; Hoffman-La Roche
204. Sarah White; Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard
205. Lindsay Clarke; Alliance for Aging Research

⁶ No comments were provided by the submitter; therefore, there is no corresponding submission page in the document.

- 206. Emily Spitzer; Cook MyoSite Inc.
- 207. Juliane Baron; Federation of Associations in Behavioral & Brain Sciences
- 208. Anonymous
- 209. Allergan
- 210. Stacey Berg; Baylor College of Medicine
- 211. Jackie Foster and Anna DeSalvo; National Marrow Donor Program / Be The Match
- 212. Elly Cohen; BreastCancerTrials.org
- 213. Joseph Laakso; Endocrine Society
- 214. Jennifer Prozonic; Emory University
- 215. Vojtech Huser
- 216. Raj Bandaru; RnD Consulting LLC
- 217. Duke University School of Medicine
- 218. Jason Resendez; UsAgainstAlzheimer's
- 219. Meg Johnson; UMass Center for Clinical & Translational Science/UMass Medical School
- 220. PRA Health Sciences
- 221. Lucia Speroni; Illumina, Inc.
- 222. Brian Alper; EBSCO Clinical Decisions
- 223. Joanne Salcido, PhD; Pediatric Brain Tumor Foundation (PBTF)
- 224. Jennifer Graff and Richard Willke; National Pharmaceutical Council and ISPOR
- 225. Priyesh Ved; NET ESOLUTIONS CORP. (NETE), an NTT DATA Company
- 226. Nancy Smider; Epic
- 227. Kathy Riley; Pediatric Brain Tumor Foundation
- 228. Sandra A. Brown; University of California San Diego
- 229. Wendy Smith Begolka; National Eczema Association
- 230. Francine Lane; TrialScope
- 231. Francine Lane; DIA Innovative Clinical Trials Working Group
- 232. Sue Buff
- 233. Dr. Ting-Chao Chou; MSKCC/PD Science LLC
- 234. Anonymous
- 235. Anonymous
- 236. Andrew Pleasant; Health Literacy Medica / C3T
- 237. Amar Patel; Wellstar Health System
- 238. Association of Medical Colleges
- 239. Anonymous
- 240. Jamie Webb; Working Group on Pediatric Gene Therapy and Medical Ethics, Division of Medical Ethics, New York University, Grossman School of Medicine
- 241. Laura Iliescu; PRA Health Sciences
- 242. Guy Becker; Microsoft
- 243. Rebecca Li; Vivli
- 244. Alissa Gentile; The Leukemia & Lymphoma Society
- 245. Maia Walker; Fight Colorectal Cancer
- 246. Katherine Regan; Pfizer, Inc.
- 247. Kristen Santiago; LUNGevity Foundation
- 248. American Cancer Society Cancer Action Network (ACS CAN)

- 249. Anonymous
- 250. Christina Eldredge; University of South Florida
- 251. Cassadie Moravek; Pancreatic Cancer Action Network (PanCAN)
- 252. Perrine Janiaud; Meta-research Innovation Center at Stanford
- 253. Simone Kraemer; Bristol-Myers Squibb
- 254. Nicole Gatto, PhD; Aetion
- 255. Anthony Keyes; Johns Hopkins University
- 256. Fred Jorgensen; Booz Allen Hamilton
- 257. Taylor Zimmerman; University of Washington
- 258. Donna M. Ludwinski; Solving Kids' Cancer
- 259. Deborah Collyar; Patient Advocates In Research (PAIR)
- 260. Rachael Fones; IQVIA
- 261. Mark Ediger
- 262. Matthew Donovan; DSFederal
- 263. Lisa Chotkowski
- 264. Anonymous
- 265. Scott Thompson; Scott C. Thompson, ELS, Independent Medical Writer
- 266. Lisa Chotkowski
- 267. Cochrane
- 268. Sara Elizabeth Siegler⁷

⁷ The submitter requested that the comments provided be excluded from the public posting; therefore, there is no corresponding submission page in the document.

Submission No.: 2

Date: 1/6/2020

Name: Tyrone Quartermann

Name of Organization: UPENN

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Ability to export directly to other interfacing websites such as REDCAP, Qualtrics.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

cross referencing journal sites such as NCBI, NLM publications, JAMA, PubMed. Ability to directly reference publication materials would greatly reduce strain on investigators and team inputting data

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Reviewing and releasing records, inputting record data. exporting into other systems for advanced metrics. Sorting and organizing as well as search functionality works well.

Improvements should be made to review criteria and logic checks to ensure consistency with reporting requirements as well as external requirements.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

A wide range of studies.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Error checks- could be improved to force or highly encourage teams to fix errors before leaving the system (e.g. you cannot close the page without fixing error)

consistency in outcome measure review- outcome measures are highly contested and sometimes it is difficult for study teams to understand how to report outcome measures.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Our institution uses an HSERA system, being able to directly link to a CT.gov webpage or hyperlink a CT.gov webpage / NCT number would greatly improve communication.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

none.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

faster review, more communication with reviewers.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Highlights / badges on the posting on CT.gov (e.g. stars for high performing investigators or teams that publish successfully with 1 or less returned submission).

Expedited review times for high volume investigators

priority webchat support for high performing investigators.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

provide specific (redacted) examples of successful submissions.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

none.

Submission No.: 3

Date: 1/6/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

It is very difficult to enter information on cross-over studies, mechanistic studies, or studies with unusual study designs.

Perhaps this could be achieved with different templates for different study designs.

Submission No.: 4

Date: 1/7/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Would it be possible to link a clinicaltrials.gov listing with a publication (when existing) rather than having to list results on the clinicaltrials.gov listing? I find the results section to be rigid and our results do not always conform to the categories and responses available. Not all studies on clinicaltrials.gov conform to the methods or results of traditional trials.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

It would be great to have reminders when expiration dates are approaching (before they expire) so that personnel would know that the study listing needs to be updated.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use involves a wide range of study types. It also involves both single center and multicenter studies including but not limited to clinicaltrials.

Submission No.: 5

Date: 1/8/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- 1) Please consider removing trials with only “advisory issues” from the Problem Report. Reconciliation of advisory issues is not mandatory; yet, trials with these issues continue to show as problem records with actionable items. It makes reporting non-compliant records more complicated than it needs to be.
- 2) Please consider requiring all of the “Oversight” fields to be required. As in, there should be an automatic logic error if they are unanswered. These fields pertain to FDA regulations.
- 3) Please consider alerting the Responsible Party with an automatic email when record errors are generated. Often the RP will complain that “they didn't know” there were errors.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- 1) Please consider creating an unassigned checkbox and open text field, visible only on the PRS side, for convenience of institutional PRS administrators. The checkbox could be used by the admin to denote anything specifically relevant to their processes. Additionally, the open text field could contain temporary notes that should not be a permanent part of the record (as the current text box is). For example, it might contain notes like “expecting IRB approval next week” or “advisory issues are unable to be addressed” or “PI is considering transferring institutions,” etc.
- 2) Although Planning Reports are convenient, adding an organizational calendar function would be excellent.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Consider making organizational account statistics available to institutional PRS administrators themselves. Because not all registrations/results reporting may go through a central PRS admin, there is not a way to easily track organizational statistics (eg. # of revisions for registration, time to results approval, etc). That information would give us the tools to advocate for institutional policy changes and incentivize ourselves internally.

Submission No.: 6

Date: 1/9/2020

Name: Peter L. Elkin, MD, FACMI, IAHSI

Name of Organization: University at Buffalo, SUNY

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I would like to see the methods for each study codified including the main variables including outcome variables. Then the data should be attached to the study and any published papers. I would like to encourage systematic reviews and metaanalyses where possible derived directly from the reuse of the clinical trial data.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

I would like to see the methods for each study codified including the main variables including outcome variables. Then the data should be attached to the study and any published papers. I would like to encourage systematic reviews and metaanalyses where possible derived directly from the reuse of the clinical trial data.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We use it to feed a cellphone application to speed recruitment to clinical trials.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

We use all trials for a given region.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

You should use NLP to code the study variables with standard ontologies (such as SNOMED CT, LOINC, RxNorm) to assist reuse of clinical trial data.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

A web service approach that takes in batch datasets of trial info would be helpful.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

NLP

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

study calendar, reimbursement and payments to participants, codified inclusion and exclusion criteria.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Fund research on methods to fairly compensate data providers as downstream work yields publications and new inventions.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Maps between ICD10 and SNOMED CT are helpful

Maps between RxNorm and NDC codes and between RxNorm and ATC codes are helpful

Ongoing alignment of LOINC and SNOMED CT.

Linkages to scientific ontologies such as the Gene Ontology, HPO, MONDO, BFO, and OGMS and IAO.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

ICD10 is available widely but not very granular

SNOMED CT is good for diagnoses, procedures and Findings (Signs and Symptoms)

RxNorm is good at modeling clinical drugs

NDC codes model pharmacy orders

LOINC is good for Lab test result names

GO is good at Gene Modeling and Systems Biology

HPO and MONDO model genetic disorders

Submission No.: 7

Date: 1/9/2020

Name: Michael Hoffman

Name of Organization: University of Toronto

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Preprints, such as from bioRxiv and medRxiv. Link via DOI.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

New submissions to clinicaltrials.gov should include a Data Management and Sharing plan describing how individual-level data will be managed and made available to other researchers

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

FAIR Data Principles <https://www.force11.org/group/fairgroup/fairprinciples>

Submission No.: 8

Date: 1/10/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

It seems clear that NIH is intent on ensnaring brief “challenge” paradigms of cognitive neuroscience (primarily neuroimaging), which briefly probe non-enduring brain responses to different stimulus conditions, into this platform which is intended for registering results of ENDURING changes in mental or physical state resulting from extended or persistent interventions such as medications, manualized therapies or medical devices. While unfortunate, the administrative burden on PIs could at least be lessened by creating a logic/flowchart registration procedure that would probe up front in the process whether the “intervention” is intended to result in a change in state that would endure beyond the laboratory visit or encounter, and if toggled “yes”, needless questions (e.g. FDA/regulatory) would be obviated. A cognitive neuroscientist should be able to register the design and record the response in 20 minutes or less, each.

Submission No.: 9

Date: 1/10/2020

Name: Liza Rovniak

Name of Organization: Penn State College of Medicine

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Clinical trials.gov is a huge headache for PI's in resource-limited small towns where it's hard to find qualified PhD-level project coordinators who have the needed skills to accurately fill out the online forms. Often, the PI has to fill out/update the time-consuming forms on their own (or provide multiple rounds of feedback to a more junior coordinator which is even more painful/time-consuming). It takes away time from research and publications. It provides no practical usefulness to PI's. All I get from Clinical Trials.gov is emails from people from other regions of the country/world (who are ineligible to participate) inquiring if they can participate in my study which takes even more of my time. I don't use Clinical Trials.gov for scientific information. The published reports in the field (protocol papers, results papers) are the best source. Investigators do a better job on the published papers because there is academic incentive (promotion/tenure) for publications, but there is no reward/incentive for doing more bureaucratic form-filling via Clinical.Trials.gov. I think a better system would simply work in an automated fashion to extract the needed info from the funded grant (e.g., an extension of the NIH Reporter system), rather than requiring investigators to take such an active role with filling out this bureaucratic paperwork.

Submission No.: 10

Date: 1/10/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The search functions are not user-friendly with respect to finding outcomes for a particular topic. Bringing CT functionality into the 21st century with search engines and functions like google, Siri, Alexa is far more likely to serve the general public than the current interface.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

No active researcher has the time to do all the manual entry necessary to link publications in the current system. The NCBI system is woefully inadequate at auto populating and linking publications. Furthermore, it only tracks PI's, not Co-I's on grants. Linking CT to scholargoogle or other much more commonly used (by the public) search engines is a must if the goal is really to serve the public's need for access. The current system is simply too cumbersome for the average person to persist beyond finding a clinical trial that they might want to enroll in.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

My lab tried to begin a service to establish a public "blog" finding and translating outcomes of trials for a particular condition. I have taught research design and statistics for 15 years, and have over 400 publications. We gave up on the task. It was nearly impossible to find understandable, reportable or analyzable outcomes. I do not believe the public in general can access trial results in any meaningful manner. In fact, the results reporting seems purposefully obfuscated. As a result, my only use of CT.gov is to comply with regulatory requirements.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use of CT.gov is now simply to comply with regulations. The search functions, the format (and lack of standardization) of outcome reporting has rendered any scientific or public service reporting of results far too cumbersome and time consuming to continue. I am a highly published, and experienced researcher with many years of teaching experience in statistics and design, and I am unable to use CT.gov to summarize findings on a given topic. Results reporting is inscrutable. We can regularly do those tasks from published results in journals, but not from CT.gov.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

There is no escaping the conclusion that CT.gov registration and information submission is an onerous chore for investigators. Many studies are forced into the rubric of “Clinical Trial” as if they are an investigative drug trial when they are not. I frequently get calls or emails from people (patients) desperate to enroll in some sort of trial to help their condition, only to disappoint them when they learn that we are studying a mechanism, not a treatment. It is a tremendous disservice to the public, that it totally a function of CT.gov registration shortcomings. Similarly, if looking for results of actual treatments, the public cannot discern what is a real clinical trial vs. CT.gov/NIH defined clinical trial.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

I would sure like not to duplicate all my efforts for the local IRB, NIH reporting, and CT.gov, but I honestly have no idea who to integrate these systems. A serious amount of PI time is wasted on the administrative reporting tasks, instead of actually doing science and reporting it to the public.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I laud the idea of positive reinforcement, rather than the current approach of threats of fines and imprisonment. The most valuable reinforcers for extremely busy researchers are 1) time, 2) research funding. Anything that can be done to reduce the time burden and anxiety surrounding threats from CT.gov would improve the lives of researchers, and increase the probability of timely compliance. As a researcher, I frequently have the impression that whomever is putting together these regs and processes has never had a grant, run a lab, or tried to publish important information.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

If an effect size cannot be provided or computed easily from the outcomes reported, it is a failure of reporting.

Submission No.: 11

Date: 1/10/2020

Name: Richard diMonda

Name of Organization: Medical Device Consultant

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Most Federal sites have poor search engines. I have been very impressed with the quality of the clinical Trials.gov website search engine. It is worth continuing to enhance that aspect of it cause it enables you to find the study you are interested in reviewing.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

might provide links to published papers as an update; request this of the sponsor. it might make it easier to show earlier results than when the sponsor gets around to posting their results.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

the main use is for new product research. If someone did a trial for an application and for example a type of device, you will need to likely do the same trial. So I use the site to gauge how involved the trial needs to be. I also use it regularly to help estimate how long it realistically might take to do a trial. Also, another good thing is to contact researchers listed as they might be interested in participating in your trial of a similar type. Its a tremendous resource for clinical / regulatory pathway research.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I use it exclusively for commercial reasons. What trial might I likely have to do and how long did it take to do it. Very valuable.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I've only submitted a long time ago. I am sure I struggled. But your format is excellent cause it enables you to really see what someone did.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Would be nice but likely impractical. No one is going to spend time filling out your stuff prior to doing what they need to do to get going. Unless, of course FDA were to force you to do that, which I think would be burdensome.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Not sure

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Not sure

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I don't think that this will matter much to anyone.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

I would be careful to force someone to comply with every bit of information as it will disincentivize submissions. I would continue to model the boxes to emulate the topics in a clinical protocol so that you can cut and paste.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Not that important. I make extensive use of this website and think it is very valuable as is. I'm a commercial medical device product developer. The obsession with data and analyzing it, doesn't necessarily need to find its way into this space. When someone is using it they likely use it as I have suggested and you need to review each study that is similar to that which you are planning to do. Hence any enhancements you make to your search engines will have more impact than these outlier things that are of interest to data miners but no one else.

Submission No.: 12

Date: 1/10/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

It seems that even if a trial does not reach its target sample size, that ClinicalTrials.gov still requires the investigator to perform data analyses and enter p-values and other results in the Statistical Analysis section. However, this is not wise. If the target sample size was not reached, then performing statistical analyses is not good practice. Thank you for your attention.

Submission No.: 13

Date: 1/14/2020

Name: Jordan Elm

Name of Organization: Medical University of South Carolina

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I only use clinicaltrials.gov to quickly check on a study that someone mentions. The study designs are usually difficult to understand as presented on clinical trials.gov.

I never use clinicaltrials.gov to review results. I always go to the primary source (published article) which provides more context.

The description of outcome measures never get reviewed until the time that results are submitted. As such the outcome measures listed when the study is first registered are usually input by the PI or project manager (not a statistician) and hence are often lacking in specific details (e.g. time range, type of outcome binary or continuous) etc. When I am inputting results I often have to revise the title and description of the outcome measures in order to be more exact. Nevertheless, I always get asked by clinicaltrials.gov for MORE clarifications to the outcome meaures before results are accepted.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I rarely use this data. If used, it is only for general reference of a limited range of studies that are ongoing (not for results).

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

A statistician really needs to submit the results. However, the trials are registered by the PI who may be at a different institution from the statistician. There is no way for a statistician to be given access to the trial without “joining” that institution. Hence I have an account with clinicaltrial.gov through the PIs university. This is award and I would prefer to have a single log in account.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

Adaptive, Bayesian, Global tests are very difficult to report within ClinicalTrials.gov.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

The system is awkward and cumbersome. It requires us to manually enter results which are already publicly available through PubMed. Why not simply link to the primary study reports which are published? Details of outcome measures (full descriptions) are difficult to understand without context (background and rationale), yet there is a character limit to the description field within ClinicalTrials.gov.

Responding to questions about descriptions of outcome measures are tedious and unnecessary since much better descriptions are already available in the published articles and within the public domain.

Submission No.: 14

Date: 1/15/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

It would be helpful if publications of a particular trial's data were linked from the page.

Submission No.: 15

Date: 1/15/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Researching medical devices and pharmaceuticals. When a brand name is searched, ClinicalTrials.gov includes generic names for ingredients in the product, leaving hundreds of trials to weed through

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use ClinicalTrials.gov to research medical devices to find up-to-date trials that evaluate products. It would help to be able to sort by date, sponsor, etc when going through the trials

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

2. When I look for information on a product, the search sometimes brings up a ton of studies that don't have the product at all. I use the "other terms" search engine. It would be useful to be able to search for "intervention" field only.

Submission No.: 16

Date: 1/15/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Be able to sort drugs by Mechanism of Action and Method of Administration

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Link results to the published paper (if applicable)

Submission No.: 17

Date: 1/15/2020

Name: Rodrigo Garcia

Name of Organization: Source Healthcare

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Adding a filter when searching for a study to select for the study model and the masking would be very helpful for narrow searches.

May I suggest adding a filter for these options on your search page. This would allow someone to find the types of studies they are looking for without spending hours on end looking for the right study.

Eg. Filter for allocation “Randomized”, masking “double-blind”.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

To build from the filtering process I discussed earlier. The filtering tool on your search page is very useful, yet it needs to have more filtering options to filter studies by masking and allocation.

Countless of hours spent looking through a variety of trials when this process could be streamlined with a box to click on the filter toolbar of the search page.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use of ClinicalTrials.gov is to look for potential studies that are looking for sites. Too often, time was spent scrolling through studies that were either specific to research institutions or did not meet the specified criteria of masking for our research purposes.

My primary use of ClinicalTrials.gov is on the latter (2), so for sites like ours it would be very beneficial to have additional filters.

Submission No.: 18

Date: 1/15/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

- Ability to sort search results by different fields (eg start date, completion dates, trial size)
- Ability to move columns for search results (eg first field being start date, then completion date, or first by indication, etc)
- Improving search such that a searching “peripheral artery disease” in the indications field only retrieves the records that fit this parameter; oftentimes, Raynaud’s and other indications are also retrieved.

Submission No.: 19

Date: 1/16/2020

Name: Vinod

Name of Organization: GSK

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1. Ability to extract data for specific studies e.g. I would like to extract 100 studies with the 100 NCTIDs I have from previous extractions or data

2. Ability to store or save search queries and alerts for specific search criteria

3.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

PMIDs can be linked - to access detailed results published for the trials; CT.gov results are not updated as and when the new data arrives

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Analysis of Trials for specific disease areas

Customized searches to understand pipeline landscape in certain time periods

Improvements needed

1.Addition of Phase I/II in filters

2.Site numbers Summaries for each trial (e.g. Locations - 130) or Sites % across geography - for specific trial)

3.Extract data for specific NCTIDs - Only 15-16 IDs can be extracted now

4.

Submission No.: 20

Date: 1/16/2020

Name: Michael Sutton

Name of Organization: Urgent Research

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use the RSS alert all the time and know many patients and professionals who also use it. Keeping the RSS feature, and the ability to create RSS feeds based on custom searches, is very important to me.

Submission No.: 21

Date: 1/16/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I would like to suggest two potential improvements:

It would be great for patients to have an easy to understand Study Duration field. For example: up to 2 Months, Up to 20-60 Weeks, etc.

Also, it would be nice to homologate the definition of “Recruiting” as some Companies choose the “Recruiting” status only if they have enrolled at least one patient. I think that the definition of Recruiting should be less flexible, as specifically for patients, it would be important to know when a site of interest is ready to screen them even if the site has no patients yet.

Submission No.: 22

Date: 1/16/2020

Name: Vidushi Khurana

Name of Organization: Course5 Intelligence

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

All the keywords mentioned in the trial are not searchable using “other terms” and even “boolean search”

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

1. Press releases by the company
2. Databases: IND & NDA, Orphan/ Fast track/ Priority review/ Prime/ Breakthrough designations, drug approval status

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

1. In the download, exclusion and inclusion criteria must also download. As many search keywords appear in these criteria which is not 100% searched while using “other terms”. E.g. in case of solid tumor trial, indications are better specified in the exclusion and inclusion criteria.
2. Change in the trial country should be searchable, as of now 90% of the location change is pertaining to site-related changes

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Data analysis and data update

Submission No.: 23

Date: 1/17/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Improvements:

- PI proxy (i.e. study coordinator, record owner) will allow the records on ClinicalTrials.gov to be released in an appropriate time frame
- Protocol Section > Study Status > Record Verification should automatically update once a change has been made, submitted, and approved

Submission No.: 24

Date: 1/17/2020

Name: Tom Crocker

Name of Organization: Bradford Teaching Hospitals

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We search clinicalTrials.gov as part of the search process for systematic reviews that we conduct. This is a mandatory task for Cochrane reviews and considered an important source of additional trials (MECIR C27; Baudard et al 2017; Pansieri et al 2017). We can download all of the search results to import into reference managers such as EndNote. We use the reference manager to conduct the screening and study selection process. However, the options to export do not enable us to bring all of the study details into the reference manager. The options in “Download”, “Download table contents”, file format: XML excludes many important details. Additionally, the available import filters put the data into the wrong fields (e.g. URL goes into Publisher). Although there is an option to download a full study record XML in a zip file, each study record is placed in a separate file, rather than all in one XML file, making import to a reference manager impossible. Please enable the export of all study details for all search results in one file, and their import into reference management applications.

Submission No.: 25

Date: 1/17/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**
 1. Please allow for push email notifications of changes to a specific trial. Should a trial have its Start Date move out for example, an email is sent to a user indicating the Before/After values of all fields where data has changed.
 2. Allow for individuals to create user accounts where they can then add in either individual trials to track, or companies. This will save a lot of time.
 3. Allow for individuals to create a list of trials that they do not want to show up in for any searches they do. Often when a search is done it will come up with trials a person is not interested in and the filters are not robust enough to filter them, and constantly updating filters is inefficient. Having a trial 'ignore list' would greatly streamline searches.
 4. Have the ability to do a side-by-side view of two or more trials so each section can be compared. This should be simple to implement since it would use similar logic to the logic use to compare two versions of a single trial.

Submission No.: 26

Date: 1/17/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I suggest that you have an export functionality one-by-one for the trial information. I end up having to copy/paste the study into a Word document and then pretty it up thereafter. It would be nice if there was a way to produce a pdf from the website

Submission No.: 27

Date: 1/17/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

I would like to see a listing for national clinical trials that don't require me to be there in person but are conducted either by telephone or by webcam.

Virtually everyone else has this option

Submission No.: 28

Date: 1/18/2020

Name: David Shapiro

Name of Organization: [Not provided]

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I explore new modified, or newly applied treatments, primarily for conditions I have been diagnosed with, and (1) sometimes offer myself as a subject; (2) sometimes investigate their risks and benefits by searching elsewhere at NIH.gov or other resources; (3) sometimes read reported results in order to consider whether to pursue particular modalities once they have been released for general use; sometimes look at results with an eye to querying an editor.

It would be helpful to be able to find all the locations of a multicenter trial without having to drill into the study.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Relatively wide. Any number of the search criteria are of value to me: age, country, date begun, phase, funding . . . I find subject-funded studies highly suspect.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Too many studies are listed as currently recruiting subject that have long stopped doing so. When a trial reaches its estimated completion date, at the latest, it should automatically be switched to “No longer recruiting” status unless the registrant revises its posted dates. If the resources are available, this should occur X weeks before the estimated completion date, X being the number of weeks that each cohort needs to participate.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I believe it is critical that studies publicized through clinicaltrials.gov be made available as sources of information regarding the value or danger of the interventions being explored. To this aim, anybody requesting such publicity should be required to make readily available, through a link or links accessible

through your site, information that may be of use to those interested in the interventions. This should take the form of standard reporting such as is presented in refereed journals, even in the case of early termination. This should occur upon completion or termination of each study. Aside from any possible fines, any institution or lead researcher failing to provide this access upon completion or termination, or whose research falls into the void of “Status unknown,” should be prohibited from posting any further notices on Clinicaltrials.gov until this requirement is satisfied.

Submission No.: 29

Date: 1/19/2020

Name: Elizabeth Molnar

Name of Organization: Seaforth Medical, Brisbane

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

As a psychiatrist, I have treated two patients with POTS who responded well to Reboxetine, an Specific norepinephrine reuptake inhibitor.

Elizabeth Molnar, bethmolnar@bigpond.com

Submission No.: 30

Date: 1/19/2020

Name: Michael Copeman

Name of Organization: Copeman Clinic, Palm Beach, Sydney, Australia

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Need to include a paragraph at the start of each trial listing that specifies what the treatment/compound being tested is aiming to do, and how the researchers think this is likely to work.

Need to ensure sponsors provide the name of each institution participating in a trial (not just a postcode), along with the name of the investigator at that site, and an email address to contact him/her or their delegate.

Need to include a paragraph that describes succinctly what patients entering the trial will likely go through, in terms of investigations, treatment and monitoring/follow-up.

Need to ensure each site participating in a trial can update (in as close to real time as possible) the status of IRB approval and logistical preparations of the trial at their site (i.e. when is it likely to start), and (when open) the actual number of places left on the trial (and any sub-requirements for patients filling those places).

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

A list of recent publications related to the treatment being investigated is helpful at the end of each trial listing.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

ClinicalTrials.gov is now the most useful part of my day, in providing second opinions to cancer patients seeking new therapies. (I can only thank the hard-working staff who see that this huge, global undertaking keeps working so well!)

In the last decade, we have identified thousands of suitable clinical trials for patients - right round the world - based on information initially sourced from your website. As a result, there are now patients alive, and in remission, who had previously been told that there was no option for new treatment available.

See above for potential improvements.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We will search for any trials, anywhere on ClinicalTrials.gov. Patients with life-threatening conditions will often travel wherever an opportunity exists - and may use private or donated funds to support them.

Patients and their families are impressed that a) the US Government is behind the site - and uses it to make sure that new treatments are being tested properly, prior to registration in the USA; b) the site is truly global - and allows researchers in developing countries to "compete" with the most-advanced/well-funded centres in USA/Europe; c) information on the site is updated regularly (whereas many other sites are out of date within a few months); and d) information on completed trials is included (although there is often some delay in this appearing!).

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Just keeping everything as close to real time as possible is the main request.

Patients don't like it if a trial that seemed to be open to patients has closed.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Although I have been involved in submitting trials in the past, I am no longer involved in this process.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Patients and their families/friends are increasingly accessing the site - but clearly need assistance to get information most useful to them. I would suggest keeping the site open to all to peruse (without any prior registration or information logging). But, patients do need a convenient way to print out (or email) trials they think might be relevant to themselves to their doctors.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

N/A

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Every six months have a merit list of individuals and organisations that ticked all the boxes.

Annually, have another list that recognises trials that recruited and completed on time.

Over time, academic institutions will use your lists to reward their staff!

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

N/A

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

N/A

Submission No.: 31

Date: 1/20/2020

Name: Timothy Fortin

Name of Organization: ICI Research

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use the site to monitor new trials in Oncology.

Please the ability to order the columns of a list of trials as well as the ability to sort the columns (ascending or descending)

Submission No.: 32

Date: 1/20/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Clinical trials should be able to send an alert when new studies match specified criterion and an option should be in the alert to limit studies based on age and/or sex of the individual and/or geographic region. Basically, the alert should be able to be as specific as the search when narrowed through selecting options.

This could be beneficial for clinicians conducting related research and for people with the condition hoping that they could match into a trial.

Submission No.: 33

Date: 1/21/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The ability to sort/order search results would be extremely helpful. For example, sorting results in ascending/descending order of the Last Update Posted date, Number Enrolled, etc.

Submission No.: 34

Date: 1/22/2020

Name: Rahul Ganatra

Name of Organization: VA Boston Healthcare System

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Asking trialists to justify why changes to changes or amendments to protocols are made is a function not currently supported by clinicaltrials.gov that would be very useful. For example, when appraising a trial, I frequently look at the change history of the primary outcome. Primary outcomes are changed for a variety of reasons, but as a consumer of the literature I am interested in appraising whether this could increase the likelihood of a type I error. Therefore, asking researchers to be accountable for any changes to the study protocol by explaining them seems reasonable to me.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Linking to the published research protocol would be useful for a trial record. For example, many times journals have trial protocols available as supplementary material on their website, but having these available on clinicaltrials.gov would put all of the relevant protocol information in the same place.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The feature I use most is the tabular view of the current vs. original primary and secondary outcomes to identify changes here. This works really well for most trials. The biggest limitation I encounter in doing this is that the language is often slightly different between the current and original without introducing a real difference in meaning. It would be easier to judge if the original and current primary outcomes are the same if the language was kept the same in the absence of a substantive change.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I use clinicaltrials.gov for a wide range of studies, but generally all of them are trials. I would really love it if clinicaltrials.gov could also be a place where protocols for observational studies and meta-analyses were housed so that I could use it as a one-stop-shop for critical appraisal of all kinds of studies.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

not applicable

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

not applicable

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

not applicable

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

not applicable

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

not applicable

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Changes to the language of the primary and secondary outcome that do not reflect an actual change in the outcomes make it difficult to determine if an actual change has occurred. Frequently, I will see the original primary outcome be something general (e.g. "time to worsening heart failure"), and the current primary outcome be something specific, like ("time to first hospitalization for heart failure") - in my view this is risky because it increases the likelihood of a type I error by not requiring authors to commit to a specific primary outcome at the outset of trial registration. I would like to see the requirements for specificity of outcomes tightened, as well as a field added for authors to provide justification for why outcomes were changed.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

not applicable

Submission No.: 35

Date: 1/22/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

none

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

none

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Web users are used to using the Go Back arrow, usually at the top left of their browser, to go back to the prior page which they had viewed. But it doesn't always work properly after doing a search and opening up a hit. For instance, if the hits display 10 to a page, and I am at the page with hits #61-70, if I open one of those, and then use the back arrow, it takes me back to the page with hits #41-50. I have repeatedly encountered such a problem. At the top of the display of a given hit, there is a Return to List link that works correctly, but as an occasional user of this website, I frequently forget to use it.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

For some conditions, such as prostate cancer, there are a large number of trials that are recruiting, even within 100 miles of my residence, but many of them are of advanced forms of cancer that are not applicable to be (at least not yet). Perhaps you could allow optionally narrowing the search by the Stage of the prostate cancer, or by "not metastasized" and "metastasized."

Submission No.: 36

Date: 1/23/2020

Name: Anonymous

Name of Organization: N/A

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b.** List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Regulatory Authority Name, ESMO and ASCO result link could be added to the data base

Submission No.: 37

Date: 1/23/2020

Name: Abdul Rahman

Name of Organization: Freelance

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

Adding an option to track recruitment status in each research site within a clinical trial record would be very helpful.

Submission No.: 38

Date: 1/23/2020

Name: Alistair Sinclair

Name of Organization: n/a

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Make access to trial “complete history of changes” 1 click away from each trial’s page

Currently requires 3 clicks

Click to “tabular view” > “change history” > then a final click to “ClinicalTrials.gov Archive Site”)

Submission No.: 39

Date: 1/23/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be helpful if the search screen would allow entry of search parameters in sentence form, as with a Google search, with an algorithm searching all fields for relevant data. An example search might be: "Show all recruiting studies in Ohio, USA, involving treatment of subjects with kidney disease, over 70 years old, including measurements of klotho."

Submission No.: 40

Date: 1/23/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The below items should be considered, specifically for the AACT (API). Each of these could represent a new column.

1. Calculating number of countries in each study (e.g. 14)
2. Calculating enrollment duration for each study (e.g. 24.1 months)
3. Control arm of each study (e.g. Placebo)
4. Standardized primary endpoint (e.g. ACR20)
5. Standardized primary endpoint timing in weeks or months (e.g. 12)

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use the website to investigate historical and current clinical trials for intelligence to what has occurred in the scientific community.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Mostly (1), but (2) could be made useful by being able to search for specific biomarkers in oncology, for example. If you are looking for a biomarker-driven population, being able to search for this would be extremely helpful.

Submission No.: 41

Date: 1/23/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I really really just want it to be blazingly fast. It doesn't have to look slick -- speed is all that I care about

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

competitive intelligence

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

an API

Submission No.: 42

Date: 1/24/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be very useful to be able to search by continent.

Submission No.: 43

Date: 1/24/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

/

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

biomedtracker and pubmed

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

searching and filtering trials for individual cancer patients looking for relevant trials

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

on a more limited range of studies because we look for trials for individual pts.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

use a set of standardised inclusion/exclusion criteria those registering their trial on the database can select from. this would allow for filtering on specific criteria while now one and the same criterion can be written in 100 different ways so you need to screen all the criteria listed and can't filter on them

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

would be easy if we could filter on studies in europe as a whole as well in stead of having to screen the lists of trials for each individual country

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

/

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

see above, harmonisation of eligibility criteria

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

/

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

/

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

/

Submission No.: 44

Date: 1/24/2020

Name: Melissa Cliver

Name of Organization: Wondros

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I recommend being able to sort by the top line identifiers such as region, condition so on...

Submission No.: 45

Date: 1/24/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I cannot find information on how to contact a study site. The language is too hard to me to understand the outcomes and eligibility.

Submission No.: 46

Date: 1/25/2020

Name: Mark Tedford

Name of Organization: Parkinson's

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Parkinson's

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Hemp , THC

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Research

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Research to help with life quality in the future

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Better questions

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

What?

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

?????

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Your research

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Find a human to wright these questions

Submission No.: 47

Date: 1/26/2020

Name: Christian Capitini

Name of Organization: University of Wisconsin

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The website could have an interactive map where one could click on a state and see what is available in the patient's immediate area. It could be further drilled down by then being able to click on cities.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

The data from the trial could link to abstracts on society websites or journal supplements. The final publication could be linked from Pubmed.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use it to find clinical trials for my own patients but also for referrals I get for various relapsed pediatric cancers. The search engine is clunky, there are 3 different fields: disease, other terms and country. It should be one search bar, like Google. Also I had a trial at my institution for relapsed/refractory neuroblastoma that one could not find bc it was not registered with the keywords. The search engine should be able to pull information on the clinicaltrials.gov page for the trial even if the center did not pick the right keywords.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I look at a wide range of studies bc I care for orphan diseases, so always have to be broad in my searches.

Submission No.: 48

Date: 1/27/2020

Name: Scott Lofgren

Name of Organization: Source One PC

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Finding the clinical trial results from a specific company.

How to ?

Need to be able ask questions on how to do the search for a company with many trials going on.

Then bundle trials for the company in one place

Submission No.: 49

Date: 1/27/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

I have been using the clinical trials.gov website for my capstone project at the university of chicago. We are building a tool that will match clinical trials to patients using their genomic data.

Two things that have caused a major hinderence to the project. 1) Too many oncogenic trials either have both a inclusion & exclusion criteria field or they just have a criteria field. Either way this makes text analytics hell because it's hard to pinpoint for certain texts when it can exist in both inclusion & exclusion! Please make these separate fields, one box for inclusion the other box for exclusion.

2) Oncogenic trials and other trials have fields called 'conditions'. Perhaps you should also look into putting in the genomic data in that condition box, i.e. gene TP53 with VRAF mutation, etc. Some trials have this data in the criteria field but again due to the messy formatting of the criteria field this data becomes murky at best. Make a separate genomic data field.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

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1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

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Oncogenic studies with clear genomic marker data

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

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2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

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2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

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2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

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Two things that have caused a major hinderence to the project. 1) Too many oncogenic trials either have both a inclusion & exclusion criteria field or they just have a criteria field. Either way this makes text analytics hell because it's hard to pinpoint for certain texts when it can exist in both inclusion & exclusion! Please make these separate fields, one box for inclusion the other box for exclusion.

2) Oncogenic trials and other trials have fields called 'conditions'. Perhaps you should also look into putting in the genomic data in that condition box, i.e. gene TP53 with VRAF mutation, etc. Some trials have this data in the criteria field but again due to the messy formatting of the criteria field this data becomes murky at best. Make a separate genomic data field.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I have been using the clinical trials.gov website for my capstone project at the university of chicago. We are building a tool that will match clinical trials to patients using their genomic data.

Two things that have caused a major hinderence to the project. 1) Too many oncogenic trials either have both a inclusion & exclusion criteria field or they just have a criteria field. Either way this makes text analytics hell because it's hard to pinpoint for certain texts when it can exist in both inclusion & exclusion! Please make these separate fields, one box for inclusion the other box for exclusion.

2) Oncogenic trials and other trials have fields called ‘conditions’. Perhaps you should also look into putting in the genomic data in that condition box, i.e. gene TP53 with VRAF mutation, etc. Some trials have this data in the criteria field but again due to the messy formatting of the criteria field this data becomes murky at best. Make a separate genomic data field.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

I have been using the clinical trials.gov website for my capstone project at the university of chicago. We are building a tool that will match clinical trials to patients using their genomic data.

Two things that have caused a major hinderence to the project. 1) Too many oncogenic trials either have both a inclusion & exclusion criteria field or they just have a criteria field. Either way this makes text analytics hell because it's hard to pinpoint for certain texts when it can exist in both inclusion & exclusion! Please make these separate fields, one box for inclusion the other box for exclusion.

2) Oncogenic trials and other trials have fields called ‘conditions’. Perhaps you should also look into putting in the genomic data in that condition box, i.e. gene TP53 with VRAF mutation, etc. Some trials have this data in the criteria field but again due to the messy formatting of the criteria field this data becomes murky at best. Make a separate genomic data field.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

I have been using the clinical trials.gov website for my capstone project at the university of chicago. We are building a tool that will match clinical trials to patients using their genomic data.

Two things that have caused a major hinderence to the project. 1) Too many oncogenic trials either have both a inclusion & exclusion criteria field or they just have a criteria field. Either way this makes text analytics hell because it's hard to pinpoint for certain texts when it can exist in both inclusion & exclusion! Please make these separate fields, one box for inclusion the other box for exclusion.

2) Oncogenic trials and other trials have fields called ‘conditions’. Perhaps you should also look into putting in the genomic data in that condition box, i.e. gene TP53 with VRAF mutation, etc. Some trials have this data in the criteria field but again due to the messy formatting of the criteria field this data becomes murky at best. Make a separate genomic data field.

Submission No.: 50

Date: 1/28/2020

Name: Granio

Name of Organization: Potentiel d'action - France

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Search tool could be improved. To this aim, entry of every information must be strictly verify and better defined.

Exemple : Town of a country where a trial is ongoing. Submitters should have a specific category to enter only the town (and no more information for this category).

To determine a complete list of towns could avoid mispelling as well. Submitters will then choose in a specific listing and NOT write the name of the town.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Could be interesting to have a link to the FDA to know the status of one molecule (approved, breakthrough designation....).

Link to some major congresses could be interesting too as for exemple in oncology ASCO and ESMO.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Link to publications in Pubmed is REALLY useful.

What can be approved? Some publications are not automatically indexed in clinical trial, mainly because the NCT number is missing. So maybe there is an improvement to do in the way to identify new publications (exemple : with the NCT number (as it done until now) AND with the name of the disease + one key word (ie molecule name, disease) OR you can ask every clinical trial submitter to add the NCT number in all publications on trial results.

In the other way some publication are added but not directly linked to the trial. I assume (I never submit a trial) that it is done by the submitter. Usually those publications are not relevant.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use of ClinicalTrial relies on a wide range of studies. I'm interesting in drug development. So I look at all studies, all phases for one given molecule in one special disease. I'm also interested in where those studies are carried on.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I never used the submission process.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

I never used the submission process.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

I never used the submission process.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

I never used the submission process.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

Good question.....

Last update posted is very important.

Explain to the submitter that a clinical trial with status UNKNOWN will not encourage Physician to include patients.

Location sites are often too 'light'. The name of the hospital is sometimes not given. And this will also not encourage physician to include patients in. Sometimes it's written Sponsor site# - Location. This is not correct. A clinical trial is always done by Physicians in a medical center. So this information must be given properly.

Some sponsors remove location sites when the study is 'Active, not recruiting'. This is also a pity. It's always good for a Physician to have the name of a hospital where a trial is on going.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

I never used the submission process.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

No answer for this.

But thank you for your great job!

Submission No.: 51

Date: 1/28/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

When navigating backward to revise a search, the previously used search terms disappear but it would be nice if they stayed in the cookies

Submission No.: 52

Date: 1/29/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

There is need for mention of statistical analysis approaches to be used, especially for novel designs like basket and umbrella trials.

Submission No.: 53

Date: 1/29/2020

Name: Ahmed Elwakeel

Name of Organization: Cairo University, Egypt

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

kindly link to pubmed, allow login using pubmed credentials to magnify the benefit

Submission No.: 54

Date: 2/2/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I would like to have a feature added to the site where a person could fill out a form with basic demographic information and health conditions and study areas they are interested in and save it to the site. That way researchers could search these for possible study subjects, and, if a person sees a study they are interested in participating in, they could just send their form to the researchers. Win-win with less effort.

Submission No.: 55

Date: 2/3/2020

Name: Joe Risser, MD, MPH

Name of Organization: San Diego Family Care (FQHC)

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Push notifications as in alerts.google.com to be notified of trials as they come online

Better would be smart filtering of notifications as in gnoosic.com

Many potential study subjects narrow results to their geographic area, not aware that some trials provide housing and transportation. It may help to identify trials that provide housing and/or transportation.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

all NIH / pubmed resources

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

as a clinical physician, helping patients find trials they may be eligible for.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

wide range w/ different study types

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

google-like correction of entries (e.g., if user enters "heart pain," a pop-up of possible alternatives including "angina pectoris")

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

most helpful would be collaboration with EMRs to store patient diagnoses, demographics, study interests and periodically recheck available studies, then notify clinician

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I really like the "NEW" designation on recently released trials. Other designations such as "first in class" or "only at NIH" would be interesting.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

a rating system for institutions and individuals indicating proportion of trials results were submitted and GCP for conducting trials. I'm particularly concerned about nefarious clinics

Submission No.: 56

Date: 2/4/2020

Name: Virginia Guptill

Name of Organization: NIH CC ORSC

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Link to PubMedCentral for associating publications with studies

Make active consents available at registration into CT.gov

MedDRA standards API

ICD-10 medical codes to link in CT.gov

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Using protocol numbers to search for studies works well, filters are very helpful. Easy for patients to use site to search for studies.

Results returned vary based on search criteria used, e.g. selecting sponsor field NIH and NIH funded. What does sponsor mean, financial sponsor, study sponsor, IND sponsor, etc.

Add option for searching phase I/II and phase IIb studies, phase 0 studies, and pilot studies

When searching for studies include a column that designates if the study includes an IND or IDE (yes/no) or both

Include information if compensation is provided as yes/no

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The system is difficult to navigate to include results reporting. Doesn't include ability to report on multiple types of studies that are common types at the NIH CC. If terminating a trial early you still have to include the results reporting based on original statistical analysis plan, which may not have been done without full cohort of participants. The system is clunky and not intuitive to use or view results. The language and terminology requested to be used in CT.gov often is quite different than what was reported in the manuscript/publications and there is a lot of back and forth with the CT.gov staff.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

consider an API for IRB submission systems

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Include a lay summary of the results

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Have a person available by phone to answer questions related to observations from results entry

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

enforce results reporting penalties for those not reporting in the required time frames

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Have an option to link specific reporting standards (e.g. MedDRA coding or CDISC) to branching logic when selected and have an API to pull those standards into CT.gov

Submission No.: 57

Date: 2/4/2020

Name: Stacy Smith

Name of Organization: Coastal Clinical Research

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be helpful if we could set up weekly or monthly email digests for certain search criteria. An example of this are the emails I can set up to deliver new publication notifications from PubMed.

Submission No.: 58

Date: 2/7/2020

Name: Alexey Strygin

Name of Organization: Cryno Biotech

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1) One of the primary objectives of CT.gov is not currently being achieved. A considerable share of the results is not reported.

Probably a mechanic which involves the community could be of use. Researchers and individuals should be able to highlight the study which should be finished but still lacks the results. Thus CT.gov management would get a prioritized list (the more highlights from the community - the more priority) of studies the posting the results of which should be enforced.

2) Plain English abstracts like the ones used by Cochrane might be useful

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Link to patents might be useful for generic producers

Link to molecular structure databases might be useful to medical chemists

This could also be achieved by community involvement. (A community member might propose an external link which then would be reviewed by CT moderator)

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I look for what studies were conducted for indications that we are considering to develop a drug for/already developing a drug for. I look for possible study locations and competitors

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

2) The more in depth data on a concrete study is much more useful for me. Detailed study design data allows to better assess possible costs, needed patient numbers etc

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I will copy 1a answer there, it is really of crucial importance for humanity as whole

- 1) One of the primary objectives of CT.gov is not currently being achieved. A considerable share of the results is not reported.

Probably a mechanic which involves the community could be of use. Researchers and individuals should be able to highlight the study which should be finished but still lacks the results. Thus CT.gov management would get a prioritized list (the more highlights from the community - the more priority) of studies the posting the results of which should be enforced.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

unapplicable for my organization

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- 1) plain English abstract
- 2) Method described in 1a and 2a

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

unapplicable

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

The harder part here is to make organizations publish unfavorable study outcomes. Some ideas:

- 1) Whereas negative outcomes are bad news for study sponsor drug developers - they are usually neutral news for CROs and for Locations. It would be wise to incentivize the CROs and locations to get results published, outlining awards/publicly available data for something like "high standard trial organizer" or something like that. This might be then used as a good criteria for selecting these organizations for publicly/government sponsored studies
- 2) Introduce best practices for CRO-sponsor, location-sponsor legal contracts to allow CRO and/or location to publish results during N months if the sponsor fails to do so
- 3) additional year of patent term to the patent of sponsor's choice if the sponsor submits data on time (minus several month to patent term to current blockbuster patent if the sponsor fails to publish data) [would be a great tool, though doesn't seem plausible]
- 4) some tax refund for a failed study if data is published on time

3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
 - 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

unqualified to provide relevant feedback

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

unqualified to provide relevant feedback

Submission No.: 59

Date: 2/7/2020

Name: Aurélien Marabelle

Name of Organization: Gustave Roussy

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

It's painful to have to go back to the home page for every search our search refinement.

Could you please provide the search bar at the top of the results page?

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Sorry but Your survey/form is way too complicated and many will be reluctant to provide feedback because of that...

Submission No.: 60

Date: 2/7/2020

Name: Sarah Morgan

Name of Organization: BIDMC Harvard University

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use the website to examine drugs being tested in my disease of interest. It is incredibly useful for our research to download all the data for Alzheimer's disease and examine the drugs in our models. This helps us with drug target prioritization. However, many submissions into the website are in need of a curator or possibly more detailed instructions to the user. For example, everyone inputs their drug treatment name differently (which makes it hard to process on a large scale) and some don't enter a drug at all (only the title gives away the drug being tested). Secondly if a trial is terminated, there is never an explanation e.g. funding run out, adverse effects etc. It only needs one sentence but this vital information is never captured. Also for completed trials another one liner is incredibly useful - saying future research required or drug was dropped for lack of effect etc.

Submission No.: 61

Date: 2/7/2020

Name: Lara Fournier

Name of Organization: OHSU Knight Cancer Institute

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Would like an 'Undo' feature.

As a CT.gov org. administrator - would be nice if the system was a little more forgiving of human error. Example, I accidentally set the wrong record to 'in progress'...when I realized my mistake, i emailed to see if CT.gov staff could help reset back to 'Public' but they said they could not...i ended having to email the PI, explain situation, and ask him to release it again.

Submission No.: 62

Date: 2/8/2020

Name: Ed Croom

Name of Organization: Pfeiffer University

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Any webscraping tool is of limited use for clinicaltrials.gov. This can be a commercial/free tool/service (e.g., Octoparse, Scrapy) or a feature added to something like R (e.g., Rvest). The problem is the results lack a report card style structure. It is great that %SAEs are always in the same place and always use the same terminology. But the rest is just a mess. Pubchem is a good example of something with real structure both for their new feature of the laboratory chemical safety summaries and their basic results pages.

<https://pubchem.ncbi.nlm.nih.gov/compound/31703#datasheet=LCSS>

<https://pubchem.ncbi.nlm.nih.gov/compound/31703>

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Researchers post their own publications but there is some automation of attachment of trial related publications. However, meta-analysis of efficacy and toxicity data could and should be attached to any relevant treatments. For example, I found a nice summary that gave a toxic death rate of 0.1% for a treatment. Low, but not zero. This is an open access article. It could and should be attached to any relevant trial using that treatment. Particularly the recruiting trials. Ding, P., Lord, S., Gebski, V., Links, M., Bray, V., Gralla, R., Yang, J. and Lee, C. (2017). Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced EGFR -Mutated Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology*, 12(4), pp.633-643.
<https://www.ncbi.nlm.nih.gov/pubmed/?term=28007626>

Clinical trials are great but there is a world of misinformation out there about toxicities associated with treatments. A 1 in 1000 chance of death from treatment versus a 1 in 1 chance of death without are decent odds. But they may not seem so if the only people reporting toxic death rates are folks trying to sell alternative treatments and therapies who claim much greater toxicities and mortality rates than really exist for conventional treatments.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I create clinical trial report cards for cancer treatments. They highlight Toxic Death rates, Complete response rates, Overall survival and % Serious Adverse events. Having the % SAEs in their own section is

great but frankly they should be near the top and not the bottom as they help answer the key question "What are the odds that this will keep me in the hospital longer?" The other three outcomes are rarely all present. Even when the data is there I have to spend time converting it as I always report both the percentage and the numbers of patients. What is most annoying is when researchers try and make survival times appear longer than they are by reporting them in weeks or even days instead of months. Standardizing that would be a big help.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I focus on interventional cancer clinical trials with results that involve chemotherapy, immunotherapy and/or radiation. Making it easier to drill down to studies with results for complete responses for outcomes like RECIST or Choi would be nice. Not just complete response results, since complete responses to antiemetics for example are not really what I look for. It is great that they help people not vomit, but I am trying to count cures so that just makes searches harder. And not just results for some outcomes having been posted, but results for that particular outcome. I never know when some relative might ask me to look something up for them and while I can download the database and rebuild it for my use, who has the time for that? Also, most users have never worked with relational databases anyway and would not know where to start.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I think giving examples online that are of a standard useful format the same way grant applications are done would be the best thing you could do. An example for all different kinds of trials, observational, interventional, first in man, crossover, expanded access. Even if you wind up using fake names and data (e.g., instamatic flu).

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

The age ranges do not allow for the level of analysis needed for cancer trials. Pediatric cancer trials often include young adults in their early 20s (e.g., 21, 25). They also can have another break point (e.g., <50 years). Cancers tend to have a U-shaped distribution in terms of age. Those in their 20s-40s have been particularly hard to cure. Allowing individuals to select studies based on those age ranges would be useful.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

ITIS.gov does a really good job of linking out to relevant resources based on species. Clinicaltrials.gov could add similar links that point patients/providers to relevant sites/services that are equally high quality. For example the PDQs provided by the NCI. These are present for even very rare cancers (e.g., sialoblastomas). Allowing users to nominate links in a similar fashion as is done with annotating biological and chemical species databases could improve the clinicaltrials.gov user experience.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

%SAEs are great. Just knowing SAEs is never enough. Two trial arms could have the same number of SAEs but very different %SAEs. All things being equal a patient would prefer the treatment associated with a 10%SAE verses a 50% SAE. Roughly 1 in 10 odds of staying longer in the hospital are much better than 1 in 2. I have talked to oncologists that are very keen on getting 95% CI interval information. Most patients don't care but providers who recommend treatments really do. That should be a regular request and frankly if they do not know how to calculate it or do not think they have the time someone should be found to do it for them for free.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

There are many federal grant receiving organizations that are doing a poor job of posting. If you are a PI who has not posted your results you could be banned from receiving any new federal funding until you post. And contracts for handling the clinicaltrials.gov data really should be limited to institutions with a grade A posting record. Looking at you Duke. Also, clinicaltrials.gov has great graphs now. You can display what places are doing a better job of posting and what places are doing a poor job. Looking at you Texas. People respond to lists. Some sponsors are good. I ran a chemotherapy efficacy database for a while. On my website I praised some companies (e.g., Lilly) for being uncommonly complete in their postings. But the comprehensive cancer centers were always so low. Posting a monthly list could really embarrass some sponsors and hopefully spur them to action. Also, the sponsors who do post should be praised because they often look worse for doing the right thing because most people do not know better having never read the results from hundreds of trials. Also, maybe letting other people submit published results for sponsors who published their results in manuscripts but never got around to posting them.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Maybe do what is done with safety data sheets and have an “other information section.”

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Drop down lists. For the love of clarity make it easy for people to go online and use drop-down lists. (Paraplatin, Carbo, carboplatin...) so many names for the same treatment. So many potential misspellings. The email option is fast and nice but so much is getting done with apps and virtual assistants and you have a relational database with lots of lists already to keep the treatments and conditions consistent there could be a much easier way. Seriously, the North Carolina DMV has an amazingly quick and effective vehicle registration App now. Not sure who designed it but wow. It is surprisingly smart. Disclaimer, these are my opinions and not those of my employers.

Submission No.: 63

Date: 2/12/2020

Name: Gregory Sizikov

Name of Organization: NA

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Please post trial consent form for every trial listed.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Please post the trial consent form for every trial posted.

Submission No.: 64

Date: 2/13/2020

Name: Alicia Leung

Name of Organization: Insmed

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Can you please provide documentation on how sponsors can develop the XML schema for uploading the AEs as well as for site updates? These 2 sections can be particularly voluminous, and manual entry increases risk of errors.

Currently, EudraCT provides this information for their site:

<https://eudract.ema.europa.eu/result.html>

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

Can you please consider adding a WARNING in the applicable results sections when the participant numbers don't match the enrollment?

It would be a helpful reminder that we need to provide an explanation for the difference in numbers.

Submission No.: 65

Date: 2/14/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

None

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

None

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

We used it to register a pilot trial and cluster RCT. It was onerous and this needs to be improved. There needs to be a better balance between reporting rigorously but not putting extra heavy workloads on project teams trying to carry out the research. The system should also be redesigned for behavioral trials - clearly the way it is set up is on the side of device/invasive/med trials.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Behavioral studies primarily. This site is not useful to me, as we have our detailed protocol and monitoring extensively done on site. See above regarding other thoughts.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

It needs to be less work on study teams that have limited resources. Doing the registration and upkeep with this site is in itself a job--labor intensive and noncontributory to progress in the study. We are on budgets that do not allow dedicated staff to manage all that is required for the study and additional significant task for Clinical Trials.gov. As it is designed, the registration is extremely time consuming, and I feel it has grown over the years into something that is unwieldy and not suiting its original purpose of ensuring studies are logged clearly in some fashion with predefined outcomes listed.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

There should be a budget supplied to anyone required to register for staffing that it takes to complete the registration and upkeep.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Would consider different sites/input for behavioral trials.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

See above.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Our institution has a person that will continually monitor if we are complying with clinical trials needs, sounds good for your site/registration but is yet another intervening body reaching out on something I and my staff have already addressed--yet creating more work when we do not have the resources for that.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Clearly there is no flexibility in clinical trials reg site. Any would be appreciated.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

It seems odd that you would ask investigative teams or users of the site for references--this is something we'd rely on from you and your staff.

Submission No.: 66

Date: 2/14/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

1. Please implement interventions hierarchy/nesting.

E.g. I want to find all trials for Ulcerative Colitis where intervention(s) is one of TNF-alpha inhibitors (ATC code L04AB). Or maybe I want to find all trials for Ulcerative Colitis where intervention(s) are NOT immunosuppressants (ATC code L04).

Not sure which exactly classification should be used... First thoughts are ATC and MeSH.

2. I want to be able to RSS-subscribe for changes in trials of interest. E.g. I find trials ABC and EFG interesting - so I want to add them to my watch-list. I may later want to include/exclude some trials from my watch-list.

3. I had difficulties contacting local coordinators of a trial I decided to enroll in (NCT03926195): clinicaltrials.gov's "Contacts and Locations" section does not list any contact info for local coordinators. It better include at least phone numbers and/or e-mails of local coordinators.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

1. I actively use RSSs to watch new trials for several conditions of interest (Ulcerative Colitis, Uveitis, Parkinson's disease, etc).
 2. I also use RSSs to monitor all trials starting in my country.
 3. I also use RSSs to detect studies that were updated to include my country/city.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

https://en.wikipedia.org/wiki/Anatomical_Therapeutic_Chemical_Classification_System

https://en.wikipedia.org/wiki/Medical_Subject_Headings

Submission No.: 67

Date: 2/15/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- link to publications
- possibility for patients that are enrolled in a trial to anonymously comment on it

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- good to get a non-exhaustive overview of trials
- very very sad that even trials completed back in 2014 do not have results posted.
- patients need a comprehensible summary of the results (like conclusions of an abstract: PFS/OS/endpoint was met/not met...)

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I use it to search for trials that specifically address my rare cancer. But because it's rare, I expand to solid tumors and then search by approaches. Would be great if studies were categorized (eg: all studies that combine immunotherapy with radiotherapy, all studies that combine different inhibitors etc etc)

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

submitting results at defined timepoints should be a requirement for the study to be posted on clinicaltrials.gov, as this is where patients go look for the information and the investigators get substantial amounts of patients through the website.

Submission No.: 68

Date: 2/16/2020

Name: Dr. Ola Landgren

Name of Organization: Memorial Sloan Kettering Cancer Center, New York

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

For a given trial: Make links to publications easy. PDFs if available.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Check status of soon open, ongoing, closed trials. Check details re trial design. Look for eligibility when it comes to patient requests.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Both. Depends on the situation. See above.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Help patients finding open trials that are open in area they live. Disease specific. Indication specific.

There are companies trying to do this. Copy their approaches, make it better, and free.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

Not sure

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

NA

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

See above

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Make specific info re update dates, make it easily available

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Not sure

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Not sure

Submission No.: 69

Date: 2/17/2020

Name: Laura

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I think being gable to search multiple countries and hospitals/institutions/clinics at once and comparing them would be useful.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Information is power, not just for doctors but to enable patients and their carers to advocate for themselves.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

You have been a an absolute wealth of information, thank you for having this site. I have used to contact researchers, investigators and doctors. I have also used to ask pertinent and educated questions on my mother's case. Thank you.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I use them all as my mother has Cancer of Unknown Primary so I need to look at different types of cancer and as she able to travel, I look at treatments in different countries.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I think being gable to search multiple countries and hospitals/institutions/clinics at once and comparing them would be useful.

Also a possibility to download a PDF version.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Same as above.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I think being gable to search multiple countries and hospitals/institutions/clinics at once and comparing them would be useful.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

As above.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I think that the it will come naturally with time as long as you keep up the amazing work modernising your server. You'll be the Google of Trials.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

I wish there was ONE name for Cancer of Unknown Primary, Unknown Origin, Cancer of Unknown Site-but I know that isn't up to you but how different clinicians write it out.

Makes me feel like I am missing things out if I dont search all the different names for CUP.

Submission No.: 70

Date: 2/17/2020

Name: Corey Polen

Name of Organization: ALS patient and advocate

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

NEALS Consortium

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

NEALS Consortium

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I look for only ALS trials.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

I use it for ALS trials. Major improvements needed. Must require patient out of costs to be published. Must flag if it's FDA approved trial/study. Must have links to previously successful phases so patients know if trial is Right To Try eligible. Bad culprit is MD Stem Cells. Never completed phase 1 and is pay to play and it's not in a FDA clinical phase.

Submission No.: 71

Date: 2/18/2020

Name: Lisa King

Name of Organization: NCI/CCR/OCD

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

A letter of recognition, plaque, certificate, monetary reward and/or recognition in the ClinicalTrials.gov Hot Off the PRS given to the individual submitting registration and results information, as well as to the organization, may help to encourage staff to increase efforts for timely submissions.

Submission No.: 72

Date: 2/18/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Results from Conferences, Publications, etc. are extremely helpful to follow-on interim results of ongoing trials or final results from finished trials.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

In general, all work very well. The NA Clinical Phase of studies should be tackled. The biggest issue is the use of different nomenclature and names of indications. Also, it will be great to have the inclusion and exclusion criteria aligned between clinical trials so we can sort trials by its exclusion and inclusion criteria. It would be also amazing to have all clinical trials classified in line of treatment (1st line of treatment, 2nd line of treatment, palliative, neoadjuvant, maintained).

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

(1) due to my line of work as a consultant for pharma.

Submission No.: 73

Date: 2/18/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

We use ClinicalTrials.gov to verify information submitted by study teams into the OnCore Enterprise Clinical Trials Management System. Primarily we look at the study title, NCT number and type of study (observational, interventional).

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

I would love to see the protocol author, and possible link to an IND number/holder. I think that it's important to know who has a stake in the research study design. As someone who works at an academic research institution, this information is vital as we map out a course of drug supply; especially when dealing with drugs that are already FDA approved (some maybe off-label use if approved in another indication, but shows promise, etc.)

Submission No.: 74

Date: 2/18/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Having the API interface with systems like Dimensions and Scopus, etc. so make it easier to follow studies that are published based on the initial trials. Ensuring indexing to cochrane library is timely.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Having the API interface with systems like Dimensions and Scopus, etc. so make it easier to follow studies that are published based on the initial trials. Ensuring indexing to cochrane library is timely.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Searching during systematic reviews. Looking at initial studies on particular drugs and then having to use another tool to look at outputs post trial. So having clinicaltrials.gov add that post-trial info would be great.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

occasionally study types are important for me to be able to limit.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

Ensuring it aligns with grant application systems.

Submission No.: 75

Date: 2/18/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Having the ability to show/hide columns on the “Record List” page is really useful. Knowing when the last update was made, and who made the last update helps me keep track of each study, and when new reviews may be needed.

Updating the map feature would be nice. Even doing an overlay into Google maps or something would be useful. Giving users the ability to filter for a given indication/indications and just zoom/pan across a map of pinpointed study sites would be a really nice feature.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Contacts/Locations section, specifically “Locations”. Having the ability to add/edit multiple sites at once would be helpful.

Locations when call centers are used - Having the ability to denote that a call center is used, so other location information is not required would also be helpful, and instead, each site would have the call center's information automatically populated from the “Central Contact”. This would allow organizations to still add location data, but not include facility name, etc. Since location data is still important for prospective subjects, it would allow the city/state to still populate in location searches, but not publicly list the facility/personnel of research sites.

Outcome Measures: Have a dictionary of well-known scales/measures to prevent the need to rewrite scale definitions. Instead of typing in the score range, and interpretation for each scale, a user could just use a search bar to find a given scale, check the box, and the basic information would populate. The user could then define any study-specific details.

Study Status (Minor): Having the “Record Verification” date update automatically when a user modifies an existing field would be useful.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

“Top Performance Studies” - When subjects search for potential studies, if an organization has consistently provided high quality data & registration, their studies/locations could appear at the top of a search and be noted as a “Top Performer”, with perhaps a disclaimer that top performer sites are based on the quality of registration/submission, and does not necessarily reflect the quality of the site/study.

Submission No.: 76

Date: 2/18/2020

Name: Dr. Jonathan D. Berman

Name of Organization: [Not provided]

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I below include a recent email to CT.gov.

CT.gov's comments on the protocol results were generally incompetent. Most importantly is my final comment---that the PRS User's Guide instructs how to edit entries on CT.gov in response to CT.gov's Issues but not how to dispute the Issues themselves.

Overall, CT.gov is characterized by breathtaking arrogance: incomprehensible (to me) instructions, incompetent review, no way to register complaints. What CT.gov needs is an "Ombudsman" or a "complaint mechanism"--ways in which users can complain about CT.gov, not just the present one-sided situation in which CT.gov complains about what users enter.

At least in my opinion, CT.gov makes its own rules, and in this way is a poster child for unaccountable bureaucracies divorced from the user community and about which there are so many complaints.

Dear CT.gov,

There is 1 protocol with a flag: "Open PRS Review Comments R D MILT 2127-3 NCT02429518"

For the protocol, there are "8 comments" but I count them as "10".

I cannot find a place to reply to the comments, just to implement them, but most comments do not make sense thus a reply not implementation is appropriate.

1. Study Design

Study Type: Observational

Observational Study Model: Case-Only

Time Perspective: Prospective

Biospecimen Retention: None Retained

Biospecimen Description:

Enrollment: 42 [Actual]

Number of Groups/Cohorts: 1

NOTE: It is unusual for an IND/IDE protocol to be an Observational study.

Comment: PMR studies are often observational but are filed to the IND and thus this study is standard.

2. Groups and Interventions

Groups/CohortsInterventions

Miltefosine

Miltefosine: target of 2.5 mg/kg/day for 28 days

Drug: Miltefosine

NOTE: Intervention Other Names have not been specified

Comment: What does “Intervention Other Names have not been specified” mean? There is no other name.

3. Advisory Issues:

For clarification, the Full Range should report the minimum and maximum *recorded* age of participants, not the eligibility criteria. Please revise as accurate and appropriate to report the collected data.

Comment: What is listed on CT.gov is the actual age, not the eligibility criteria.

4. Advisory Issues:

For clarification, the Full Range should report the minimum and maximum *recorded* height of participants, not the eligibility criteria. Please revise as accurate and appropriate to report the collected data.

Comment: What is listed on CT.gov is the actual height, not the eligibility criteria.

5. Advisory Issues:

For clarification, the Full Range should report the minimum and maximum *recorded* weight of participants, not the eligibility criteria. Please revise as accurate and appropriate to report the collected data.

Comment: What is listed on CT.gov is the actual weight, not the eligibility criteria.

6. Advisory Issues:

The Time Frame provided is not specific. The Time Frame should indicate the specific time point(s) at which the outcome measure was assessed and for which data are presented (e.g., “Screening, Days 14, 28, and 42”, etc.). Please revise, as appropriate.

This applies to all remaining Outcome Measures.

Comment: It is elsewhere stated that that treatment was for 28 days, and it is here stated that QTc was measured up to 2 weeks after the end of treatment. There is nothing wrong with the dates presently specified on CT.gov. To request more work is petty.

7. Major Issues:

- 1) The number of participants appears to be inconsistent with the number of participants enrolled in the study.

The Overall Number of Participants Analyzed in one or more Arms/Groups is greater than the number of participants included in the Participant Flow module. Please revise the numbers or explain the discrepancy in the Outcome Measure Analysis Population Description.

Comment: The number of patients analysed is consistent with the number of participants enrolled in the study, once it is recognized that not all enrolled patients are evaluable. If CT.gov does not recognize the common occurrence that # analyzed is generally less than # enrolled, CT.gov should not be reviewing data.

8. Advisory Issues:

Information regarding plasma Cmax/Cmin appears to have been collected or calculated. If this information was ascertained via a separate study, or based on otherwise known values, please use the Outcome Measure Description to clarify how these values were determined.

Comment: PK was not collected in this study. PK is given in the Product label. Sponsor should not have to submit the total PK report submitted to FDA for CT.gov.

9. Major Issues:

- 1) The number of participants analyzed does not appear to be consistent with data here or in other parts of the record.

As presented it is understood that each Row corresponds to a different concentration range, and accordingly, not all participants are represented in each Row. Accordingly, please use the Edit button next to the Number Analyzed for each Row to designate the number of participants evaluated for each Row.

Comment: see #7.

10. Major Issues:

- 1) The number of participants analyzed does not appear to be consistent with data here or in other parts of the record.

As presented it is understood that each Row corresponds to a different concentration range, and accordingly, not all participants are represented in each Row. Accordingly, please use the Edit button next to the Number Analyzed for each Row to designate the number of participants evaluated for each Row.

Comment: This is something that has value, and can be done in the context of addressing all of CT.gov's comments, that is, CT.gov rescinding the comments that are inappropriate.

Overall comment:

Almost all of CT.gov's Issues are incorrect. With breathtaking arrogance, there appears to be no way to address CT.gov's Issues other than implementing them even if they should not be implemented. For example, the PRS user's guide instructs :

"Record Owner:

Open the record and read the PRS Review Comments.

Modify the record as needed to address the comments.

Select Entry Complete."

At this point in time, CT.gov is soliciting comments

Submission No.: 77

Date: 2/18/2020

Name: Carmen Gonzalez

Name of Organization: [Not provided]

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

A missing element is the use of video to explain a given study, its context in the current clinical landscape, and how participation can help scientists answer specific questions – all in keeping with the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (The National CLAS Standards). The following video example explains a given type of cancer (ductal carcinoma) and may serve as a template in how to draft language for a study video:
<https://www.youtube.com/watch?v=QCFTD96jInA>. However, this example would be too long for an ideal study explanation video, as an ideal time frame would be under 5 minutes.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

A link to a reputable patient association (e.g. American Diabetes Association, American Heart Association, etc.) may assist patients in finding local resources that support their clinical trial participation.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I have typically looked to see what studies are currently recruiting to see what competition for patient recruits exists in a given market. I also check to see the progress of a study that I am interested in. While the topic tab is helpful to view a clinical category, I appreciate the “Accepts Healthy Volunteers” check box to locate healthy patient subject participation opportunities. Finally, the map showing studies by location has been helpful in the past when researching geographic availability by disease condition.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I have occasion to use the website for a wide-range of studies, and at other times, for a more limited range of studies. If I want to understand what research is underway, no matter the time, I need a broad search to get a handle of what is taking place across the country and internationally. When I am in need of finding a precise study with select traits, then I will look for a particular type of study in a specific place(s) with other relevant dimensions. It just boils down to what the assignment is or what question I have to address.

Submission No.: 78

Date: 2/18/2020

Name: Samantha Spear

Name of Organization: TrialSpark

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Use to identify early stage assets by drug development partners. e.g. CROs, investors etc.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Currently we use ct.gov to pull lists of assets and sponsors running studies in specific phases in specific indications. It is challenging because much of the data is not input in a uniform fashion and sponsors are not consistent in what and when they upload.

Submission No.: 79

Date: 2/18/2020

Name: Bettina Ryll

Name of Organization: Melanoma Patient Network Europe

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

To be honest, ClinicalTrials.gov has - with a few glitches- been exactly what we needed, so it's only now that I start thinking about what else might be useful. My interest is Melanoma, so having a screen overview of anything that has been trialed over time and right now to get an idea about the overall direction of research could actually be helpful.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Link-outs on the drugs tested, including but not limited to PubMed references. and an automatic glossary for technical terms- just saw eg 'BID'- would make it easier to evaluate the general interest of a study as well as increase the usability for non-HCPs or scientists.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We are a European patient network and extensively use ClinicalTrials.gov to look for treatment options for those of our patients who have exhausted all available lines of therapies or in whose countries certain therapies are not reimbursed. We also train patients in the use of the website. The ONE thing that we really find questionable is that it is possible to submit clinical trials WITHOUT information about the concentration and the dosing schedule of a given drug- e.g.

<https://clinicaltrials.gov/ct2/show/NCT03329846?term=bms&cond=Melanoma&draw=2&rank=5>- 'specified dose on specified day', so a patient does not know whether they are receiving less, exactly or more than the approved dose of a drug?! Overall and that is not a clinicaltrials.gov issue, we have found that contact details for trials are often useless as patients don't receive answers; also, the site lists are often not updated, missing trial sites.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

We use the website to find clinical trials for Melanoma patients who have exhausted all treatment options. We are based in Europe but also get contacted from a way larger area, so we search globally. As trial sites tend to be not accurate, we do NOT like the geographic restrictions as that can then exclude potentially relevant clinical trials. Also, we have used the existence of trials in other places to advocate

for similar trials in Europe. Overall, we use the website to follow the research that is ongoing in our field and monitor for publications/ abstracts/ conference presentations giving insights into the progress of a trial. Having all associated publications of a given trial in the same place would be a nice-to-have as avoiding lengthy PubMed searches as publications are not always obviously tagged with the trial identifier.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- the concentration of the administered drug as well as the dosing schedule should be mandatory

- some studies lack a description of the motivation for the study while some are really well-written - would be nice to have the same quality for all

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

n/a

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

n/a

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Maybe some type of badge system as already existing for other platforms?

Submission No.: 80

Date: 2/19/2020

Name: Megan von Isenburg

Name of Organization: Duke Medical Center Library & Archives

Attachment: Request for comment from Clinical Trials gov.pdf



February 19, 2020

ClinicalTrials.gov Information Team
National Library of Medicine
register@clinicaltrials.gov

Re: Response to RFI: Clinical Trials.gov Modernization NOT-LM-20-003

Thank you for the opportunity to provide feedback on this exciting modernization project.

Our primary interaction with ClinicalTrials.gov is in identifying studies for potential inclusion in systematic reviews of the research literature. Librarians at our institution develop search strategies for dozens of published systematic reviews of the literature per year. As such, we have extensive knowledge of article and grey literature databases, controlled vocabulary, search syntax, and search strategy development. ClinicalTrials.gov is an essential source for identifying studies that may not have been published. In the context of systematic reviews, inclusion of unpublished trial data helps to overcome publication bias, in which mostly positive results are published as journal article manuscripts. The value of having this tool for the systematic review process cannot be understated. There are, however, several concerns with the existing search interface and the ability to retrieve trial data.

Currently, searching ClinicalTrials.gov requires developing a separate, simplified search strategy than that which can be used in PubMed, other interfaces to MEDLINE, and other databases such as Embase, CINAHL, and the Cochrane Library. This is due to both limited interface options in ClinicalTrials.gov and an ambiguous and substandard indexing system. The current interface offers no option for combining index terms with keywords using nested concepts and Boolean operators, which is a standard expectation for databases. The ability to process complex searches is essential for maximizing precision and recall. As Glanville et al noted, the most reliable options in ClinicalTrials.gov are "highly sensitive single concept searches," which creates long lists of results, many of which are not relevant to the clinical topic of the systematic review. This creates wasted effort and additional time for both developing and testing these searches and for screening through these long lists. Should searchers attempt to embark on more sophisticated and specific searching, the searcher runs the risk not only missing relevant trial data but also adequately documenting their search strategy in a way that is transparent and reproducible. A hallmark of sound systematic review methodology is reproducible searches, and the current interface of ClinicalTrials.gov makes it challenging to do so.

Currently, it is also difficult to match results from ClinicalTrials.gov to results from PubMed or other articles databases due to sub-optimal integration and cross-linking of NCT and PMID numbers. We and others have tried to match records without these identifiers in place, but have had poor success due to vague and inconsistent information (Adam et al 2018 and Zarin et al 2011). In addition, ClinicalTrials.gov records cannot be exported for easy integration with other article citations in software such as EndNote. When conducting matching against article citations, ClinicalTrials.gov records did not contain the appropriate fields (Adam et al 2018).

An ideal search interface would allow the full utilization of MeSH terms as well as keywords, Boolean operators, and nested concepts to maximize precision and recall. In this ideal version, MeSH mapping should work similar to how it does in PubMed and Cochrane Library (i.e., exploding narrower concepts).

Ideally, ClinicalTrials.gov records would integrate PMID numbers from the published articles on the study. Similarly, PubMed records of the published articles on ClinicalTrials.gov studies should have NCT numbers in standard fields. Having standard identifiers facilitates matching across databases. Preferably, these identifiers would be in fields that export to third party software (such as EndNote, DistillR, or Covidence) for analysis.

We recognize that records in ClinicalTrials.gov are often missing data due to compliance and not due to negligence on the part of ClinicalTrials.gov as a whole. We encourage any policies and processes that increase prospective registration and timely compliance with updating study details and results.

We are actively working on many open science initiatives, including local research data repositories and indices and believe that ClinicalTrials.gov has an important role to play in this emerging area. We encourage any efforts that can allow for linking between the ClinicalTrials.gov record not only to published articles but also to participant-level results in data repositories such as Vivli, NIH repositories, or discipline- and institutional-specific repositories.

We cannot speak to issues regarding information submission as that responsibility lies elsewhere at our institution.

Megan von Isenburg, MSLS, AHIP
Sarah Cantrell, MLIS, AHIP

References:

Adam GP, Springs S, Trikalinos T, Williams JW Jr, Eaton JL, Von Isenburg M, Giersch JM, Wilson LM, Robinson KA, Viswanathan M, Middleton JC, Forman-Hoffman VL, Berliner E, Kaplan RM. Does information from ClinicalTrials.gov increase transparency and reduce bias? Results from a five-report case series. *Syst Rev*. 2018 Apr 16;7(1):59. doi: 10.1186/s13643-018-0726-5. PubMed PMID: 29661214; PubMed Central PMCID: PMC5902969.

Glanville JM, Duffy S, McCool R, Varley D. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? *J Med Libr Assoc*. 2014 Jul;102(3):177-83. doi: 10.3163/1536-5050.102.3.007. PubMed PMID: 25031558; PubMed Central PMCID: PMC4076126.

Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med*. 2011 Mar 3;364(9):852-60. doi: 10.1056/NEJMsa1012065. PubMed PMID: 21366476; PubMed Central PMCID: PMC3066456.

Submission No.: 81

Date: 2/19/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be helpful if it were more useful to patients who have critical diseases and are less knowledgeable about science, with a section that explains the current standards of care for the disease and then lists what potential other options exist without having to wade through long lists of research studies. For example, if a person has a specific cancer, then what would most drs do for that cancer and what is potential treatment that is not yet standard of care (in order of those with useful results).

Submission No.: 82

Date: 2/20/2020

Name: Jordan Wilkinson, CRA

Name of Organization: Tufts University

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

N/A

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

N/A

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

As the organization's central administrator for ClinicalTrials.gov, I use the site solely to manage the trial records of our organization. I do not enter scientific trial information. I create/modify accounts for researchers and departmental level administrators. I otherwise notify users of "problem records" when they arise. A key problem with the functionality of the site is the inability to delete records that may have been entered by mistake, such as non-applicable clinical trials.

If the Responsible Party – at our organization the Responsible Party is always the Principle Investigator conducting the trial – has left our organization, any and all information regarding the clinical trial has left with them. Unless the trial is still ongoing and the Responsible Party role has transferred to a local PI, it would be logical that any closed clinical trials then be transferred to the conducting PI's new organization as the reporting requirement burden is theirs.

Furthermore, both the "Responsible Party" and "Record Owner" should be notified whenever a trial under their name(s) becomes a "problem record" so they are notified that there is an issue for them to correct. As it stands, I as administrator am also not notified and need to log in and look if there 'happen to be' any "problem records", then the onus falls to me to notify the Responsible Party that they are obligated to make edits.

If there are already automated email notifications of trials in problem status to the Responsible Party and Record Owner, they do not appear to be clear enough or may appear as 'junk mail' as in many cases the problem records are not followed up with until instruction to do so by our central organizational offices.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of

studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

At this point, there is a lot of confusion surrounding the longevity of the reporting obligations of trials registered in ClinicalTrials.gov. The regulations on this point are vague. It seems that once entered, the Responsible Party has a reporting requirement that is in perpetuity, sometimes years after the actual clinical trial has ended and years after the results were reported. There are instances where PRS kicks back a trial from 15 years prior requesting an update. By that point, the Responsible Party – at our organization the Responsible Party is always the Principle Investigator conducting the trial – has often left the university, or in some cases has even died. In those instances, it becomes quite impossible to obtain any further updates.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

N/A

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

N/A

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

N/A

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

This has been a key issue for us. To the scientists conducting the trials, the requirement of ClinicalTrials.gov reporting seems to be a distant paperwork issue with no real impact to their daily science work. As a result, it is difficult to spur their follow up with “problem records”. It would be beneficial if there were some form of notification that went to the Responsible Parties of the problem records that noted what the real-world penalty is for not complying with ClinicalTrials.gov reporting requirements. The penalty for non-compliance is not made clear on the website.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3a.** Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

N/A

- 3b.** List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

N/A

Submission No.: 83

Date: 2/20/2020

Name: Alyssa Bartoshevich, MPH

Name of Organization: Gulf South NCORP

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b.** List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Please verify "study type" before posting trial -- the information is often incorrect on NCI trials (we always double check using funding sheets through NCORP-SYS).

Submission No.: 84

Date: 2/20/2020

Name: Anonymous

Name of Organization: N/A

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

The information on what Health Authority has oversight to the study was removed from the details provided. This information was helpful in determining if the product was investigational. There is a field that denotes whether a medical device is approved, but it does not clearly identify if it is approved for its intended use, or if it is approved in different geographies than the US. Adding back that information along with which IRB or Ethics Committee would be accountable for oversight would be helpful. Additionally, I think the risks associated with the study should be included as well as more clear definitions of the intervention. These should be identical to the protocol or patient informed consent. These are often vague in device studies.

Submission No.: 85

Date: 2/20/2020

Name: Michael FitzGerald

Name of Organization: Submittable

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1) pro-active search.. I'd like to put in my dx, TMB and other specifics to my cancer, save it to a profile, and then get emailed when 1) new good-fit trial are open and 2) when results come in for trials targeting me.

2) better onboarding via a smart form-- contextualize the experience

I realize ResearchGate says they do pro-active search. My experience with that platform hasn't been I going get updates from low risk trials around food or exercise.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

I'm not sure what this is asking. But maybe travel resources... a list of close airports, average price from most major cities, recommended hotels or care house like the Hope House in NYC.

Even if a trial is attractive to a patient, the first hurdle is whether they can actually get themselves there and participate.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I've played with api and am trying to set up a CRC specific version. It's pretty half- baked:
<http://dev.haipump.com/trialfinder/>

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I'm personally trying to identify trials that are specific to CRC patients who are MSS KRAS-Wild TYPE.

I'm also trying to build something on the api, but very secondary.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Yes there seems to be a huge opportunity to onboard better. Having the user submit a short form that learns with each input (usertype=Patient, cancer=CRC, Stage=4, Dx Date, etc) and then they get results based on that data to start, instead of having them build the query themselves.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Not applicable to me.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Personalize the experience using tools similar to Clearbit, Segment, etc.. I'm sure there are hurdles with HIPPA, but I think most Stage 4 people would be ok with that risk if they could easily get the information that will save them.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

I'm not sure what this means... submission of the trial or of the patient data?

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Allowing outside comments on trials to show engagement beyond the lab. Patients are already updating the public in FB and other social media but if you allowed for the forum to happen in the Clinical Trial itself, that would be super valuable feedback who say, Might be only considering a Phase 2 trial and are going to see the anecdotal results somewhere other than CT where the organization could at least see and respond to what patients are saying.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Standard around updates.. regardless of if there are results yet or if the existing results are bad. Tranches of gov funding shouldn't go out if the milestones on reporting aren't public.

Submission No.: 86

Date: 2/21/2020

Name: Michelle Jenkerson

Name of Organization: Washington University School of Medicine

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Do you think ct.gov would consider adding a custom filter or another planning report for studies that are under the “2018 Common Rule” regarding posting of consents, if they are posted to ct.gov and not Reg Docs? I am thinking this would help with compliance sooner rather than later.

There is a field for “Collaborator” where responsible parties can list different entities providing support. Perhaps if there was a new field that cross referenced “Collaborator” with the current common Rule agencies (attached) that could populate a new column in the Planning Report (e.g., “Common Rule Agency”). This would be a tremendous benefit to compliance and would likely be very simple to do. This solution would cover the vast majority of cases. Of course all this is self-reported so if the responsible party does not correctly identify the collaborator this will not work.

Submission No.: 87

Date: 2/21/2020

Name: Joyce Hauze

Name of Organization: [Not provided]

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Potential improvement: When we post results, we are able to insert rows for different time points at which the same outcome measures are collected. However, NIH QA allows only one time point per outcome measure timeframe, making us create separate outcome measures for each time point a measure will be collected - even if it is the same outcome measure and will be in the same table when we post results. The improvement would be to allow multiple time points to be entered into the timeframe data element in the registration for phase 2-4 trials (like you do for phase 1 trials). This will allow the registrations to be more accurate and not misleading.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

My primary use of ClinicalTrials.gov relies on (1) a wide range of studies and multiple different study types, intervention types and geographical locations.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The ability to amend our standard facility names and addresses would make that functionality far more useful.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Toward harmonization of data element definitions, it will be useful to incorporate the work from the CDISC Protocol Entities as the appropriate packages are rolled out, updating the data element definitions accordingly. This is particularly true with regard to requiring that "outcome measures"

(measurements collected from trial participants, reported as summary aggregate tables) are posted in the registry. Too often it is not understood that outcome measures are not calculated results - those are statistical endpoints. Deb Zarin would be the perfect person to provide detailed explanation of what an outcome measure entails (as opposed to an endpoint). This is an important distinction to make, because basic results of outcome measures are required by regulation so ICMJE does not consider them prior publication. However, endpoints are not required to be posted, so ICMJE journals and presentation conferences might consider posting them as prior publication.

If it is made clear to clinical teams to accurately define their primary and secondary outcome measures in their protocol, then disclosure teams will disclose the outcome measures in the registry, which are understandable to patients and the public, eg, pain on a scale from 0-10).

This will leave discussion of statistical results for presentations and publications, where the intended audience will understand the statistics involved, eg, sum of the pain intensity difference over 30 days (SPID 30), thereby alleviating concerns over prior publication and/or cross-venue congruence, in the timelines for posting required results.

Submission No.: 88

Date: 2/24/2020

Name: Ian Lock

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The filter feature that prioritizes by stage does not encompass inclusion features such as survivorship treatment.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use this website to look at current trials in the disease that I had as well as survivorship studies that I can participate in. It would be helpful if there was a user friendly questionnaire when you enter the site. This could allow you to describe your background and better tailor result to the individual. This is similar to the advanced search feature, but that feature is NOT very easily used and consumable if you are not familiar with your disease or terms in the field.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Stage of disease

Submission No.: 89

Date: 2/24/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I'd suggest having a Logout hyperlink on every page.

Submission No.: 90

Date: 2/24/2020

Name: Carol Smith

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The site cannot be searched based on cancer subtype, ie, HER2 + breast cancer. The results therefore are over-responded. The site cannot be searched based on mutations found in FoundationOne or similar studies. The Zappos.com website or Amazon.com site allows for very detailed searches.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Linking from clinicaltrials.gov to other cancer-specific sites would allow users researching those cancers to find what they are looking for very quickly; perhaps even with commentary from others on the trials.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I look for trials for myself - someone with metastatic breast cancer. When I get 143 results for my criteria the search gets unwieldy.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I look for a limited range of studies.

Submission No.: 91

Date: 2/25/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Please add highlights for most recent changes to record, or better would be to have a field at the top of the record listing the most recent changes. I use clinicaltrials.gov to monitor the progress of certain trials. The RSS updating feature is incredibly helpful but often I will receive records that it is difficult to tell what has been updated. I know I can click through to the archive version and compare the two most recent records but that is fairly time consuming to click through on. thanks!

Submission No.: 92

Date: 2/25/2020

Name: Joyce Hauze

Name of Organization: Mallinckrodt

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The planning report is extremely useful, but would be far more useful to me if we were able to input information into Results Status, such as Not Required per 42CFR11 for results that are not required because the product was not marketed yet on the primary completion date that was before the final rule.

Submission No.: 93

Date: 2/25/2020

Name: Lindsay Satterwhite Mayberry

Name of Organization: Vanderbilt University Medical Center

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Mediation and moderation (or effect modification) analyses are not supported (or if they are, it's unclear how to enter the results).

Details:

Mediation: To my knowledge, there is no way to register a mediation hypothesis. A mediation hypothesis would have 3 effects: a total effect, indirect effect, and direct effect, each with an associated confidence interval. However, the main test of mediation is the presence of the indirect effect.

Often our hypotheses take this form: Primary outcome is objective clinical outcome, secondary outcomes are behavioral outcomes, we test whether improvements in the behavioral outcomes mediated improvements in the clinical outcomes. I don't see how to show this in clinicaltrials.gov as a registered hypothesis.

Moderation: It is also unclear how to enter results from a model with an interaction term. For instance, the primary outcome is A1c. We found an interaction between baseline A1c and intervention effect such that the intervention was more effective for those with a higher starting A1c value. I don't understand any way to enter this information into clinicaltrials.gov currently.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We do longitudinal trials where we assess outcomes at multiple points. It is ideal to include an omnibus test (was there an effect on this outcome or not) as well as point estimates and confidence intervals for each of the time points (e.g., what was the effect at 6 months, 12 months, etc). Right now, these results can be entered but they are all entered separately and it's unclear how to relate them and specify the omnibus test. This seems like a common approach in long-term trials so more clear advise on how to do present this is needed.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Entering results. As of right now, I have a trial requiring 56 separate parameters and associated information be entered for results. This is because we measured multiple outcomes at multiple time points. It's information overload for a viewer and the way it is shown is not intuitive. It looks like we ran 56 different analyses but we did not - we ran a single analysis for each outcome and obtained point estimates for each time point with associated confidence intervals.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

It's confusing why a published protocol paper can't be submitted as the protocol, instead of the IRB document. The published protocol paper includes far more detail including planned analyses.

Submission No.: 94

Date: 2/25/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I closely follow research in type 1 diabetes. I routinely check clinicaltrials.gov for actively recruiting studies. I use the filter features and download as a CSV file.

1. Regarding the website format: The major area for improvement would be to modernize the busy, complicated website. It would be a major benefit to all clinical trials if the average patient could easily access the critical information of recruiting studies: where is the study? What does it entail? Who do I contact?

2. the study summaries should clearly explain what is expected of the patient and what the patient may experience as a benefit.

Submission No.: 95

Date: 2/25/2020

Name: Thomas Kirby

Name of Organization: DES

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Would like to receive notifications of changes/updates to specific trials. Just add a Track or Watch button with a few simple selections of aspects of the trial to be tracked, with user email or phone for texts.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Looking for the latest successful trials...

Submission No.: 96

Date: 2/26/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Need to add a new section for “mechanistic” clinical trials, since patients may be confused by the expanded NIH definition of a clinical trial. They may be looking for Phase I/early intervention-development clinical trials, but may inadvertently find many results for ‘mechanistic’ trials that aren’t really looking to treat anyone at all.

Submission No.: 97

Date: 2/26/2020

Name: Brian Lenescar

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Filter studies by date whether its 1 year 3 years or customizable.

Also possibly sending inquiries to companies conducting studies to turn in results

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Create a platform maybe on Instagram or YouTube channel that does an overview on the studies that are most innovative or beneficial to everyday consumers and specialists can learn from that explains studies.

examples of this would be:

<https://www.youtube.com/watch?v=zz4YVJ4aRfg&t=2153s>

or

<https://www.youtube.com/user/VHFILM>

or

<https://www.youtube.com/user/NutritionFactsOrg>

You'd also be able to ask viewers what they want to learn more about in regards to studies being done and with your position would be able to bridge the questions and opinions of many to those conducting studies and the companies behind them.

Submission No.: 98

Date: 2/27/2020

Name: Paul Hession

Name of Organization: Philip Morris International

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Study registration: PRS reviewers are not always consistent with feedback. It would be helpful if study registration could be uploaded from an Excel file, using a standard template.

2. Submission of results: this is a manual process. It would be helpful if results could be uploaded from an Excel file, using a standard template.

Submission No.: 99

Date: 2/27/2020

Name: Zucker Chad

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I am a patient and study participant. There should be some way to register to receive an email notification if ever an update is posted to a particular study

Submission No.: 100

Date: 2/27/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.
-
1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.
-
1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Search for clinical trials about a specific molecule or a specific sponsor. I would suggest the option to download the searchs as excel format.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

2

- 2.** Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.
-
2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
-
2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- - 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**
- - 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**
- - 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
 - 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**
- - 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Submission No.: 101

Date: 2/27/2020

Name: Grant Bakewell

Name of Organization: Eskaton Senior Programs and Services

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

PLEASE provide one or more links to publications which have published the results of a trial which has already been completed. I searched for well over an hour about a study at Stanford on the effects of Magnesium L-threonate on cognition and, especially, Alzheimers. The study looked well designed, and appropriate for my search. But there was, and still is NO LINKAGE TO THE RESULTS OR TO ANY PUBLICATION WHICH HAS EVALUATED OR PRINTED THE RESULTS. Please consider using the taxpayer's money to make these studies available to the taxpayer, and the public whom our government is supposed to serve! Thank you.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Referring to residents and patients in longterm care.

Submission No.: 102

Date: 2/28/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Dear all,

Per your request of comments to modernize ClinicalTrials.gov., I have a suggestion of change for the Contacts/Locations, part, in the Locations section. At this moment, when you are creating a new study, you have to select for all your sites the country (one by one):

1. First you click in add location,
2. Secondly, you have to select the country,
3. And at the end you have to enter the site, with the site name and also is a field for the country.

If you have a lot of sites, this is a lot of work, so I think it would be better if you:

- Firstly create a country, and inside the country you create all its sites
- or,
- you only select the country in the facility section.

I hope you find my suggestion helpful.

Submission No.: 103

Date: 2/28/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

use zip code field often for searching for trials across the country. It would be nice when searching with a zip code, if when you input that zip, the associated state and city would populate in their respective search fields as well. This would make sure that the correct zip and city are being matched up when searching.

Submission No.: 104

Date: 2/28/2020

Name: Rob Wudlick

Name of Organization: GUSU2Cure Paralysis

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Www.scittials.org is a good example for consumer friendly searching

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Finding trials for my condition and searching exsisting research for my research.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Spinal cord injury specific

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Make it easier and faster to upload information.

Submission No.: 105

Date: 2/29/2020

Name: Allan Konrad

Name of Organization: [Not provided]

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Use of clinicaltrials.gov search results would be far easier to use if the result could be:

1. sequenced by a particular column, e.g., Last Date Posted, so that the most recent changes can be grouped together.
2. filtered by country(ies) where trials are underway, e.g., just trials in the US.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

For currency on selected topics, i.e., current awareness service.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

specific niches over a wide range of topics, e.g., CAR T-Cell therapy within the domain of cancer, or a specific product within the topic of BPH.

Submission No.: 106

Date: 3/1/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

poorly adaptable to non-drug trials, many sections should have a not applicable option for items that are not appropriate to other types of clinical trials, such as cluster trials. results reporting really needs an update. it is now common practice to publish study protocols including all components required, uploading or linking to published protocols should be an option for the protocol attachment requirement. multi-site studies of broader areas do not fit well, as the system wants a single city listed!

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

wide range of studies, large geographical areas such as districts rather than cities, which do not fit well into the current format, and a variety of non-pharmacological interventions.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Allow for linkage of published protocols to be used where system asks for protocol to be attached. The published protocol is really the standard that most would compare to and meets the requirement of being developed and published prior to participant enrollment.

a bit more flexibility in general for less localized studies, ie. multicenter studies, and/or studies covering large geographic areas (not just a specific city)

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

as above, but also more flexibility to include results from mixed methods study components, ie. qualitative findings from trials.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

allow for a not applicable option for data fields that are not relevant and opportunities to include non-quantitative results, for mixed methods studies that include trials.

Submission No.: 107

Date: 3/2/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be nice to have a way for an investigator to submit study interests and receive an automated email every time a study related to those interests is approved by ClinicalTrials.gov. Similarly, it would be nice to receive email notifications when a study with matching areas of interest has provided data or was revised/updated. It would be ideal if ClinicalTrials.gov could be integrated with other reporting programs for publication submissions, application submissions, and study progress reporting.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Currently, our investigators use the website to explore active studies with populations of interest that match the current focus of our research. Investigators have connected with other study sites through ClinicalTrials.gov for potential collaborations. We have used trends, charts, and maps to explore sites actively recruiting in the same population of interest.

One of the investigators in our department works with families of young children with rare disease. The families report attempts to use ClinicalTrials.gov to explore ongoing studies. They are overwhelmed by the vastness of the website, indicating that there is too much written information and reporting that they find it difficult to navigate. Less jargon and more visuals within the system would be beneficial for the layperson.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

As a department, our use of ClinicalTrials.gov relies on a wide range of studies, but individual investigators are often interested in a more limited range of studies, as it related to their work.

Often investigators are trying to identify completed or ongoing studies of interventions related to specific outcomes. Limiting criteria that characterize types of studies (pharmacological and non-pharmacological) and also outcomes (specific measures or constructs) would be useful. There is a free search button for “other” that is sometimes useful, but that depends on the investigator using the exact terms the authors used. Framed in some sort of taxonomy might be beneficial (also challenging).

When searching to studies related to a focused population and focused diagnoses, it would be useful for the clinicaltrial.gov to provide dates of study enrollment and when the study ended. It's difficult to determine how old the study is based on how the search results are currently displayed.

It seems best developed for efficacy drug studies. For studies with multiple outcomes or interventions that have a structure but not a prescription, it's difficult to use the inputs.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

It would be beneficial to be able to enter the measure, measure description, measure timepoints, and results related to that measure on the same screen. The system currently places measure and description in different locations which made the entry process complex. We were also confused where to enter the reasons for participant withdrawal. The entry process could be made more intuitive.

The system is not designed to capture the dynamic nature of non-pharmacological interventions, more specifically the system is limited with respect to capturing pragmatic trials in which facilities are the unit of randomization (not individual people). Including a system which enables the researcher to select the unit of analysis (e.g., individual, organization) when entering sample would enhance clarity on a sample of "80" to clarify if that is 80 individuals or 80 healthcare systems. Currently "Study Design Section under Enrollment" only specifies Number of Participants.

For the purposes of Health Services Research studies where enrollment numbers are based on the number of sites or facilities, it would be beneficial to be able to specify this in the Study Design Section under Enrollment (currently this section specifies Number of Participants).

During the submission process, some investigators have found that if they provide very detailed information, then the study is returned to them with multiple questions. This has resulted in investigators providing the least amount of information necessary to explain the study and, hence, obtain approval more efficiently.

Terms used within the system are confusing. For example, the term "Primary Endpoints" implies a timeline or final study follow-up, but the system is actually looking for study "outcome measures".

The study timelines on ClinicalTrials.gov are limiting. Inclusion and exclusion criteria are rigid, too. If exclusion and inclusion criteria are for the purpose of recruitment, it isn't the best way to recruit individuals into a study if that study does not want to promote themselves as a diagnostic study.

The Record Summary in the Protocol Registration and Results System is difficult to navigate given the multiple categories within each section. It may be easier to navigate if each section was tabulated, so a user could click back and forth between sections with one click versus multiple clicks. This would also be beneficial with trying to navigate the system to find errors within a submission.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Interoperability with the clinical trials information in ASSIST would help. Interoperability with institutional IRB systems would also help, but this seems challenging given the variance across institutions.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Materials that would be beneficial for the user:

- 1) A decision tree determining which aspects of reporting are required based on funding source and publication intentions
- 2) Clearer guidance from PRS defining who should remain the responsible party in the case of mentored research (e.g., doctoral research where the student is the PI)
- 3) A template document or codebook for entry fields that are multiple choice, required/optional, and give clear definitions of what is intended to go in that field
- 4) Guidance on results entry for quasi-experimental study designs (case series where the journal guidelines require ClinicalTrials.gov, delayed baseline, etc)
- 5) Visuals would work well to help navigate the system and quickly find the areas that need revisions/updates.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

We are not sure that credit/incentives are appropriate. Ultimately it is up to the PI to submit a record, either by mandate or by choice. The individual institutions should be providing oversight to ensure all studies are submitted and should provide some recognition to their PIs, departments, etc.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

It may be prudent to analyze the current study designs submitted to the database and then develop templates that researchers could select based on two or three primary types of studies.

Very specific guidance provided by ClinicalTrials.gov would be useful. When investigators copy and paste from their approved IRB protocols, they receive comments requesting that they revise and resubmit their protocol to ClinicalTrials.gov.

Submission No.: 108

Date: 3/2/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

MDA--helps find clinical trials for subtypes

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Always looking for new gene therapy clinical trials for limb girdle 2i

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I use it to find trials relating to limb girdle 2i for my son to possibly participate in.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I have used emails on these sites and some never reply. make sure they are up to date and that someone will reply.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

type of trial, age, exclusions/inclusions, projected outcome, etc.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

make sure email on site will reply

Submission No.: 110

Date: 3/2/2020

Name: [Not provided]

Name of Organization: Huntington's Disease Society of America

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

nonprofit websites - for patient support

industry websites - for more information about the drug

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We use the site to provide information to Huntington's disease families about ongoing clinical trials. The information links to our clinical trials matching service. We like the geographical listing of sites. We would like to see better/more consistent patient-friendly information and updates to contact information, study closures, etc.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Our primary use is limited to Huntington's disease studies. It's very helpful to us to have all of the different existing recruitment criteria (recruiting, not yet recruiting, etc)

Submission No.: 111

Date: 3/3/2020

Name: Amanda Haddock

Name of Organization: Dragon Master Foundation

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

ClinicalTrials.gov should be more proactive in helping a patient find a clinical trial for which they qualify. I haven't used this site, but I imagine that eHarmony (or similar dating sites), lead people through a list of questions that will then help them find the right match. Results could be returned with the percentage that matches the patients criteria, with information on why it is or isn't a good match. For example, a trial may match the patient's genetic markers, but have side effects that are unacceptable. There was some good work done on this around the data reuse contest sponsored by NEJM and using the SPRINT data. (You can find more on that here: <https://challenge.nejm.org/posts/5826>)

There is also a need for information around expanded use of the clinical trials. I understand this is a sensitive area, but this is a great place to educate patients about what is and is not possible, along with possible criteria to consider. Real world examples of successful and unsuccessful expanded access requests could go a long way toward helping people understand this process.

It is important that this be built with the patient's needs and perspectives in mind. Clinicians are already overworked and don't recommend trials often enough. Far too often, patients are only referred to trials at their original hospital site, without regard to what trial might actually suit the patient best.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

I am not sure why we are still insisting on de-identified patient data for use in platforms like this. We need to use these tools to enable precision medicine, which almost insists that a patient's own data be included. We can protect that patient's data (as well as genomic data can ever be protected) and still enable that data's use in an environment that can help them make decisions about their own care and help researchers and clinicians learn more about the disease.

I'd like to see ClinicalTrials.gov combined with a system like Cavatica.org so a patient's own genomic and clinical data can be associated with their treatment decisions. Cavatica is a particularly interesting tool in this circumstance because biosamples from patients are also linked, so it can help determine if there are bio samples available for potential trials.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I use the current site to help patients find clinical trials. There needs to be more standardization and cross referencing of terminology. For example, there are a number of trials for DIPG and GBM, but only 3 that say they are for DMG, even though that could easily encompass GBM and DIPG. Newly diagnosed patients are not familiar with all the possible terms, and so need the system to help them navigate the acronym swamp. The system should be proactive for those entering the trial information, so if they type in a term, it should give them other suggested terms that are complimentary.

I think the ability to search by mutation is good and will only become more and more relevant.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

From the patient's perspective, a search of clinicaltrials.gov is often because there are no curative therapies open for them. Therefore a wide range of studies is of great interest. It is not always possible for a patient to travel for a study, but sometimes they are able to make that happen. It is critical that the patient be able to choose what is best for themselves because only they know their tolerance for the financial, physical, and psychological impact.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I don't remember much about the registration process, so I won't speak to that. However the results information, and the site as a whole, would benefit from a more visually friendly interface. The very look and feel of the current site is very intimidating to patients.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

Not applicable in my situation.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

Not applicable in my situation.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

There is certainly always a need for greater funding for all research and trial efforts, but I think the incentive is already here - to increase enrollment in their facility's clinical trials. I would be leery of credits or financial rewards in this area, but I could definitely see issuing some type of rating for users so it is immediately obvious who is doing good quality work on their submissions.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3a.** Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

We need more cross-referencing of terms, and maybe even a more proactive glossary. Make terms clickable so that people understand they can quickly find out more information. I never even knew there was a glossary on the site until I started working on this survey. Even so, there are many disease specific terms that are left unexplained.

- 3b.** List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

The NIH has a working group around data interoperability, and I think that is a good place to start. There are a number of resources on GitHub that are addressing this issue, as well as many groups formed around the different subsets of data like HL7 for clinical data and GA4GH for genomic data.

Submission No.: 112

Date: 3/3/2020

Name: Eric Braverman, MD

Name of Organization: PATH Foundation NY

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Eric Braverman md New York State health commissioner Nirav Shah published a new standard and Obesity measurement using the DEXA scan showing that the BMI mis classified Obesity 60% of the time. All Obesity trials that are done with BMI or simply inadequate , Medical history and comorbidities are inadequate , Studies are missing longitudinal or ipsative data on the patients, Missing standard psychiatric instruments To identify confounding variable's ! Similarly research instruments and addiction allergy continue to ignore various skills created by Ken Blum and Eric Braverman M. D. at times with the help of Nora Volkow the head of the national Institute of drug abuse and others

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Similarly research instruments and addiction allergy continue to ignore various skills created by Ken Blum and Eric Braverman M. D. at times with the help of Nora Volkow the head of the national Institute of drug abuse and others

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Pub med research of Eric Braverman M. D. Ken Blum Mark Gold and others Nora Volkow Eric Nestler

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Pub med research of Eric Braverman M. D. Ken Blum Mark Gold and others Nora Volkow Eric Nestler - I would like to speak to one of your Researchers to identify targeted papers to the issues above

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

I would like to speak to one of your Researchers to identify targeted papers to the issues above

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I would like to speak to one of your Researchers at 347-266-9361 pathmedical@gmail.com

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Please have your research team contact me at 347-2669361 @pathmedical@gmail.com

Submission No.: 114

Date: 3/3/2020

Name: Leslie Norins, MD, PhD, FIDSA

Name of Organization: Alzheimer's Germ Quest

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I applaud the NLM's search for, and openness, to improvements in CT. I have one earnest request: Please have each entry of "Results" of a completed trial include, first, a section titled, perhaps, "Actual Data". Clearly present therein the RAW DATA of number enrolled, number treated, number of "successes", and number of "controls".

Only after that, perhaps in a following section titled "Statistical analysis," present the fancier statistical and other mathematical calculations. This will enable other researchers to double-check, or even question, the formulaic findings and assertions.

Submission No.: 115

Date: 3/3/2020

Name: [Not provided]

Name of Organization: IQVIA Biotech CRO

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

My usage includes a wide range of studies that include combination therapies with intricate treatment arms. When it comes to updating the registry listing it is difficult to simplify those treatment arms to be accepted by PRS system without multiple rounds of review and comments.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

As a sponsor I would like to limit the visibility of my site listing information to weary of other competitive sponsors that they may try to target the same sites and limit participation on the sponsored clinical trial. I would like the option to limit the site name and investigators that may be involved with my sponsored trial.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

I would suggest not requiring the study collaborator's/main contact/s detailed contact information as a requirement, but leaving a tick box to give the option to see if the main study contact collaborator would like all details to be visible once the listing live.

Submission No.: 116

Date: 3/3/2020

Name: Sean Rinehart

Name of Organization: PFS Clinical

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Please include drug IND and device IDE numbers in the API used in clinical research studies. It appears the feed indicates the FDA approval status, but it should also include a link to the approval information if possible. We need this to inform clinical billing accurately for those research studies.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Link to CMS.gov so we can determine via an API or feed the status of approved IDEs as listed on <https://www.cms.gov/Medicare/Coverage/IDE/Approved-IDE-Studies>. It is not uncommon to find an IDE is approved at CMS, but the ct.gov record for the corresponding study says the device is NOT approved and then redacts the information.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The RRS feed works nicely. We query that with an NCT number and return selected fields. Those are then imported into our local system, saving us time in data entry.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

NA

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

It would be great if sponsors could post their current version of the protocol, brochure, and possibly their consent form to ct.gov where sites could access it via API. Also, many time we find that sponsors will be recruiting sites, but the sponsor has not established an NCT record number at ct.gov or the protocol number is not referenced so finding the NCT number is challenging. This is strange as many of

these sponsor studies already have an EudraCT number. If they can take the time to get that, why can't they get an NCT number earlier in the process as well?

Submission No.: 117

Date: 3/4/2020

Name: Greg Bauer

Name of Organization: [Not provided]

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Include exact enrollment numbers for each trial (how many spots vacant, how many taken; no this is not impossible as sponsors do know how many people are enrolled in their trials)

2. Include sources of funding for trials (EU does this on their clinical trials registry)

3. Require monthly updates from sponsors so that we know which trials are actively enrolling and that the contact list for trials is updated and accurate

4. "Paid" programs should be marked clearly (there are some "trials" that people would pay for in order to participate)

Submission No.: 118

Date: 3/4/2020

Name: Sara Bernstein

Name of Organization: National MS Society

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

When available, links to publications of study results on PubMed

<https://www.ncbi.nlm.nih.gov/pubmed/>

When available, links to topics on MedlinePlus (such as disorders/conditions, or drugs/supplements)

<https://medlineplus.gov/>

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We link to clinicaltrials.gov in the recruitment information that we provide to people affected by MS, to ensure that we have the most recent updates to that information (e.g.,
<https://www.nationalmssociety.org/About-the-Society/News/MS-Trial-Alert-Seeking-People-Newly-Diagnosed-or>)

We link to clinicaltrials.gov as a resource on the topic of clinical trials:

<https://www.nationalmssociety.org/Research/Participate-in-Research-Studies/Participate-in-Clinical-Trials/Clinical-Trial-Resources>.

We download information on clinical trials in multiple sclerosis to keep people abreast of the latest studies on our website (<https://www.nationalmssociety.org/Research/Research-News-Progress/Clinical-Trials-in-MS>) and in quarterly reports on our strategic plan (<https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Documents/Strategy/FY19-Strategic-Plan-Progress-Report.pdf>, page 6)

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Our use is limited to studies of multiple sclerosis, but we look at all studies for this disease and use limits to help search, like date submitted, phase, geographic area. Having more options to limit intervention type would be helpful.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Just 12% of the studies on clinicaltrials.gov report results. The process of reporting results must be simplified. Perhaps it can be synched to registration. For example, once people have registered the primary outcome, another field would allow them to submit information on whether that outcome was met in the study.

Study listings would benefit from a brief lay description (just a few lines) that would let people know why the study is being performed and what would be expected of them. Ideally, this would be a standard description added by clinicaltrials.gov staff.

Submission No.: 119

Date: 3/4/2020

Name: Cynthia Rajan

Name of Organization: NeoImmuneTech

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

No comment

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

No comment

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Please allow a feature that would allow for users to search terms specifically within the Inclusion/exclusion criteria of a particular study.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

No comment

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

No comment

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

No comment

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

No comment

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

No comment

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

No comment

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

No comment

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

No comment

Submission No.: 120

Date: 3/4/2020

Name: Thomas Newman

Name of Organization: UCSF

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

I wanted to access the original study protocol for a clinical trial (NCT01462344) that was published in the NEJM. Specifically, I wanted to know if they followed a pre-specified statistical analysis plan. I could not find it on ClinicalTrials.Gov. It was directed to an outside link when I clicked on Analysis Plan, which took me to CLinicalStudyDataRequest.com, which had a whole requesting process I do not want to bother with.

Submission No.: 121

Date: 3/5/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

N/A

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

N/A

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Some studies (from my experience alone) do not tick the typical clinical research trial boxes. It would be great if the ClinicalTrials.gov system had some preliminary questions that could help inform what information may or may not be pertinent to enter.

Currently I work on a study that isn't blinded, all participants receive active medication, and aims are based on cessation outcomes between two groups.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2d.** Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

It would be great to have automated communication set up to the PI and coordinators of studies, or other people on a study. Emails that remind us to update information every year or can alert you when you're close to the "estimated completion date" etc.

Submission No.: 122

Date: 3/5/2020

Name: Maher Ghalmoush

Name of Organization: Tufts Medical Center

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

3 suggestions which would greatly enhance the usability of the website:

- 1) Adding the ability to log in and save search results
- 2) Adding the ability to send alerts when study status changes (i.e. from recruiting to completed), and when the study results are published, similar to the citations in pubmed

https://www.nlm.nih.gov/pubs/techbull/so19/so19_pubmed_updated.html

- 3) Allowing institutional review boards to upload multiple study inquiries to confirm that required studies are being registered on the clinicaltrials.gov website and a feature that allows sending an alert to the IRB staff who have authority over the site when studies of that specific site register

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

See above comment

Submission No.: 123

Date: 3/5/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Healio/Infectious Disease News (infectiousdisease@e.healio.com)

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Healio/Infectious Disease News (infectiousdisease@e.healio.com)

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Great resource for clinical trials available. I look for information that could be helpful to myself or my family and friends.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Links to sign up for trials.

Submission No.: 124

Date: 3/6/2020

Name: Paul O'Regan

Name of Organization: Cancer Research UK

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Incentivise / make it easier for users to maintain up to date value for recruitment status at each site.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Natural language processing of uncontrolled values to map to controlled data structures.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Separate eligibilities.criteria into inclusion and exclusion, ideally store each individual criterion separately;

Add fields to eligibilities table to indicate whether any of the criteria are specific to a design_group, and if so which design_group;

Add fields to result_groups table to explicitly link result_groups to design_groups

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

OHDSI data standards: could use a tool such as <http://www.ohdsi.org/web/criteria2query/> to validate and/or structure text;

Submission No.: 125

Date: 3/6/2020

Name: Ian Kleckner

Name of Organization: University of Rochester Medical Center

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

I think it is great to link publications to Clinicaltrials.gov so people can see what was published in relation to this trial. Maybe Clinicaltrials.gov can routinely search Pubmed and link abstracts that mention the Clinicaltrials.gov ID id within the text of the manuscript to do this automatically

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I search for projects related to my own research, as part of a literature review. I like how much detail I can see in these studies.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Wide range of studies.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

I think it's OK as is.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

I think it's OK as is. I copy/paste information from my IRB to Clinicaltrials.gov. I write the IRB protocol and Clinicaltrials.gov entry at the same time. It's only tricky when the IRB comes back to change some things and then I have to change it on Clinicaltrials.gov. Maybe it would be better if Clinicaltrials.gov automatically got the info from my IRB.

But I just view this as one item on a long list of things that the PI has to do as part of running a study. Yes, it takes more work, and it is somewhat redundant, but an automated method might not be any better.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I think my BIGGEST suggestion to improve Clinicaltrials.gov is to have it track the history of changes made to a clinicaltrial.gov entry. There are a couple key cases here:

(1) Changes in study procedures or eligibility. Some studies of course have amendments as they go on, and I don't know if / how this is reflected in clinicaltrials.gov.

(2) I reviewed a manuscript once describing results from a clinical trial that was registered on clinicaltrials.gov. In the paper, the primary outcome from clinicaltrials.gov (CT.gov) was null and secondary outcomes were positive. In the paper, authors switched the order of outcomes and said that the positive outcome was the "primary" one. I read CT.gov and basically said, "hey you can't just later switch which outcomes are primary and which are secondary...it's supposed to be a priori specified and it's supposed to match CT.gov."

To my surprise, the authors' solution was to edit the CT.gov entry! There was no tracked change of this on CT.gov. So this could have been a false positive. There are no checks on this type of thing as far as I know and this is a big deal.

In this particular case the study was Phase I (exploratory) so it's probably not a big deal. But this could also have been done for a Phase II or Phase III study which would be a MAJOR error.

It would be great if CT.gov tracked changes over time, with a timeline or something and PI notes as to why changes were made.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

I don't know. It's like reviewing papers. You just do it to help the whole system. There is no incentive structure for reviewing papers but people do it because that's how the academic system works.

It's easy to imagine penalties for NOT updating CT.gov entries, but I don't know about incentives.

Submission No.: 126

Date: 3/6/2020

Name: Kathleen McNaughton

Name of Organization: Mayo Clinic

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Record verification: suggest changing the record verification to an automated field where it is automatically updated anytime a change is made to the record. Alternatively, keep as a manual process but have the system generate an error to the user if changes to the record are made but the verification date field is not updated. Make this a hard stop so the record cannot be released until the record verification date is updated.

Primary completion dates/study completion dates: suggest implementing auto-generated emails direct from Clinicaltrials.gov notifying record owner of upcoming results due. The semi-annual non-compliance emails currently sent by the CT gov system are effective and similar emails notifying of upcoming results due may help investigators better prepare for the inputting of results and/or prompt an update to the study record completion date as necessary.

QA Reviewer process: suggest establishing more consistency with PRS reviewers during both registration and results quality check. If changes/corrections are required of a record based on PRS reviewer comments, ensure the record goes back to the same PRS reviewer for the subsequent review(s).

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Non-traditional studies: suggest increasing flexibility in study record for registering and reporting of non-traditional studies. Create free text fields within the study record to assist with inputting information and/or data that don't fit into the 'traditional' study format (e.g. genomic studies).

Submission No.: 127

Date: 3/6/2020

Name: Scott Weinberg

Name of Organization: American Medical Informatics Association (AMIA)

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

See attached

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

See attached

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

See attached

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

See attached

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

See attached

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

See attached

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

See attached

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

See attached

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

See attached

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

See attached

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

See attached

Attachment: NLM RFI - ClinicalTrials.gov Modernization - AMIA Response.pdf



March 6, 2020

ClinicalTrials.gov Information Team
National Library of Medicine
8600 Rockville Pike, Bethesda, MD 20894

Submitted via NLM webform

RE: Request for Information (RFI): ClinicalTrials.gov Modernization

To Whom It May Concern:

AMIA is pleased to provide input that will inform NLM's modernization of ClinicalTrials.gov. Our members consider ClinicalTrials.gov an important resource for their research and appreciate the opportunity to guide its further development.

Health Informatics is the science of how to use data, information, and knowledge to improve human health, the delivery of health care services, and the execution of scientific research. AMIA is the professional home for more than 5,500 informatics professionals, representing frontline clinicians, biomedical researchers, public health experts, and educators who bring meaning to data, manage information, and generate new knowledge across the healthcare system and research enterprise. AMIA members advance health and wellness by implementing and evaluating informatics interventions, innovations, and public policy across settings and patient populations, adding to our collective understanding of health in the 21st century through peer-reviewed journals and scientific meetings.

While only a handful of members provided feedback, AMIA staff and leadership are eager to provide additional input or facilitate more targeted feedback as the ClinicalTrials.gov Information Team develops next steps. Thank you for considering our members' comments.

Should you have questions about these comments or require additional information, please contact Jeffery Smith, Vice President of Public Policy at jsmith@amia.org or (301) 657-1291. You may also reach out directly to the AMIA member respondents. We look forward to continued partnership and dialogue.

Sincerely,

Patricia C. Dykes, PhD, RN, FAAN, FACMI
Chair, AMIA Board of Directors
Program Director Research



Center for Patient Safety, Research, and Practice
Brigham and Women's Hospital

(Enclosed: AMLA Member Detailed Comments)

| Information Requested | Response(s) |
|---|---|
| <p>Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).</p> <ol style="list-style-type: none">a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you. | <p>[Alexis Carter MD, Alexis.Carter@choa.org] “I have had good experience with the website. I love the ability to do URL calls to do searches by age range and gene, for example. It would be nice to be able to search by specific variants of genes using full HGVS Varnomen nomenclature (e.g., NM_004333.5(BRAF):c.1799T>A(p.Val600Glu) or at least the c. and/or p. nomenclature (e.g., BRAF p.Val600Glu) http://varnomen.hgvs.org/. Similarly, please ensure that the website is up to date on the latest HUGO standard gene symbols at www.genenames.org. Please keep the ability to search for studies that are open to pediatric patients, and further differentiation of age range for participants would also be good.”</p> <p>[Alexis Carter MD] “We want to be able to link to ClinicalTrials.gov directly from molecular pathology reports which are pertinent to the variants that we find.”</p> <p>[Wayne Liang, MD, wliang@uabmc.edu] “ClinicalTrials.gov needs more discrete age range searches. It also needs to support identifying genes of interest for precision medicine trials. PubMed can be linked to relevant ClinicalTrials.gov listing and vice versa.”</p> <p>[Yanshan Wang, PhD, wang.yanshan@mayo.edu] “We would benefit from an API or a tool that could retrieve the information systematically. For example, we want to retrieve all the “inclusion criteria” for all “Alzheimers disease” clinical trials. Our goal is to build informatics tools to facilitate clinical trials recruitment, and to find similar ongoing clinical trials.”</p> <p>[Xia Jing, MD, PhD, xjing@clemson.edu] “Would it be possible to filter the search results based on ethnicity?”</p> |

“In the search results page, within ‘By Topic’ tab, is it possible to list the related topic in the form of knowledge graphs, which show the relationship of the target condition and the relevant conditions?”

“In the search results page, it would be helpful to visualize the results of the Search Details tab? In my view, this visualization in the search results page will provide an overview of the relevant trails in the system, which may help me to decide what to do next.”

“I second Dr. Liang’s suggestion about age groups needing more granularities. The current groups are too large.”

“In the trail detail page, is it possible to list the potential benefits and potential risks just like ‘Study design’ or ‘Outcome Measures’ in a tabular format?”

Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.
- b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
- c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.
- d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.
- e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

[John Methot, john_methot@dfci.harvard.edu]

“The eligibility criteria on ClinicalTrials.gov are both imprecise (not all expressed in structured form) and incomplete compared to the detailed criteria contained in (often proprietary) protocol documents. Automated clinical trial matching to patients requires structured data in a consistent model that can map between patients and trials. Currently, many parties are attempting to divine structure downstream via natural language processing (NLP) or other means, but this is imprecise and inefficient when the data could instead be provided in structured form by the protocol authors/sponsors. NLM should guide/encourage/accelerate the development of a formal model for eligibility criteria. Permitting (or requiring) submission of structured eligibility criteria for every trial and making that information publicly downloadable in structured form would enable more innovation (and more success) around trial matching.”

[Wayne Liang MD]

“NLM should support development of structured eligibility criteria authoring that generates both human readable as well as machine readable formats.”

| | |
|--|--|
| <p>Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).</p> <ul style="list-style-type: none"> a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan. b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov. | <p>[Alexis Carter MD] “SNOMED coding of variants may be useful as the US extension already has a way to encode variants in a scalable manner. LOINC coding would not be useful in this context. See answers above regarding the use of HUGO gene symbols and full HGVS nomenclature. All of these are international standards.”</p> <p>[Xia Jing, MD, PhD]</p> <p>“I think UMLS can be critical leverage to improve the reuse of ClinicalTrials’ data and the cross-referencing of ClinicalTrials with existing other resources by NLM. For example, MeSH has detailed age groups; if ClinicalTrials data can be indexed in MeSH terms, which will provide the potential to connect publications in PubMed with existing trials via MeSH Major terms.”</p> <p>“Another use case is to cross-reference the ClinicalTrials data with resources used by the general public if they share the same terminology. For example, to cross-reference Clinical MedlinePlus with MedlinePlus if MeSH is used in both resources.”</p> <p>“Since the scope of clinical trials is large, it perhaps is not realistic to use one terminology to meet all needs site-wide, which is another reason UMLS can be a critical tool in improving the standardization of ClinicalTrials data.”</p> <p>“FHIR is another potential here, which can make the metadata of clinical trials more universally recognized and reused.”</p> |
| Other relevant topics for NLM consideration? | <p>[Xia Jing, MD, PhD]</p> <p>“I do not know if other devices, e.g., smartphones and tablets, are supported to browse ClinicalTrials.gov. There are more and more users use these devices on a daily basis.”</p> |

Submission No.: 128

Date: 3/6/2020

Name: Charlene Liggins

Name of Organization: NIH

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Have a 'Like' or 'Similar' tab similar to NIH Reporter to find similar trials to the one being viewed.

Download/export grant number associated with projects to link trials back to funded grants

Download/export clinical trial descriptions

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Assess similar research from non-NIH, international, private funders

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Comparative portfolio analyses

Submission No.: 129

Date: 3/6/2020

Name: Dr. Jonathan D. Berman

Name of Organization: self

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I have found it impossible to enter data into clinicaltrials.gov. The reasons probably are unique definitions (for example, clinicaltrials.gov has a unique definition for a “controlled” clinical trials that differs from that of the FDA) which means that what the user wants to enter is rejected by the website, since the user means one thing and the website means another thing; overly rigid templates which again are unique to clinicaltrials.gov so that minor variation means rejection of the entry; incomprehensible (to me) definitions; overly rigid review of entries by review personnel resulting in endless revisions to conform to rigid requirements; uninformed review personnel who question entries because they (the personnel) just do not understand clinical trial reporting.

A more fundamental issue is the lack of a “complaint office” to which fundamental criticisms of the sort I am raising can be submitted. The present mechanism of recording complaints is a one-off item without face-to-face discussion that cannot substitute for in-depth complaints. If clinicaltrials.gov has a “complaint office”, please direct me to it [jbe9320457@aol.com]. If there is no complaint office, please constitute one. It is remarkable, and hypocritical, for an organization founded on transparency [the clinical trial community must transparently present results] to itself be non-transparent and closed to criticism.

Submission No.: 130

Date: 3/6/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

We currently pull weekly searches of downloadable content for specific types of trials (specific tumor types, CV diseases, etc) and format of the downloaded excels are great (in particular, we use the start/end dates, status, Conditions, funded bys, Sponsor/Collaborators, Phases, Enrollment, and Location). This is made very easy by using the same download link every week. However, there are times where we have a list of NCT#s that we want to check on a regular basis, but this is made difficult by the fact that the search will not return more than 15 trials if you put in "NCT#1 OR NCT#2 OR" If there is a way we could enter such a list of NCT# so we can download the current data, that would be enormously helpful

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We look for primarily interventional studies in particular disease types, wide range of location is good (but info on those locations is a must). Essentially, we are trying to be up to date on novel drug development in each of our disease types of interest, so corporate development is of highest priority, but keeping abreast of interesting academic studies is also important.

Submission No.: 131

Date: 3/6/2020

Name: Lisa Gallatin

Name of Organization: BRIGHT Research Partners

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Being able to link to clinical publications rather than re-entering study results allows for more efficient and accurate information to be made available in a more timely fashion. The NCT number is a helpful link, especially when you are trying to locate a specific study among multiple search results, but not all publications include the NCT. If the NCT number were required for publication, would that improve compliance with the requirements?

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Completion of clinicaltrials.gov data entry requires cross-referencing other documents for guidance on terminology, formatting, and required content. Modify data fields to incorporate definitions or sample content. Examples include:

- o Add pop-ups or rubrics for the “Data Element Definitions” next to the relevant data entry fields
- o Build logic checks that review required formatting listed under “Protocol Review Criteria” and “Results Review Criteria” when draft entries are initially saved

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

It would be helpful to receive notification when a record has completed PRS review and been made public.

- 2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

It might be useful to have contact information auto-populate under Human Subjects Review for common central IRBs.

Submission No.: 132

Date: 3/6/2020

Name: Katie Goodman

Name of Organization: Florida Cancer Specialists

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Clinicaltrials.gov utilizes the main 1572 address as the single location where atrial is conducted when many additional sites are often listed on pg 3 of the 1572.

All patient advocacy group websites reference back to clinicaltrials.gov at the “single source of truth” resulting in wide spread misinformation to the public.

For example, my organization Florida Cancer Specialists www.FLCancer.com opens cancer trials in 37 locations geographically spread throughout Florida - but patients searching for trials on any search engine linking to clinicaltrials.gov would be misinformed about what trials are available because they would only see our 4-5 central research office locations used on our 1572.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We currently link our own website www.FLCancer.com/clinicaltrials to yours to inform the public and our own providers of our active trial menu.

We also use this site to help identify trials when we do not have an option available for our own patients

Submission No.: 133

Date: 3/6/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Wide range of study types and intervention types.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Results need to be more understandable to lay persons and clinicians alike. A text summary of results, or when no results exist a statement of reason for no results would be very helpful (i.e. failure to recruit, closed due to adverse event profile, etc.)

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

Harmonization of collection of racial and ethnic data with other formats used by IRB.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

Provide government standard definitions for race.

Submission No.: 134

Date: 3/6/2020

Name: Trial Transparency

Name of Organization: Sanofi

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1. Use of mapping application programming interface (API) such as google maps which will help users to see location of site facility (when available) and driving distance, after relevant location has been provided to the individual. In patient global survey for Registry of the future, patients expressed need for this functionality in order to better choose the trial and trial site for treatment benefit and convenience.

2. A portal concept (like iConnect) should be used so that users can create account and save the search results in order to refer in future while consulting with HCPs.

3. As Spanish is another major language in US, there should be functionality to translate the website to Spanish.

4. An API that allows third party developers, or NLM, to develop mobile apps that can search and extract data from ct.gov and present it to individuals in a user-friendly format that is helpful to their specific needs – i.e. searching for relevant clinical trials in their area.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. Connection to different Disease based patient advocacy groups

2. Connection to ICMJE registration and publication guidance

3. Connection to different relevant policy/regulations related to interventional, non- interventional disclosure

4. CT.gov should be more interoperable with FDA's systems, including e.g., Drugs@FDA, which includes information about drugs, including biological products, 'approved' for human use in the United States; drug trials snapshots, integrated review approach at OND

5. Connection to PROSPERO

6. Interoperability with EU systems. If there's a way to streamline disclosures, making them more consistent and more broadly accessible to stakeholders, reporting out in similar ways, that would be helpful. Patients and other members of the public should not have to be looking at several different sources with different requirements and read-outs.

7. Allow Sponsor to provide a link from results to the corresponding Lay summary when available, either on EU site or other website.

8. Allow sponsor to block automatic indexation from PubMed for unrelated publications with NCT number cited

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

As sponsor company & data provider, we use clinicaltrials.gov website for searching already posted clinical trials and creating a report for audit purpose; to check on competitors/licensed/transition company's posted information; to verify accuracy of the record posted against protocol/protocol amendment/routine updates, to generate KPI/metrics on disclosure activities etc. However, some suggested improvements to the existing features are:

1. The search result can be saved and refreshed/retrieved every time the sponsor needs to download information.

2. The search result can be produced in report format with grouping options (group by product/indications/timeframe etc.)

3. In PRS, enable extraction in Excel format of a higher number of fields, similar to the option provided on public site.

4. In NIH fund type, provide sub-categories NIH-FUNDED extramural and NIH- FUNDED intramural and then other universities where no federal funds are used.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Clinicaltrials.gov is used for both 1) and 2). As mentioned under #c (above), depending on need, the search can be wide range or narrowed to pinpoint the extraction of certain information.

1. There are fields like location, disease/condition, for which the search functionality can be improved in order to pinpoint the information.

2. There is some information which is not available for download and can be made available for user/sponsor to analyze some KPIs (e.g. in result sections before result is available, there is information posted on review cycles (date of submission, date of comment back from reviewer, date of re-release by sponsor etc.)).

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Automated Record Consistency Check/Validation: Within a registration record, simple automated consistency validation can be added to flag obvious errors. For example, the protocol title has Phase 1/2 but in the Design module/Phase, Phase 1 is selected by the user. Eg 2, Brief title has pediatric patient, but under the Eligibility Criteria minimum age is selected as 18 years. Eg 3. If primary endpoint timeframe is shorter in comparison to timeframe of any one secondary endpoint, system can raise a warning flag if primary completion date = study completion date.
2. Like EudraCT system, PRS should give flexibility to define 2 or more different designs used in the same protocol with 2 or more different periods. Eg. Period 1 double blind, double masked whereas Period 2 is either single blind or open label.
3. Results module should allow uploading a graph. For people who are not scientists/researchers a graph is more meaningful and more visual than data.
4. Most importantly, there should be designated field/s to capture data for exceptional or atypical study scenarios (e.g. study suspension), such as "termination date" (which does not coincide with the primary [=actual primary endpoint LPLV as per PRS definition] or study completion date [= actual study LPLV as per PRS definition] and creates compliance issues), "termination reason" field with more characters (1000 characters) than what exists now. On public site, these fields should be visible at "overview" level covering both protocol and result sections.
5. Additional fields to be available:
 - protocol amendment #- it would help to see a particular amendment and its related changes.
 - study duration, frequency of visits: It will help patients to commit to a trial and narrow down the search.
6. Having version comparison functionality (similar to what is available in public site/archive section) will be helpful in internal sponsor review cycles.
7. Some type of linking between sister studies, umbrella/basket trials etc in PRS (as done for Expanded access program) so that data entry can be minimized by transferring similar data from an already existing record to a new record.
8. Observational study record needs to remove the fields related to Interventional studies, for example Observational disease registry study for which there is no drug involvement asking for intervention is misleading. Similarly, asking for primary purpose and giving the option relevant to interventional study but no relation to observational study is also not very helpful.
9. Can the interventional study record be less stringent for primary outcome description for studies with descriptive design (typical for Phase 1 and 2 studies), eg more than one time-frame allowed
10. Move the "limits & caveats" section to the top to inform upfront readers (public/scientists/researchers) to take results disclosed with caution
11. If only a publication link is added, it should not go through a full results review cycle
12. In short, much like some FDA systems (e.g., data base tracking PMRs), the way that ct.gov reflects shortcomings/ delays/ failures to meet deadlines can result in many false positives / seemingly bad

results. For example, when patient groups and / or journalists look to measure the extent to which companies have posted information, they frequently and very publicly report out that pharma is not fulfilling its requirements. However, things like late starts/ late posting, changes to studies (sometimes due to FDA, or talks with other HAs) that result in postponing posts, are not accounted for. So, the results can look significantly worse than they are. (see examples below)

<https://www.sciencemag.org/news/2020/01/clinical-scofflaws>

<https://www.statnews.com/2015/12/13/clinical-trials-investigation/>

<https://www.nejm.org/doi/full/10.1056/NEJMsa1409364#t=article>

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

1. If NCT #, initial release date, initial public posting date, similar dates for amendment related release can be fed back to Sponsor's clinical trials management system, it will save a lot of time in tracking this information manually and reduce data entry error.
2. In the Contacts Area allow use of or linking to a displayed WebForm to collect queries from the public and transmit them directly to the Sponsor and/or to the Sites. A WebForm will facilitate the management of queries by structuring the query and associated data. Many public queries by email or phone require multiple back and forths between Sponsor and patient due to incomplete information, and time is lost. The current space provided for Contact information and Contact instructions is not sufficient.
3. In the same manner, in the Contacts Area or an adapted space, allow inclusion of direct links to Sponsor screening websites during the recruitment period, to facilitate patient access to information.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

1. Content reuse by extracting information directly from protocol as XML and uploading to PRS. This will ensure content alignment between Clinicaltrials.gov and protocol. (Clinical Protocol template)
2. Use of small intelligent tools which can be embedded to PRS which will help enforce required data into field. E.g. "clinical registration tool" prepared by TransCelerate enforce the elements required to be mentioned in brief title and brief summary.
3. An embedded outcome measure library by disease and variable would be extremely helpful to sponsors and will also ensure consistency in outcome measure reporting within industries & academia. This will also reduce the NIH-Sponsor review time and cycles for the record.
4. A connection to FDA drug approval site or embedded functionality to flag a drug as already approved in US or not will be very helpful to PRS users.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

1. Existing useful documents: ACT checklist, protocol registration review criteria, result review criteria, voluntary submission flow chart etc.

2. Suggestion for New document:

a) If PRS embedded Outcome library is not possible as suggested in c # 3, an extensive excel spreadsheet of accurately written outcome measure from different therapeutic areas with complex measurement should be prepared.

b) A complete data element definition document in excel format with clear field for data type, limitation (character or numerical), suggested values, whether required or conditional or optional etc. would be very helpful to users.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

1. A yearly email to recognize organization for achieving

- 100% compliance on achieving ACT data submission deadline
- above a certain percentage (e.g. 90%) of studies disclosed without any comment cycle for registration and result disclosure. NLM should get credit for these kind of evaluations rather than leave them to third parties (academics and the press)

2. Help organization by providing important KPIs related to disclosure activities/quality such as:

- By Organization: how many studies registered in a year, how many are ACT and how many are non-ACT, how many did not receive any comment, how many 1 or more than 1 cycle of comments, what was the duration from submission to publicly posted as a clean record by study.

- By Organization: how many studies' results are disclosed in a year, how many are ACT and how many are non-ACT, how many did not receive any comment, how many 1, or more than 1 cycle of comments, what was the duration from submission to publicly posted as a clean record by study.

- Alerts to PRS user (to owner of the study record, organization account holder(s))

- a) 3 months before Result is due
- b) When any milestones are in past
- c) 3 months before Delay result certification expires

Submission No.: 135

Date: 3/6/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Within the ClinicalTrials.gov PRS interface have the ability to (1) select multiple studies currently registered, (2) download a pre-populated Excel template with existing site data, and (3) have the ability to edit the site data on the template and upload the updated Excel template back into the system.

Submission No.: 136

Date: 3/6/2020

Name: Jessica Yingling

Name of Organization: Mosaic Life Care/Heartland Regional Medical Center

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Have clinicaltrials.gov interface with our existing systems we have in house: Flatiron (Onco Trials), Cerner, and Aria (radiation technology).

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

We use a screening program called Onco Trials. The company that has built this system is called FlatIron. Currently, we can type in the NCT number of a trial and certain content populates from your website. I'm not certain if this is pulled directly from your site, or if it is manually entered by someone at FlatIron. The information that is populated really isn't very specific and it does not include any eligibility criteria. We also use Cerner. Cerner has a Research module in it that can help us screen for clinical trials. If information about the trials could interface with the Research module, it would save time entering all of the trial specific information into the system.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I currently use the website primarily for searching for clinical trials for our patients at our hospital. You have improved the site so much from the days back when I first started using it (around 2006 or 2007). I love the way you can filter trials based on location, trial type, etc. I have had some issues with the content for eligibility for some of the trials. At times, the trials do not have enough specific eligibility criteria for us to evaluate our patient's eligibility. This has gotten better, but there are some that still only have 4-5 inclusion and exclusion criteria and you know that those aren't the only criteria written into the protocol.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

We rely heavily on the studies that are on the website. We see all cancer types at our institution and we are looking at expanding into cardiology, neurology, and infectious disease studies this year. The filters that exist in the system are enough for us to find clinical trials for our patients outside of our practice. With the filtering that is provided, we can also search based on location. For example, with us being in Missouri, we can search for trials in Missouri, Kansas, Oklahoma, and Nebraska. Having the option to

search in different states allows more options for our patients and also helps us narrow down which trials are closer to “home”. In the future, I could see where the need for a filter for genetic markers may be needed with more targeted cancer therapies coming out. Having a way to search through trials based on a specific mutation for the patient would also be very helpful and make our trial search more efficient.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I personally have not used this portion of the website yet.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

??

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

??

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

??

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

??

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

??

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

??

Submission No.: 137

Date: 3/6/2020

Name: Anastasiya Shor

Name of Organization: [Not provided]

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I use the website for many things, but one of the most useful is the links on the bottom of each clinical trial detailing the publications that have been done. Sometimes it is really hard to identify that multiple publications are talking about the same study, and I ABSOLUTELY LOVE this feature. I also love the terms and synonyms feature because then I can see variations of the search terms, and sometimes I use this feature to come up with search terms in pubmed.

I do have a comment-show/hide columns should allow you to select more than one option at a time. I know this is hard to do, but I would also appreciate it if it were possible to indentify studies used in FDA approval as such... since the label lists them usually as "study 1" or the like, it's really hard to find the appropriate publication.

Submission No.: 139

Date: 3/7/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I'm looking for studies I can participate in to make some extra money.

Please include compensation if the study is looking for participants .

Maybe add a time commitment including how many visits to the research location are required because traffic and parking are usually miserable here in the city.

Please include a search feature that is distance from my zip code/current location.

Also make it easier to search by qualifying condition .

Submission No.: 140

Date: 3/7/2020

Name: Stephan Schwebke

Name of Organization: Nonesuch

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I am an investor & use the site to find candidates. Sometimes, I look for clinical trials for a specific company and, in that effort, occasionally get results for other companies listed, along with the company of interest, making the list longer than it otherwise would be.

My main interest is in companies having medium or less market capitalization and have little interest in anything larger, so it would be helpful if the name of the company sponsoring the trial were entered on the list of trials, along with all the other information you already provide, so I could merely skip over that trial, rather than waste time opening it. Also it would be extremely helpful if the results of the trial were posted, as required, to better gauge the quality of the company's research.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

The methods used to look for companies: look for specific date ranges, limiting to phase 3 & 4; look for specific types of therapy, such as immunotherapy, metabolic therapy, effector cells, or jhu083.

You already provide these tools, and I can think of no other needed.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Occasionally get results including other companies, other than a company I am interested in.

Submission No.: 141

Date: 3/7/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The clinicaltrials.gov page could be incredibly valuable for patients but it needs a refresh. 1. We want you to include exact enrollment numbers for each trial - how many spots are available and how many are taken

2. Include sources of funding for trials
 3. Require monthly updates from sponsors so that we know which trials are actively enrolling and that the contact list for trials is updated and accurate
 4. "Paid" programs should be marked clearly (there are some "trials" that people would pay for in order to participate)
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use it to look into ALS clinical trials available. I also know that other groups incorporate your data into their tools - Antidote, ClinWiki - if your data is not clean and updated then it 'bleeds' over into what folks think are helpful tools. Please do your part.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Only looking for intervention types for ALS

Submission No.: 142

Date: 3/9/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

it would be advantageous if you could search for names or medical devices

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

a link to EUDAMED would be inserted

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

information about investigator and which and/ or how many studies he/her are participating

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My use is limited to the sub-item 1.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The interface and the processing of the request is not customer-friendly and very old-fashioned. These are not sufficient instructions to complete the fields and the designation is partly misleading. There is no sufficient guideline to complete the fields.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

NAP

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

no input

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

NAP

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

on your webpage?

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

no input

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

pls refer to ISO 14155

Submission No.: 143

Date: 3/9/2020

Name: Katja Theobald

Name of Organization: Edwards Lifesciences

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Missing device or drug name function. Would be easier as by study name (short title).

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

would be good to be linked to the new EUDAMED homepage.

Link to PubMed

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Looking for trials conducted for specific diagnosis and treatment

investigator search: in which and how many studies he/she is participating

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use is related to 1) in all terms described.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The required field description is sometimes misleading, e.g. Primary Endpoints. Too often questions are coming back on the same field. If information entered is not clear the note next to should be describe better what is required. The information fields , hints, are not detailed enough.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

company submitt via PRS directly

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

no input

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

unknown

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

should be awarded by recognition on the homepage.

SPONSOR has been always in time...

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**

- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

the copy / paste function for adding incl./excl. criteria would be a big support.

Entering them one by one is very time consuming and can lead to human error.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

For device studies: ISO 14155 and MDR should be reflected as regulation/law which the submission requires. Also the wording such as IRB are not correct for the EU region. The global aspect should be reflected not only North America.

Also for pharma, the same should apply in regards to the requirements and laws.

Submission No.: 144

Date: 3/9/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

1. Inclusion of a more lay friendly “overview” tab, in addition to ‘study details’, ‘tabular view’ and ‘study results’, modeled similarly to patient-find websites

2. For Patients section, currently at bottom of main page is easily missed, consider adding as a more prominent link on home page and including guidance (text and video) on how to search for trials. FDA and CTTI are working on a similar initiative (Patient Engagement Collaborative) is NIH/NLM involved?

3. Contacts/Site Locations should perhaps be a separate tab or more accessible than having to scroll to the bottom of a registration record.

4. Recruitment status: Terms such as “Active not recruiting”, “Enrolling by Invitation” are confusing to the patient population. Consider more patient friendly terminology.

5. Resources tab should include resources for Patients and Families, such as links to available training sessions on how to find trials, what is a clinical trial, videos and other forms of media.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

1. Request inclusion of a new field to capture the global protocol version being registered within the registration record.

Submission No.: 145

Date: 3/9/2020

Name: Jennifer Brown

Name of Organization: Medical College of Wisconsin

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

- Trials Today (link: <https://vanderbilt.trialstoday.org/>), developed by Vanderbilt University, allows institutions to extract their recruiting trials from ClinicalTrials.gov and use it as a searchable database specific to recruiting trials at their institution.
- The CITI Program module “Protocol Registration and Results Summary Disclosure in ClinicalTrials.gov” serves as a great foundation for training on record registration and results reporting. It would be beneficial if a similar video and or visual screenshots could be incorporated into the Protocol Registration and Results System (PRS) training materials.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- Studies registered to ClinicalTrials.gov with an NCT identification number can be linked to a journal article with a PubMed identification number (PMID), which is a great resource to link publications to a specific study.
- The ability to link to ClinicalTrials.gov is a great tool to help facilitate subject recruitment. Our institution has linked our Clinical Trials Management System (CTMS) to our affiliated hospital websites, providing the ability for patients, families and referring physicians to search for available clinical trials in real time. In turn, the individual study pages are then also linked to the specific study record on ClinicalTrials.gov, to provide additional information. (Example: <https://www.froedtert.com/clinical-trials/cancer/obinutuzumab-or-without-pi3k-delta-inhibitor-tgr-1202-lenalidomide-or>). Similarly, documents uploaded to CT.gov, including results, could be exported/linked to other websites to provide updates on research results and publications in a convenient, visible format.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Currently, ClinicalTrials.gov is utilized for registration and results reporting of our institutional studies. Useful features include the problem list and planning reports, which allow monitoring of investigator and institutional compliance. The website is also useful for looking up regulations and as a learning tool for PRS.

Areas for website improvement:

- To facilitate institutional metrics reporting, it would be helpful to have an institutional search feature for new registrations, and/or assign a specific center ID to study sites. Unfortunately, filtering data based on study site names/locations is often inaccurate, as site names can be misspelled, etc.
- Being able to download Demographics and SAE/AE XML files for a study without needing to enter the ‘Results’ section would be useful to provide examples for case report form builds in OnCore, data managers and statisticians. Entering the ‘Results’ section while the study is ongoing makes future updates (e.g., opening/closing arms, adding/deleting outcome measures) more cumbersome.
- It would be beneficial to develop auto-notifications to responsible parties and record owners to alert them when their record appears on the institutional problem list and action is required. Alerts emailed in advance of the record’s annual review/release date, or prior to results expected date would improve compliance of reporting regulations.
- To improve instructional content on the website, it would be helpful to incorporate more graphics (screenshots) and/or use instructional videos to demonstrate standardized registration and results reporting (similar to the CITI educational module).

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our institution utilizes ClinicalTrials.gov for a wide range of study types. Many investigators post their research studies (including Non-ACTs) in order to meet criteria for ICMJE requirements for publication. It would be helpful to incorporate a multiple response checkbox to select the reason for registration (ACT, NIH, ICMJE, CMS etc.).

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

The functionality for study results reporting requires a significant upgrade. Improved navigation and user-friendly features are needed to facilitate registration and results reporting. As an example, there should be a visual process flow of what sections must be completed for an ACT vs an observational study (color code or deactivate sections that are not applicable). The current functionality is not intuitive and is a burden to responsible parties/record owners to complete. However, the current feature to upload documents into the PRS system (i.e. informed consent forms) is beneficial and could potentially be expanded to help facilitate with results reporting functionality.

An additional function and process that could be improved is the approve and release functions. Rather than requiring a three-step process for responsible parties to approve and release changes to a record, it is recommended that these steps are combined. Often, investigators will approve and assume the record has been submitted; only for it to remain in a pending state, leading to delays in submission and require a subsequent login to release. Automatic push notifications should be sent to a responsible

party (RP), which they could then approve/release directly from their email, rather than requiring them to log-in to do so. A change in process that prioritizes when the RP needs to submit would be beneficial (i.e. allowing the Record Owner to address and submit minor error correction).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

More institutions are utilizing a Clinical Trials Management System (CTMS) as a central data repository for protocol and subject enrollment data. If the functionality exists now or in the future, it would be beneficial to automate the transfer of demographic and AE/SAE data from CTMS systems into PRS. If connectivity/automation is not feasible, it would be useful to permit the upload of an excel template (like the AE/SAE reporting function), to help facilitate demographic/results reporting and eliminate hand entry/duplication of effort.

Our institution currently uses OnCore, which can generate an XML file to be uploaded to PRS. The vendor, however, does not keep up to date with the changes to CT.GOV. Since OnCore is a widely used CTMS, any enhancements to interoperability would be welcome so this could become a truly useful tool to end users.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Institute a dashboard tool (i.e. Qlikview or Tableau) to help visualize institutional metrics (i.e.. ACTs vs Observational studies registered, or non-compliance percentage). Similarly, a dashboard tool could also be helpful to visualize study results, especially for viewing by the general public.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

As previously noted, enhanced e-learning tools (videos) that demonstrate the software and how to enter information, especially for entering data in the results section(s) accompanied by mock study designs would be helpful.

We recommend increased partnership with the Clinical Trials Registration and Results Reporting Taskforce (CTR) to identify best practices and serve as a communication forum to address issues.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Develop a top list of institutions who are most improved in the area of "Problem Records" or the reduction in the back and forth between the initial registration/results submissions. Consider a "badge" system to publicly acknowledge investigators who maintain all compliance standards for their record(s). This would be visible via other public forums such as FDAAA Trials Tracker or PubMed, and can be recognized when the investigator is submitting work for publication or applying for future grant funding.

Compatibility with the Clinical Data Interchange Standards Consortium (CDISC/CDASH) and Electronic Common Technical Document (eCTD) standards would make uploads of study results more uniform and easier to automate.

3. **Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. **Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**
 - Set parameters for data table fields that will only allow numeric data to be entered into specific results fields (vs free text).
 - Build a standardized AE vocabulary into the software so it's not left up to individuals and their institutions.
- 3b. **List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

N/A

Submission No.: 146

Date: 3/9/2020

Name: C. Marc Taylor

Name of Organization: ISRCTN registry

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Why does your web site do so little to convey the importance of reporting results?

I am the chairman of the not-for-profit company that owns the ISRCTN registry at www.isrctn.com. In recent years we funded improvements implemented by our service provider BioMed Central. I recommend you look at the presentation of isrctn.com which aims to encourage research teams to give equal weight to registration, updating and reporting. It conveys a continuing relationship. Registration leads on to adding the protocol and other key documents, correcting the dates of commencement and conclusion, and reporting summary results promptly when publication in journals is delayed.

Failure to declare a study transparently on an internationally accessible public register is a legal and moral misdemeanor that primarily offends the scientific community. By contrast, by not reporting their results, scientists undermine the evidence base for real-life decisions and damage public trust in research. The consequences and penalties should not be consigned to the small print on clinicaltrials.gov.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

The most important linkage is with the international network that follows the standards for registries agreed at the World Health Organization. ClinicalTrials.gov should continue to prioritize close alignment with and support for the WHO's International Clinical Trials Registry Platform, which links over twenty primary registries and their partners around the world. The WHO's portal signposts nearly 550,000 studies. ClinicalTrials.gov holds records on over 330,000 studies. Over half of these are in countries other than the USA.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Personally, I mainly use your website to generate statistics about the numbers of registered trials in different parts of the world, and the proportion of registered trials with no reported results. For this purpose, I value the facility to present search results on a map. It would be a bonus if the mapping facility generated higher quality images for copying into slide presentations.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of**

studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

It relies on all of these features at different times. It would be a bonus if you made it easier to search for studies for which there is no summary report one, two and three years respectively after the end date for those studies. This would facilitate action by those sponsors, funders and regulators that are short of the resources needed to follow up unreported studies for which they are responsible.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I have no personal experience on which to base a comment.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

The British Health Research Authority is updating the software it uses to manage applications for review by ethics committees (IRBs). The ISRCTN registry has drawn its attention to the API used for the sharing of information across the WHO network of registries, and by ClinicalTrials.gov in its collaboration with that network. The HRA has been criticized for not auditing compliance with conditions attached to health research approvals, including registration and reporting of clinical trials. Many UK research teams have chosen historically to register their UK-based trials on ClinicalTrials.gov rather than with ISRCTN or another registry that actively follows up studies when reporting is overdue. Because of this it is a matter of concern that reporting is overdue for rather a high proportion of older UK based studies registered with ClinicalTrials.gov.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

No comment

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

No comment

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Could you use flags or emojis to reward and incentivize complete and timely updating?

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

No comment

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Publicly available

Submission No.: 147

Date: 3/9/2020

Name: Joseph Stacey

Name of Organization: Self

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Want to register for the coronavirus virus vaccine study

NCT04283461

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

To help formulate vaccines

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

My first time.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

To offer a study scenario of a male of my type with current conditions

- 2.** Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Any scenario study that I could possibly provide

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Not sure

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Possibly ways of contacting the virus

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

Reading infectious disease materials found online .

Perhaps ways the virus Infection affects people of different regions

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

By providing as much material possible about the virus

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**

- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

By using many different culture types

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Really do not have any

Submission No.: 148

Date: 3/9/2020

Name: Darren Taichman

Name of Organization: ICMJE

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Please see attached letter from the International Committee of Medical Journal Editors. Thank you.

Attachment: ICMJE - NLM RFI re ClinicalTrialsgov Modernization.pdf

March 9, 2020

RE: Request for Information: ClinicalTrials.gov Modernization

Dear Colleagues,

I write on behalf of the members of the International Committee of Medical Journal Editors (ICMJE) in strong support of your continued efforts at the ClinicalTrials.gov registry.

As the largest clinical research registry worldwide, ClinicalTrials.gov plays a critical role in the advancement of clinical science and care.

The ICMJE has required the prospective registration of all clinical trials since July 1, 2005 (www.icmje.org). Prospective trial registration is essential to prevent selective publication and selective reporting of research outcomes. It helps the research community avoid the unnecessary duplication of research efforts. It enables patients and the public to know what trials are planned or ongoing into which they might want to enroll. It gives ethics review boards considering the approval of new studies a view of similar work and data relevant to the research they are considering.

As journal editors, we rely on the information provided at ClinicalTrials.gov to ensure that studies submitted to our journals have met all 24 of the criteria we require for ethically appropriate, prospective trial registration. Among these criteria are the meaningful designation of primary and secondary endpoints, how and when they are to be assessed, inclusion criteria, and statements regarding the planned availability of collected trial data for use by other investigators. Each of these is instrumental in our efforts to prevent selective reporting and to ensure that the public's investment in clinical research and the efforts of trial participants are maximized. Additionally, ClinicalTrials.gov enables journal editors to gauge the scope of completed, ongoing and planned investigation within a field to help contextualize a submitted report.

An even more effective ClinicalTrials.gov can further help advance the conduct and reporting of clinical science, which can translate into improvements in the care patients receive. Areas for improvement include the following:

-The provision of detailed information regarding quality control issues raised in the evaluation of submitted registration materials. A substantial number of submitted registration materials fail the initial quality control assessment made by ClinicalTrials.gov staff (e.g., owing to inadequate specification of the primary outcome measure). It would help journal editors if we could see the specific quality issues that delayed the posting of a registration record. This information would help us to make determinations of whether a trial was conducted in compliance with the requirements for prospective registration (e.g., by

allowing assessment of instances where the the “first submitted [date] that met QC criteria” is after enrollment of the first participant).

- The reliable availability of quality-assured and structured results tables. Currently, many completed trials fail to post summary results, which include all secondary outcome measures, all-cause mortality, and adverse and serious adverse events tables. High-quality, structured results tables would help journal editors understand the full set of study results, and journal reports could link to them. It would be especially helpful if journal editors could more reliably know which trials are expected to submit results, and when those results will be due. Submitted registration materials should include such information.

-Require posting of trial protocols and associated materials with the initial trial registration. The inconsistent posting of trial protocols, as well as the posting of multiple versions of trial protocols with a study’s many publications, interferes with transparent reporting and efforts to ensure it. While the recent addition of trial protocol posting with results submission is helpful, it would be ideal to require posting of trial protocols (and associated materials such as statistical analysis plans and standard operating procedures) when the trial is first registered. As changes to protocols do occur during the conduct of a trial, an ability for investigators to readily up-date and for others to track such changes would be essential.

-Provide links to a trial’s participant-level data. It is currently difficult to find information about data sharing plans for ongoing trials and links to data for completed trials. By enabling their findability and use, updated information regarding the availability of and links to individual participant-level data would be instrumental in maximizing what is learned from clinical trials. As journals begin to publish information regarding and links to data underlying individual analyses from a trial, a trial’s registration could provide a unified (and logical) location to view all such related information.

-Create an alerting system to inform interested persons when changes to a trial’s registration have been made. Users could sign up for automated notifications of interest (e.g., at trial completion or results reporting).

Thank you for this important work.

Sincerely,

A handwritten signature in black ink, appearing to read "Taichman".

Darren Taichman, MD, PhD

Secretary, ICMJE

Submission No.: 149

Date: 3/9/2020

Name: Kerry

Name of Organization: [Not provided]

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I use the website to find the Registry number for clinical trials listed that we as a site participate in

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Finding the Registry number for a study should be easier

Submission No.: 151

Date: 3/10/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

ClinicalTrials.gov can be linked and data from it integrated in clinical trial matching pages. Such pages transform certain data fields (e.g. inclusion criteria, condition) into a questionnaire, that is offered to a user - an interested patient, a caregiver or a healthcare professional to complete. Answers are compared with the existing open trials, a potentially matching trial is then shown to that user, and he or she can contact the investigational site using the contact information from ClinicalTrials.gov. This can be considered as a pre-screener for a trial, optimising the recruitment process. Findmecure.com, viomedo.de are examples of such solution.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The greatest strengths of ClinicalTrials.gov are the largest amount of high quality information on ongoing and completed trials, results data on studied investigational and marketed drugs, and overall the largest number of trial records in one place. The opportunity would be to extensively improve the finding of the right information for patients - the interface today is rather professional-oriented.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

(2) - studies mostly with results on treatments in question, new developments on selected indications.

Submission No.: 152

Date: 3/10/2020

Name: [Not provided]

Name of Organization: ResMed

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

It would be good to have a “watch” facility whereby an email alert digest could be sent of trials on a watch list when they change. PubMed has this capability.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Overall the usability of the website is far from optimal. It would not score well if they did formal human factors testing as navigation and understanding the acronyms is sub-optimal.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Although the database is clunky, I find data entry the first time okay. When it comes to entering results, it takes some time to get used to the structure; but this is due rather to different study designs.

The UI is difficult to navigate. It's not easy to shift through the difference pages of the application. Would be handy if there was a flow graphic to show which specific stage you are up to and the progress level of each part. It would be beneficial if there was more context for the fields. On the record summary page it would be handy if the page more clearly indicated which fields are still to be completed. It would be good if the application more clearly identified which fields are mandatory, desired and not mandatory.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

Some of the fields that need to be completed it is not clear the information that is required, especially when you are entering a study that is not an RCT design such as observational cohorts (registries). When CT.gov have issues that they wish you to address it is not so leasy to navigate through the issues raised to make addressing them easier.”

Submission No.: 153

Date: 3/10/2020

Name: Jimmy Wah

Name of Organization: Common

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Independ-FA9056.Jimmywah.jimmywah.net route ipv6 in-ARRP net.jimmywah.jimmywah.indpend-FA9056 /Independ-9054 /Indpend-fa9056 /Indpend-9054 /Independ-FA9056

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

IPv6 tunneling development mode citation via jimmywah@pacbell.net ISDN

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I have been informed the pi network capabilities in addition to the contra counterindication terminology as suffice to suggest the cleared signature LM is a dark Horse code name vessel

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

And County oF San Francisco southeast industrial naval ship yard

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The relay is listed for the end tunnel in time netbeans and sql operations

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

None applicable as site specifics are exemplary

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

None applicable as site is exemplary

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The nomenclature in the presentation of supervisory Canada hybridization of legal in nomenclature jargon of common practice, in additions to possible functional parameters in coordination of a nationalized academic hub for the procurement and sourcing of USA CAN MEX clinical trials for further processing as patent hub San Jose Canada

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

APA citations disavows the supports authors and thus credit are established within the competition theory model. As suffice, the institutional privacy is allocated and therefore misunderstandings to the process of intellectual dynamics ability is affected in . Overall this is considered a dynamic process and to date have not found major resistance.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

None quoted other than time synchronization patterns to collaborate with the temporal nature of subscribed reality, advise to initiate Ad non limit tracking in privacy to come to this heisenburg like positioning. Collaboration in macro hard is advisory.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

None available for concept modal

Submission No.: 154

Date: 3/10/2020

Name: Dr. Arturo Loaiza-Bonilla, MD, MSED and Selin Kurnaz, PhD

Name of Organization: Massive Bio

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

At Massive Bio we have developed a Deep Learning platform called SYNERGY-AI for clinical trial matching, currently focused in oncology and malignant hematology trials, which has already shown not only feasibility but scalability and optimized matching and enrolment. Optimization of some data sources, including clinicaltrials.gov would be an ideal opportunity to maximize such benefits for all stakeholders.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

PubMed and links to drug databases describing the investigational drugs from NCI Thesaurus would be empowering and helpful to understand the potential benefit of such interventions.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

As mentioned earlier, SYNERGY-AI utilizes public sources and also specific information from protocols provided by sponsors and/or CROs. However, many studies listed have multiple arms, and eligibility criteria which is not listed. Our technology is able to discern those nuances for matching, however only if that information is available; it would be ideal to ask sponsors to include all inclusion and exclusion criteria, not only for our platform but also for public consumption, as patients and providers would likely benefit from this information for referrals, and even for payers and institutions, etc.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Interventional studies, across the globe, mostly in oncology. It would be nice to have a differentiation between specialties as a filter.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Use OCR and NLP for protocol digitization in real time, that would also be important to reflect changes in protocols, arms, IRB approvals, and inclusion/exclusion criteria. We already have such capabilities using our ontologies, would be nice to see that in a public platform as we know it is potentially feasible. Also we recommend to have the ability to show the efficiency of the trial, by calculating the number of patients enrolled over time per active site, for each study.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

The API should be compatible to any EHR and platform wishing to parse this information, using HL7 protocols.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

As above.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Reports of access to the study pages, and collaboration with study sites, CROs, analytics companies and others (like Massive Bio) to correlate optimized information and correlation with improved access over time to the studies, and enrollment. It is in the best interest of patients, study sites, sponsors and CROs to enroll patients in a timely fashion, and this is only possible by readily available and complete information.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

If you use OCR/NLP capabilities to digitize the synopsis of the studies, there is a major opportunity to enhance the upload of information and to speed up data updates. Collaboration with local and central IRBs to reflect changes as part of the submission may also be an important step which would also improve quality, fidelity and regulatory compliance.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

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Ho, D. Artificial intelligence in cancer therapy. *Science* (80-.). 367, 982–983 (2020).

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Submission No.: 155

Date: 3/11/2020

Name: Vilmantas Navickas

Name of Organization: Boehringer Ingelheim

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Our recommendation pertains to the “MASKING” section on your website, where we are missing the “sponsor” role, and further role clarifications:

According to ICH E9, a “double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff involved in the treatment or clinical evaluation of the subjects are aware of the treatment received”. This definition (along with “single-” or “triple-blind”) may be used loosely in the literature. Hence, CONSORT 2010 has called that “authors and editors should abandon their use”.

Although it is difficult to abandon the use of these terms as advocated by CONSORT, we would like to recommend an approach that can support the transparent reporting, as well as the ICH E9 guideline.

Our proposal is as follows:

- 1) Within the Masking section include additional tick boxes: “sponsor/clinical trial team” and “database”
- 2) Within the definition section indicate precisely who is meant by:
 - a. “care provider” – this may be e.g. a study nurse or the care taker of the participant
 - b. “outcomes assessor” – this is the function that judges the outcome for the endpoint, e.g. this may be an assessor of level of tumor response or a person who reads a diagnostic image
 - c. “sponsor/clinical trial team” – this may be the study team that supports data collection at the site and/or the clinical trial analysis team
 - d. “database” – this option should be checked if the database was kept blinded until database closure
- 3) Add clarification which tick boxes should be selected in order to meet the ICH E9 definition of “double-blind”; otherwise introduce an additional masking list of values field (e.g. “Open label”, “Single blind”, “Double blind”) so that it can be selected by the responsible party to reflect the information provided in the official title. The masking should not be automatically determined based on the number of masking roles selected.

Submission No.: 156

Date: 3/11/2020

Name: Amber Hicks

Name of Organization: UT Southwestern Medical Center, Dallas, TX

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1. Have more reports available, such as all records a particular user is on.
2. Be able to still have emails sent to PRS administrators for only NCT records they are responsible for. We are a large academic institution, and we have PRS administrators for every group, however when you select to receive email notifications of system generated messages, it sends out for ALL records, not just the ones they are listed on.
3. Ability to send an email to record owners/users within an NCT record, from within PRS. It would have a link to "create email" and open it in your email box. - even templated email, "x" record has "X" problem, please resolve. It's alot of work to have to look up and add users, since it shows username, which isn't their name at our instituition. I have to view users, scroll down to see who they are, then go to email and add.
4. Is the email users feature for everyone that has had a CTgov log in?
5. Be able to move columns within the webpage

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I like the link to open the record. I use in my spreadsheet, it makes it useful, when I am checking to see if a change was made. Rather than having to search for the NCT number, I can use the link to pull up the record.

I am the PRS administrator for a large academic institution, I use it most days of the week.

Submission No.: 157

Date: 3/11/2020

Name: Karen Creekmore

Name of Organization: purpleangel-global.com

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

I was diagnosed with Unspecified Symptoms of Xementia in 2014 @ 59. This site is the most unfriendliest navigation site for dementia I've been on.

I live alone & comprehend what I read. I signed up for 3 studies, clicked on saved 3 studies. An hour later I couldn't figure out how to submit.

Dementia is horrendous. You have no idea unless you're living w it.

I already feel bad enough about my progression.

What would help?

Simple step by step instruction before the list of clinical trials ie

1. Select city, state

2 To select a study, click on select box

3. (At end of study-have 'review selected studies', 'print/download studies', 'submit studies'

4, Most important: Contact info

I've been on this site several times to no avail over the years. I spent 3 hrs today trying to figure it out & trying to leave a comment. Hopefully ya'll will get it.

I know there's no cure in my lifetime. My purpose is to perhaps help one person improve their quality of life and ultimately find a cure.

Thanks

Submission No.: 158

Date: 3/11/2020

Name: The ChEMBL Team

Name of Organization: EMBL-EBI (European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, UK)

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Search by chemical structures: In the situation where the intervention is a compound and its structure is known, this would allow to collect all the related studies as you can currently do with the intervention name. The difference is that names have synonyms and even if ClinicalTrials.gov has improved the mapping between synonyms, one can expect it to be incomplete (and it is often the case). As the molecule structures, in particular their InChI or InChI key, are unique, under the condition that this information is available, searching with this would return all the studies.

For example would it be possible to ask depositors to use the UNII codes linked to the compound names.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

-Link studies to bioactivity databases such as ChEMBL or PubChem would potentially be useful to ClinicalTrials.gov users. We provide links in ChEMBL to ClinicalTrials.gov. For example:

VELIPARIB (drug Indications section):

https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL506871/

-Links to ClinicalTrials.gov compounds in other resources and from other resources to ClinicalTrials.gov: we have done this mapping using our UniChem resource e.g.

https://www.ebi.ac.uk/unichem/frontpage/results?queryText=SILDENAFIL&kind=src_compound_id&sources=46&incl=exclude

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

-We currently use the downloads but are also interested in the API having more functionality.

-Search by study identifiers: works well

-Search by intervention names: could be improved as depending on which intervention name synonym you enter, you may get different study numbers.

Eg: sorafenib 849 results

<https://clinicaltrials.gov/ct2/results?cond=&term=Sorafenib&cntry=&state=&city=&dist=&Search=Search>

Nexavar 516 results

<https://clinicaltrials.gov/ct2/results?cond=&term=NexAVAR&cntry=&state=&city=&dist=&Search=Search>

If sorafenib and nexavar were both mapped to the same molecular structure then searching for one or the other would return the same studies.

-Also more strict rules about what can be added to certain fields would aid searching - for example there are trials where the intervention is a drug but not listed as a drug e.g. appears as other - for example

<https://www.clinicaltrials.gov/ct2/show/NCT00177086?term=NCT00177086&draw=2&rank=1>

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We are interested in clinical trials where the intervention is a drug or a biological. We extract these drugs together with disease associations from ClinicalTrials.gov.

The drug-disease associations that we obtain from ClinicalTrials.gov are currently shown in ChEMBL and Open Targets platforms, and linked back to ClinicalTrials.gov. Examples:

ChEMBL: (See drug indications section): the drug vidupiprant is associated in ChEMBL to asthma through ClinicalTrials.gov

https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL1951575/

Open Targets:

The goal is to link diseases with targets. In Open Targets asthma is associated with prostaglandin D2 receptor, target of the drug. This is done by first obtaining the drug-disease associations from ClinicalTrials.gov, and then obtaining the disease-target information from ChEMBL.

https://www.targetvalidation.org/evidence/ENSG00000168229/EFO_0000270?view=sec:known_drug

We have identified two situations that make it more difficult to use ClinicalTrials.gov database with our purpose of extracting information on diseases and which drug/s are being tested for each disease.

The first one is that some clinical trials report "Healthy" as condition. This is particularly more frequent in early clinical trials where the drug is given to healthy patients. Although the recruited patients are healthy it would be useful to know, if possible, which is the condition that the drug is intended to treat.

The second situation is that in some clinical trials there are several conditions listed, but in some cases only one of them is what the drug is intended to treat. For example:

<https://clinicaltrials.gov/ct2/show/NCT02137252?term=NCT02137252&draw=2&rank=1>

In this case the drug (naltrexone) is intended to treat the fatigue caused by the treatment against breast cancer, but not the cancer itself. The conditions listed are both breast cancer and fatigue. It would be useful for our purpose if we could distinguish between what is the indication for the drug, as opposed to other diseases that could be listed as context or background.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

-It would be useful if the intervention names, particularly drug names were standardised. For example, sometimes the intervention name is a drug name followed by the doses used, or shortened names for drugs. This makes it difficult to extract the information and easily map the drug names to a chemical database.

-It would be helpful to have standardised names for conditions, and/or improve the mapping between the conditions and the MeSH terms provided to make it more precise. For example, there are trials where the only condition is “Chronic Hepatitis B”, and the MeSH terms provided are all the following: “Hepatitis”; “Hepatitis A”; “Hepatitis B”; “Hepatitis B, Chronic”; “Hepatitis, Chronic”.

-It would be useful to have the reasons for withdrawn or terminated trials in a standardised format instead of free text, to be able to analyse and query these reasons more easily.

-We would also be interested in specific information about whether trials met their primary/secondary objectives.

-We are also interested in the adverse event data and again it would be good if the adverse events were consistently recorded against a controlled vocabulary (e.g. MedDRA)

Submission No.: 159

Date: 3/11/2020

Name: [Not provided]

Name of Organization: American Society of Hematology

Attachment: ASH Letter re RFI on Clinical Trials_.pdf



AMERICAN SOCIETY OF HEMATOLOGY

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March 11, 2020

2020

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Re: Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003)

Dear Dr. Brennan,

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the National Library of Medicine (NLM) on its RFI regarding the modernization of ClinicalTrials.gov (NOT-LM-20-003).

ASH represents more than 18,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

Additionally, ASH established the ASH Research Collaborative (ASH RC) in 2018 to foster collaborative partnerships to accelerate progress in hematology, with the goal of improving the lives of people affected by blood diseases. The foundation of the ASH RC is its Data Hub, a technology platform that facilitates the exchange of information by aggregating in one place, and making available for inquiry, research-grade data on hematologic diseases. The ASH RC also launched a Sickle Cell Disease Clinical Trials Network in 2019 to accelerate the execution of clinical trials in sickle cell disease.

ASH members often utilize ClinicalTrials.gov in a variety of ways, including submitting their research studies into the system, as well as searching for trials for their patients and for their own reference. Also, as clinical trials are executed via the Sickle Cell Disease Clinical Trials Network, those studies will be added to ClinicalTrials.gov. The Society is pleased to provide the following suggestions in response to the topics outlined in the RFI as they relate to improvements to ClinicalTrials.gov.

Website Functionality

Clinical trials provide potential treatment options for many individuals with hematologic conditions, but the process of finding clinical trials is complicated and can be overwhelming to patients and clinicians. ASH is committed to advancing research, as well as improving access to research and care for individuals with hematologic conditions. ASH and the Leukemia & Lymphoma Society's (LLS) Clinical Trial Support Center (CTSC) recently launched a collaboration to expand access to LLS's service providing clinical trials navigation

and support to clinicians and patients with blood cancer and their families. The goal of this initiative is to connect more patients to appropriate clinical trials. ASH encourages the NLM to make the following changes to ClinicalTrials.gov to make the interface more user friendly for patients who are unable to access this type of ASH-LLS service.

➤ **Make the interface more user friendly for patients and clinicians by making the following modifications:**

- Consider ways to streamline the scope of the search function in the system by providing more options to personalize the search by age, location, and diagnosis for open and appropriate trials.
- Place the contact information for the trial at the top of the page rather than hidden within the page, so the user can easily find the point of contact's email and phone number. This information is included in a link in the top right corner of the site, but it would be ideal to have the information spelled out rather than linked.
- Update the map in the system as it is currently outdated, and the user must click through several times just to find the studies and locations.
- Change the default selections, such as those displayed after the user searches for a study. Users can "show/hide columns," but the screen is very busy and hard to navigate. Consider hiding certain columns (e.g. "locations" and "row" columns) to help the user focus on the important details.
- Institute a more frequent review of content to ensure study details are current.

Important Items to Consider re: Both Website Functionality and Information Submission

As precision medicine continues to progress rapidly with advanced diagnostics and genetic sequencing, especially in the treatment of individuals with hematologic conditions, ASH encourages NLM to ensure that ClinicalTrials.gov is able to capture this information when it is associated with clinical trials. When patients know more about their individualized disease, they will approach the portal with a better definition of their disease. Likewise, trials will include information that better defines disease type, so investigators will be able to target populations more by biomarker or genetic alteration of the disease. Therefore, the portal should have the capability to (1) allow researchers to more specifically define their target population; and (2) allow patients to search by biomarker so they can find a trial that matches their specific disease.

Information Submission

ASH members have indicated that the reporting portal in ClinicalTrials.gov is inflexible and burdensome. The challenges with the system also often delay the related publication of trial findings. The Society encourages the NLM to make the following changes to make the interface more adaptable for researchers submitting information.

➤ **Improve clarity of standards for submission and reporting.**

- Although primary, key secondary, secondary and exploratory endpoints are listed, only require entry of primary and key secondary results. Sometimes secondary and exploratory endpoints turn out not to be analyzable. There should be a clear option for each outcome measure to indicate when endpoints were not analyzed, which would then remove the requirement for all the related details that are not available. Additionally, it is important to also develop an option for the investigator to indicate why an endpoint was not evaluable.

- Allow linkage with a publicly available paper reporting results and consider this as an acceptable way to report the primary analysis.
- Improve the availability of technical assistance for ClinicalTrials.gov. It would be helpful for an investigator to have the ability to ask questions and respond to comments in real-time, rather than the current process of guessing how to respond to comments, then having to wait to see if that was successful. Additionally, a record of all the comments and data revisions would be helpful.

Additional Questions to Consider

ASH recommends that NLM consider the following questions as the system continues to be modernized. The Society would be pleased to engage in additional discussion about how these inquiries could be more effectively addressed.

- Should observational studies, including real world evidence assessments, be included within the site?
- Should the Registry of Patient Registries, previously managed by the Agency for Healthcare Research and Quality, be integrated within Clinicaltrials.gov?
- Should clinicaltrials.gov become the repository for the required deposition of phase III clinical trial data?
- Does the system have the flexibility to change the deadlines for the reporting of study results to accommodate potential delay in data analysis?

Again, ASH appreciates the opportunity to provide these comments. Please consider ASH as a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (schaplan@hematology.org or 202-776-0544) as your point of contact.

Sincerely,



Stephanie Lee, MD, MPH
President

Submission No.: 160

Date: 3/11/2020

Name: Joy Rusthoven

Name of Organization: SURVIVEiT

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

SURVIVEiT.org

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I'm looking for open trials for a certain mutation, or cancer type. I could also be looking for principal investigators to refer patients. Suggestions: make it easier to identify contact info for someone related to the trial, consider adding certain exclusion criteria in filtering option.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

I use this website for both - depending on resources available to patient I'm helping, how rare their disease and/or mutation(s) are. The more we can filter with regard to inclusion/exclusion criteria - to prevent the user from having to contact PIs individually, the better. The goal is to deliver viable trial options as quickly and efficiently as possible.

Submission No.: 161

Date: 3/11/2020

Name: Jennifer

Name of Organization: Cleveland Clinic

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

It would be great to link studies to published results on PubMed. So you could find a link to the article in the results section for a study on ClinicalTrials.gov.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

A more limited range of studies, those I am involved with.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Entering the results is tedious. Having to fill in each little box. Especially if we've already published results somewhere. It would be great to be able to link to a published paper or poster rather than having to populate bits and pieces of a paper into the CT.gov form.

Submission No.: 162

Date: 3/11/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

As a ClinicalTrials.gov administrator, I assist researchers in creating and maintaining their records but am not the owner or responsible party for any study. I am also responsible for approving and releasing records. One of the challenges I have is when researchers update their records independently and I get a notification that the record is ready for review and approval. There does not appear to be any way for me easily to determine what has been updated until after I have marked it approved and click on the button to release it. At that point, the record shows a list of the sections that have been modified, although no detail. It would be extremely helpful to have an easy way to see what changes have been made before I approve the record. The best case would be to have, for example, a "Show changes" button next to the "Approve" button which would open up either a copy of the record with changes tracked or the previous and new version of the changed sections side by side so that I can easily see what changes have been made. If that is not possible, at least being able to see what sections were changed (as is currently shown on the record release screen) before approving the record would make my job easier and potentially make the PRS reviewer's job easier as I would be able to catch errors and problems before releasing the record.

A second technical change I would like to see is in the results section. Currently when the results section is started for a record, the outcome measures from the original record auto populate the results section. At that point they become fixed or flat records. That means that if I need to modify, for example, the description of the treatment, I manually have to make the change every single place it appears in the record. It would be really, really helpful if that information was dynamic so that when I make a change in one place it automatically updates all the places where that specific information appears.

Finally, in my opinion, the way CT.gov handles studies involving deception violates the spirit and intent of requiring registration prior to beginning data collection. Currently records involving deception have to omit those elements about which participants will be deceived. Since one of the reasons for registering trials prior to enrolling the first participant is to enable the public to know what the original planned or hypothesized outcomes are relative to what outcomes are reporting, omitting the outcome makes it impossible to do that. I would like to see a check box for studies which involve deception which, when checked, allows researchers to enter the full information about the study into CT.gov but then gives the option to select sections which should be hidden from the public because of the deception. These sections should potentially include elements of the inclusion/exclusion criteria and the outcome measures at the very least. This would allow a full and complete description of the study to be recorded prior to data collection while also protecting the integrity of the study.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

My institution tracks the number and nature of the records that appear on the problem report. It is not possible to predict how long it will take for the PRS reviewers to review the results submitted and researchers sometimes are not able to submit results 2 or 3 months prior to the 1 year deadline. If results have been released but are still under review by the PRS reviewers after the 1 year deadline has passed, the record gets flagged as having "Late result, per FDAAA." This creates conflict when reporting metrics. Senior compliance leadership at my institution has suggested that having studies whose results have been submitted by the researcher but are still under review flagged as "Results pending" rather than "Late results" would be a more accurate indication of compliance.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

As far as I can tell, the current help files are not searchable. Sometimes I need the answer to a specific question and may not know where to look for it. Also, guided tutorials are fine for people who have no experience with PRS but are not helpful for people who know how to use PRS but need information about something they haven't encountered prior or they don't use often. Right now I use web search engine but it can be very inefficient.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Currently results are posted as soon as the PRS reviewers complete their review even if there are errors. CT.gov administrators have publicly admitted that this is being done, in part, to shame researchers. This actively dis-incentivizes researchers from entering their results early in order to be able to correct errors before they get posted since they will be posted with the errors regardless. If you really want to incentivize timely results information submission, please find a way to delay posting of records with errors until the 12 month submission deadline has been reached. At the very least, give researchers one attempt to correct the errors before posting them. Posting them immediately sends a message to researchers that it is presumed that they are trying to be deceptive instead of recognizing that there may be a lack of understanding of exactly how results should be posted and that honest errors can be made even by researchers who are trying to open, honest, and timely.

Submission No.: 163

Date: 3/11/2020

Name: Ellen Ciesielski

Name of Organization: UConn Health

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

As a PRS Administrator, I do not have professional duties related to extensive use of the website and so, do not have comments for this section.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

No comment.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

No comment.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

No comment.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

As a PRS administrator assisting in registration and results posting, I have noted that the PRS Help Menu lacks an interactive element. Making Help Menu offerings more dynamic would make the system easier to navigate, saving time on the part of both the user and the Administrator, and saving frustration on the part of a novice user. For the novice user, it is not obvious how to perform basic functions necessary to maintain a record, like adding access for other users, or approving and releasing a record. Below I propose four specific additional Help offerings to help alleviate these common issues.

Pop-up Windows:

Many times, a Responsible Party has “approved” an update to a record and logged out without “releasing” the record. The record then sits in limbo because the user did not understand that an additional step is required. Adding pop-up windows with pertinent messages or reminders would resolve these types of chronic issues. If a Responsible Party clicks “Approve” but not “Release” the pop-up window message might read, “Without clicking Release, this record will not be submitted to ClinicalTrials.gov. Would you like to proceed?” Related, consider allowing Responsible Party PIs to click a single button to release the record for its quality assurance review.

I also have found that many users end their interaction with the system unaware of “next steps.” I propose adding a “What’s Next?” pop-up window that appears prior to logging out. This window would remind users when they will need to log in next to the system. For example, after a record has been successfully submitted the message might read, “Your record had been submitted. You will next need to log in to update the record with any changes in recruitment status, etc. Please see <update requirements>.”

Hover Text:

Adding Help in the form of “hover text” that appears when the mouse hovers over a term on the screen would also facilitate record registration. Users are more likely to spend time reading hover text than clicking on the Definitions link that is currently provided at the top of the page.

Format Restrictions:

Specific formatting requirements need to be built in to the system so it is impossible to enter data in an incorrect format. For example, for properly formatted inclusion/exclusion criteria, required bullet formatting should appear automatically for each criterion entered into individual entry fields rather than the current open text box.

Revising Field Titles/Adding Questions:

For fields that are consistently entered incorrectly by users, I propose trying a new way to get at the same information, by varying the semantics, and providing more detail. Asking a question rather than using a field title may also elicit the proper response. The “Time Frame” field in the Outcome Measures is an example of a term that is vague and ambiguous. The desired response is very specific and can be difficult to surmise, which results in records consistently returned to users.

Related, the feedback we receive on records returned to us can be very confusing. When feedback is generic and not customized to the individual record, it can be difficult to decipher what action to take. I am concerned that users tend to receive identical feedback for the same errors, even multiple times. More personalized critique, including examples and suggestions, would be appreciated.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

1. The ability to identify the regulations or agencies requiring the registration for individual records would be very useful to me as a PRS Administrator and to my organization’s processes, which are currently decentralized. For example, I would recommend adding a field that identifies the study as an NIH clinical trial, an “applicable clinical trial,” and/or intention to comply with ICMJE policy, etc.

2. Allowing PRS Administrators the option to be copied on all correspondence with users would make communication efforts more transparent. It is difficult to determine where possible miscommunication originated if the PRS Administrator is not receiving individual reminders and notices. An added bonus would be to have access to the standard wording of this correspondence so that I could help users anticipate what they should receive from the system. However, recognizing that various institutions operate differently, it should be an opt-in option.

3. I have received feedback from users that regular automated messages about individual record status would assist them in their efforts to remain compliant. More reminders from the system should be sent to users automatically prior to an error messages appearing in the record. Automated emails should also be sent at intervals when a record has remained in limbo (an updated record has not been approved/released).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

No comment.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The new “Hot Off the PRS!” newsletter has been a welcome form of communication and I appreciate it as an ongoing source of information for all users.

The Support Materials webpage is overwhelming due to the amount of links and resources. I would suggest simplifying the look of the page and highlighting where novice/infrequent users can go for information.

The Review Criteria document is useful for trouble-shooting; however, a more timely remedy for commonly found issues would be to implement pop-up window reminders and Help hover text as proposed above. The Review Criteria document is lengthy, and users are generally not accessing training materials, due to time restraints.

So, while training materials and video presentations are helpful for the dedicated user, changes to entry system itself will yield the biggest improvement across all types of user submissions.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

One way to recognize efforts on an individual-level is with real-time “virtual reinforcement” of the work done to bring a record back into compliance. This can be accomplished by embedding recognition for the efforts in the system itself, using gold stars, changing colors, or dramatic disappearance of error messages. We have learned from the popularity of modern app games how these small, free, visual images subtly reinforce behavior and at the very least, add a bit of fun and satisfaction for the user.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

No comment.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

No comment.

Submission No.: 164

Date: 3/11/2020

Name: Nate Root

Name of Organization: PHUSE and Ionis Pharmaceuticals

Attachment: PHUSE Response to ClinicalTrials.gov Modernization RFI 2020.pdf



Kent Innovation Centre
Millennium Way
Broadstairs
Kent
CT10 2QQ

Reference: PHUSE Data Transparency Group's Response to NOT-LM-20-003: Request for Information (RFI): ClinicalTrials.gov Modernization

Attention: ClinicalTrials.gov Information Team, National Library of Medicine

11 March 2020,

We would like to thank the NLM for the opportunity to review this important request for information for the modernization of ClinicalTrials.gov. The comments and answers were developed by a subgroup of volunteers from the PHUSE Data Transparency Working Group, consisting of Protocol Registration and Results Disclosure experts. Please find our comments in the pages below, which are not prioritized in order of criticality, though some may be more straightforward to implement and so could be considered first. We hope they are useful.

PHUSE is an independent, not-for-profit organization run by volunteers. Since its inception, PHUSE has expanded from its roots as a conference for European statistical programmers to a global membership organization and platform for the discussion of topics encompassing the work of data managers, biostatisticians, statistical programmers and eClinical IT professionals.

The Data Transparency Working Group was launched by PHUSE in 2014, gathering a cross-multi-stakeholder team including pharmaceuticals, CROs, software professionals, clinical trial disclosure experts and academics to share expertise knowledge, develop data transparency standards, and take on current challenges in the environment. The Working Group released, in particular, the **Clinical Trials Data Transparency Toolkit: Clinical Trial Transparency & Disclosure - A Global View**, which is used by numerous organizations to review current global regulations and requirements for Data Transparency.

PHUSE is also a stakeholder of the FDA, EMA and PMDA and hopes there will be other opportunities to assist the NLM with relevant regulations or guidance where its expertise can add value.

We would like to acknowledge the importance of public disclosure to patients, family members, researchers, and regulators, and would encourage the NLM to continue to work with other regulators to promote global harmonization where possible.

PHUSE recognizes that system updates need to be viable for all Responsible Parties and appreciate the breadth of the community invited to provide comments to ensure that solutions that are viable for all. We are also mindful that information disclosed cannot be promotional in nature, whether deliberately or accidentally so, and our following comments strive to maintain the non-promotional nature of this registry.

Respectfully submitted on behalf of the PHUSE Data Transparency Working Group,

Nate Root
PHUSE Data Transparency Project Lead

1. **Website Functionality.** NLM seeks broad input on the [ClinicalTrials.gov](#) website, including its application programming interface (API).
 - a. List specific examples of unsupported, new uses of the [ClinicalTrials.gov](#) website; include names and references for any systems that serve as good models for those uses.
 1. Improvements to support complex clinical trials with multiple parts and/or multiple protocols (e.g., umbrella trials) in the protocol registration – for example:
 - Some studies include “Parts” in the registration where Part A and Part B include two separate, randomized patient populations but are performed chronologically, which may include separate start and completion dates for those specific populations, as well as specific outcome measures for each part.
 - Studies may include the same control groups across the different protocols.
 2. In relation to comment #1 above, it would also be helpful to have the ability to link records together in ClinicalTrials.gov, similarly to connecting NCT#s for Expanded Access Records; for example, linking between a master study and the sub-studies of an umbrella trial or related trials, such as a global study and an extension study (current guidance states to enter this information in the detailed description).
 3. The ability to upload or generate a graph/chart in the results for a specific outcome measure to more appropriately represent the data.
 4. Pre-populated reporting groups in results reporting, similarly to EudraCT (i.e., per protocol population, safety set, efficacy set) where the population descriptions, arms, and N=X are saved and the user is then able to select that population for each outcome measure instead of having to enter/edit it for every outcome measure, which would reduce the chance of manual entry error.
 - b. Describe resources for possible linking from [ClinicalTrials.gov](#) (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.
 1. In the results portion, provide a field where there is an optional link for postings that do not require results disclosure (e.g., for publications, lay summaries, organizational trial sites, etc.) instead of listing them in the citations field, which would provide users proof of due diligence for results reporting.
 2. Adding a link field in the “Overall Contacts” field in PRS (within the Contacts/Locations) to provide study specific website links or resources for patients; for example, a clinical trial website that provides resources for patients that is more user friendly.
 - c. Provide specific examples of how you currently use the [ClinicalTrials.gov](#) website, including existing features that work well and potential improvements.
 1. For many organizations in this working group, ClinicalTrials.gov is used as a standard for registering and disclosing studies, not only per global regulations but also for organizational policy standards, and other requirements like ICMJE recommendations, as it is recognized and respected globally; this includes all interventional studies (Phase 1-4), as well as some non-interventional studies (natural history, chart review, epidemiology).
 2. The “Other ID’s” field is particularly useful when it comes to quickly searching for other possible registries in which the study is listed.
 3. The results on ClinicalTrials.gov are useful for researching comparable studies that are ongoing or recently completed, as well as secondary-purpose analyses such as estimation of bias and certain types of meta-analysis not requiring Individual Patient Data.

4. As we try to be as transparent as possible, we are at times restricted by the character limit of some of the fields, which may lead to the inability to fully explain results and potentially receiving a Major Issue comment; we recommend the following fields to be increased:
 - Recruitment Details – Expand to 500 Characters
 - Pre-assignment Details – Expand to 100 Characters
 - Milestone Title – Expand to 62 Characters
 - Other Reason (For Reason Not Competed Data Type) – Expand to 200 Characters
 - Category or Row Title – expand to 100 characters
 - Arm/Group Title – expand to 100 characters
 - Baseline Analysis Population Description – expand to 500 characters
 - Measure Analysis Population Description – expand to 500 characters
 - Analysis Population Description – expand to 500 characters
 - Limitations and Caveats – expand to 350 Characters
5. While there is a plethora of great guidance resources, it can sometimes be challenging to find a specific topic, so we suggest to add “pop-ups” or “info links” to the specific Data Element Definitions next to each field for easy referencing and specifying specific sections of the FDAAA Final Rule for easy referencing; this is useful especially for new users or those who do not frequently use the system.
6. Due to the broad spectrum of Observational Studies, it can sometimes be difficult to “retrofit” a study design into the current Observational study template; it would be helpful to make updates to the observational “template” and/or fields to better align with non-interventional studies – for example:
 - Chart Review studies – there are no locations, which is a required field and can be misleading to a patient if they think there are enrolling sites when there are not any.
 - Natural History Studies – consider adding “assessments” rather than primary and secondary outcome measures, as these studies are to just understand the disease.
 - When trying to “retrofit” studies, often we take time to request feedback from the NLM on how to fit these studies within the current template – adding additional study types would benefit the time/bandwidth for both the responsible party and the NLM (e.g., NCT03889444 and NCT03868254).
7. The use of the History of Changes section of the ClinicalTrials.gov public website is useful, however when only the “record verification date” is updated, the History of Changes reflects an update to the Study Status, which can be misleading; we suggest to add a “record verified, no changes,” or similar status.
8. Additionally, a way to download all History of Changes would be helpful rather than having to open each release individually or comparing two records on the public site.
9. The search functionality of ClinicalTrials.gov, specifically the advance search, is very useful in researching recently approved records for verification of similar outcome measures before submitting for NLM QA review; this is helpful both for registrations and results.
10. Adding a “date acquired” or “date transferred” field would be helpful to see when the legal responsibility has changed Responsible Parties as well as a “sponsorship has changed” identifier when relevant; it is understood that a definition of either date would need to be developed and entered into the Data Element Definitions.
11. ClinicalTrials.gov results data can be useful in the context of quantifying the risk of re-identification when disclosing individual patient data or clinical documents. The registry can be used to evaluate the number of patients and their characteristics in

- similar studies (the reference population) to the study at stake when using statistical estimators for residual risk analysis.
- d. Describe if your primary use of [ClinicalTrials.gov](#) relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.
1. In addition to the response to 1.c.1 above, the studies registered by this working group span globally across several therapeutic areas, study designs, population sizes, and indications from rare diseases to common conditions. Using ClinicalTrials.gov as a standard registry allows for organizations to list consistent, unbiased information accessible to the public. As mentioned in 1.a.1 though, the system currently seems focused and limited to a “standard” interventional study design, limiting the ability to appropriately capture some study designs in the registration, as well as results disclosure; for example, only allowing for one specific unit of measure for each outcome and requiring all separate measures to be disclosed separately (e.g. PK parameters).
 2. In relation to 1.c.3 above, when researching comparable studies that are ongoing or recently completed, a systematic search may be used which could require more specified search criteria, like studies that are randomized vs. open label. It would be helpful to include more study design criteria in the advanced search.
2. **Information submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the [ClinicalTrials.gov](#) Protocol Registration and Results System (PRS).
- a. Identify steps in the [ClinicalTrials.gov](#) registration and results information submission processes that would most benefit from improvements.
 1. A ticketing system for queries would be very helpful, similar to the EMA’s help desk, that can track open requests as well as include an urgency scale (high, medium, low); the current process of direct email has no timeframe of response or urgency level. We do appreciate the staff at the NLM for providing their time and expertise to respond to these queries, a ticketing system could be beneficial to both Responsible Party and QA reviewers.
 2. Also, setting up a mandatory instant QA validation system to check for inconsistencies/ discrepancies prior to submitting, similar to the EudraCT system, would provide benefit to both the responsible party and QA reviewer, for example:
 - Region of Enrollment
 - Score/Scale Description Missing
 - Wrong unit of measure based on outcome measure title
 - Number of deaths in reasons for discontinuing study greater than in the All-Cause Mortality table
 3. A way to upload site information in the Protocol section similarly to the Adverse Event excel template that is currently available for use.
 4. Develop a library/database of commonly used outcome measures (e.g., common PK parameters or “Change from Baseline” measures) with a possibility to insert them into the outcome measures in a registration posting.
 5. Consider tying a single QA reviewer per NCT# so the same reviewer oversees the lifecycle of a single NCT#, as well as aligning experiences and/or training in specific therapeutic areas (this aligns with the recommendation above to add an outcome measure library).
 6. A description for commonly used scores/scales would be helpful in determining what the NLM is looking for in terms of descriptions; a disclaimer would be

necessary to state that these are “commonly used” but may change per study specific measures.

7. When an estimated milestone date (e.g., primary or study completion) has passed, an automated notification to the Responsible Party would be helpful as a reminder to update it.
 8. Suggestion to keep decimal places consistent for all PRS generated calculations; specifically, in the AE section the auto-population of percentages are giving inconsistent decimal places.
 9. In the arm descriptions (in registrations and results), if changes are made to one arm in a section, it would be helpful if the system can automatically update or ask if changes should be copied to other sections as well.
 10. When results are entered as rows (instead of categories) in the Baseline Characteristics section, the public view of this data does not change. We suggest not receiving QA comments for such cases (e.g., NCT02487030 and NCT02600351).
 11. In the guidance for the intervention fields, it is unclear if we should include dosage form, frequency, and duration in the intervention description or arm description; QA comments have been received regarding this in the past. For clarity, it is best to include dosage in arms only if the doses differ per arm. It would be helpful to include the following text in the PRS when entering arm/group descriptions: “Do not repeat information already included in intervention descriptions.” Alternatively, we suggest making the interventions field optional.
 12. Is it possible to change the order of the interventions per arm? Using the cross-reference module, it automatically presents the interventions in the order entered into the PRS. However, for some arms (example: NCT03100942), we may want the order of the drugs presented in the order received during the study.
 13. When entering Eligibility Criteria, the data entry box is defaulted to a small view. Is it possible to have the default in a larger view; we also suggest separating the inclusion and exclusion criteria into individual fields instead of one field.
 14. We suggest the acceptance of special characters into the registry postings (e.g., α, β, μ, subscripts/superscripts, or any non-keyboard symbol).
 15. The ability to choose which XMLs to download if wanting to download multiple records; currently, there are only 2 options (download each one individually or all at once).
 16. The ability to “shrink to fit on one page” when downloading the PRS draft receipt so all columns are viewable as shown on the portal.
 17. Provide XML downloads and accept XML uploads of individual sections of the posting, similar to the ability to upload AE information; PharmaCM and other software systems currently have this ability.
 18. Record updates to add links to external resources (e.g., publications, IPD data sharing, Additional information) should be possible without triggering re-review of other data fields that were not changed.
 19. Remove the legacy fields from the “Oversight” section to avoid confusion.
- b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
1. Provide a record of “commonly seen” Major Issues to help users review, as well as a way to search for each Responsible Party's Major and Advisory issues within their own PRS account.
 2. With more organizations requiring the registration of non-interventional studies per company policy, it would be useful to provide updates to the observational

study records (e.g., incorporation of patient years for observational studies; see also 1.c.6 above).

3. Add a record review notification for when results have been reported on the primary outcome measure/interim analysis, but the overall completion date has not yet been reached (e.g., results needed for remaining outcome measures).
- c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the [ClinicalTrials.gov](#) website.
 1. Adding a “Date Terminated” in case a trial terminates early. This may be considerably later than the date last data were collected, as the decision of whether or not to terminate the study is established by the Responsible Party.
 2. Consider adopting recommendations emerging from ISPOR’s Real-World Evidence Transparency Initiative (<https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative>). Some new functionalities may encourage voluntary prospective registration of non-interventional hypothesis testing (e.g., time stamps, “lock boxes” for confidential documents), and prospective capture of detailed information about planned analyses, could improve validity of study findings.
- d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.
 1. The checklists are useful when developing a submission and to integrate into internal quality review processes.
 2. Examples of study types currently in the “Training Materials” section of ClinicalTrials.gov are very helpful; however, we’ve noticed the style is not consistent throughout, so it would be helpful if NLM provided a preferred style for each section to promote consistency amongst Responsible Parties.
 3. The FAQs on ClinicalTrials.gov are very helpful.
 4. The Planning Report currently only shows “Update Expected” for 1 year from the record verification date. It would be helpful if the report included when updates are expected 30 days following the primary or study completion dates or if the report could be used for tracking when updates are needed per company policies/procedures (e.g., if our SOP requires monthly updates)?
 5. Add date of delayed results certificate (DRC) submission in PRS for ease of checking compliance of studies (especially those acquired or legacy studies). DRC details are unavailable once the results posting is started. This will provide a readily accessible audit trail for the Responsible Party QC to confirm compliance to regulation and for inspection readiness
 6. Consistency in keeping “Record Log” field updated in PRS at the bottom of each record. In the past, the details added in the Record Log have not always been consistent. We have seen this become more consistent recently with notes regarding there being QA comments in the record. We would like to understand under what conditions are notes added to the Record Log field and if there are guidelines for NLM reviewers.
- e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.
 1. We suggest the ability to check for submission success rates of the Responsible Party, similar to the report the NLM provided per request in 2018. This could be an annual report provided to each responsible party and/or a live report based on records released within that PRS account.

3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
 - a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.
 1. Adoption of a standard protocol template for global harmonization alignment (like the TransCelerate CPT or the WHO Trial Registration Data Set (TRDS) with 24 standard registry template fields) and being able to then import/export data from that template directly into and out of the PRS via XML (there are currently “smart” protocol templates available that have this capability for export).
 2. Provide more options for entry of voluntary observational studies for alignment with study design, conduct of study and ease in entry. (e.g. Date of data extraction, rather than study start date) is more easily understood for some retrospective designs such as chart review/sec databases designs. Consider definitions from the ENCEP/EU PAS Register.
 - b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.
 1. Bayesian statistical reasoning and/or calculations to improve adaptive clinical trial design registration and results.
 - Reference: FDA Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics, Section VI. SPECIAL CONSIDERATIONS AND TOPICS, Part B: Bayesian Adaptive Designs
 - Reference: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657986/>
 2. Using CDISC Standards (CDASH, SDTM, and ADaM) would be helpful in consistent results reporting and data utility when it comes to secondary analyses.
 - Reference: <https://www.cdisc.org/standards/foundational/cdash>
 - Reference: <https://www.cdisc.org/standards/foundational/sdtm>
 - Reference:
https://www.cdisc.org/system/files/all/standard_category/application/pdf/adam_ae_final_v1.pdf
 3. Consider innovative technical solutions (e.g. AI) for “smarter” search results and automatic QA validation check.
 4. As mentioned previously, adopting recommendations emerging from ISPOR’s Real-World Evidence Transparency Initiative may encourage voluntary prospective registration of non-interventional hypothesis testing.
 - Reference: <https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative>

Submission No.: 165

Date: 3/11/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Great fund of knowledge but not easily helpful to those of us with specific cancer. Suggest one place for studies of each major type of cancer which is updated often.

Submission No.: 166

Date: 3/11/2020

Name: Zach Weingarden

Name of Organization: TrialAssure (MMS Holdings)

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

As a disclosure management software system, we utilize the direct import API to upload study data and find that this works well

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our primary use involved a wide range of studies, and we find the existing search and filtering parameters to be adequate for our needs.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Summarization and query resolution

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Being able to pull information in from a CTMS – specifically site information, which takes a considerable amount of time to update on a monthly basis. Being able to download registry queries into a report for metrics reporting (KPIs, etc.). Being able to download validation messages (errors, warnings, notes) in a similar fashion. Increased functionality in APIs allowing outside systems to pull this information from ClinicalTrials.gov and return updated data.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Being able to upload pre-generated tables that fulfill reporting requirements, rather than manually populate the tabular structure in PRS. I'm thinking along the lines of being able to upload actual tables/documents – not just uploading something that populates the registry fields. This would cut down on the amount of time it takes to register a study or post results.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Advising staff to give more detailed and concrete responses to nuanced user questions, rather than just pointing to the regulations that are not easily interpreted by most users.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Possibly some collaboration with Good Pharma Scorecard or other industry organization that recognizes compliant sponsors. A display of the current top-10 pharma companies on the clinicaltrials.gov home page, for example.

Submission No.: 167

Date: 3/12/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

better functionality for exporting total number of sites and number of sites per country, also including enrollment duration and rate. Citeline as a potential reference site.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

unknown.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use the website to look for competing clinical trials to assess competition in a specific indication as well as looking at completed trials to assess what enrollment rates were achieved.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Being able to limit studies by interventional or observational, location, drug helps me better assess competition in order to make recommendations to pharma companies on where to conduct new trials.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

further breakdown based on age or cohort (if study includes more than one), would be beneficial to draw conclusions relevant for future studies.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

not applicable

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

not applicable

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

not applicable

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

unknown

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

unknown

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

unknown

Submission No.: 168

Date: 3/12/2020

Name: Neha Tickoo

Name of Organization: Kinapse

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1. ClinicalTrials.gov has separate tabs that capture information on "What's New, Trends, Charts" etc. If these features are made more visible directly on the homepage, it would be really useful. Many users may not go to specific sections or tabs unless they are aware of where to look for the information. Therefore, having the information on the homepage will make these features that ClinicalTrials.gov already offers more visible/accessible to the general public. For example, something like the home page for the National Institute of Health Research UK (<https://www.nihr.ac.uk/>).

2. The presentation on ClinicalTrials.gov can be made more user-friendly by use of graphics and/or lay language. If we can have a lay language presentation for information on ClinicalTrials.gov in addition to how the information is presented currently, it would make it easier for the general public to understand the information. For example, protocol information can be categorized into two sections - one technical version that is currently available and another simplified version of the same information with friendly headings/captions for the patient and patient families. (For Reference:
<https://bepartofresearch.nihr.ac.uk/trial-details/trial-detail?trialId=2969&location=&distance=>)

3. On the search results page, there should be an option to sort studies based on study dates (e.g. first submitted, study start date or first results submitted dates). This will help in identifying the latest studies and can be viewed for reference by data providers.

4. A "Live-chat" option available through the ClinicalTrials.gov website would add value. There are many CROs and teams worldwide who can support in this area. ClinicalTrials.gov can connect with various disclosure specialist groups who are well versed with both ClinicalTrials.gov and PRS to help the public with their queries in real-time. Kinapse would be willing to help and support if ClinicalTrials.gov is interested in exploring this option.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. It would be beneficial to have ClinicalTrials.gov listed as one of the primary registries for the WHO International Clinical Trials Registry Platform (ICTRP). This would improve the consistency of information and reduce the effort needed to maintain information on multiple registries.

2. It would be good to have a feature of hyperlinking parent studies with extension studies. If the NCT number for parent studies appeared as a hyperlink in the extension study, it could be used to directly navigate to the parent study.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

1. Search/Advanced search option is something that we use very frequently while visiting the website. It would be very helpful if this feature is further refined and more specific advance search options are added to further enhance the user experience. Some suggestions:

- a) We often search for similar types of studies for reference and examples. This helps the data provider to maintain consistency within sister studies (for example, studies with the same type of allocation method/units of measure/intervention model etc.). Therefore, it would be good to have these options added in the advanced search field.
- b) It would be good if the advanced search option is updated to include additional filter options based on studies with Delayed certification filed.
- b) It would also be helpful if there is a feature or option for the user to search for an exact match based on their criteria.
- c) It would be good to add “Sponsor Name” search field directly from the Homepage rather than going to the advanced search option.
- d) In advanced search option for observational studies, it would be good to have further search options for “Prospective” and “Retrospective” studies to get more refined search results.
- e) Data providers may also use the website to perform different types of analysis (For example, how many studies had major issues identified when the results were first time submitted or no NIH issues within a given duration). Therefore, it would be helpful to have filters for “Study Results Posted in First Attempt”.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- 1) If ClinicalTrials.gov can align with EudraCT results format for multi-period studies, it would be helpful for data providers. This would help us to create arms specific for individual periods and avoid repeating arms that are not applicable in a particular period. In addition, this would make the US and EU result more aligned for such multi-period studies.
- 2) There should be an option or checkbox in PRS to apply the changes done in one section for reporting arms to all the other relevant sections. This will make editing and updating results considerably easier.
- 3) When safety is not collected/not assessed for a study, we currently need to report number affected as “0” and number at risk as “0”. Ideally, in such cases, there should be an option to select “NA” and then provide justification in a comment box.
- 4) Character limit should be increased for Pre-assignment, Analysis population and Time frame sections:

a) Analysis Population: Data providers are expected to include different types of relevant information in the analysis population section (like the definition of analysis set, the reason why data is not provided for all arms, clarification on any pre-specified intent in analysis, the reason why there is a change in overall population etc.). It sometimes becomes difficult to capture all information under the provided section due to character limit constraints. An increase in character limit will help us capture the information more clearly and would reduce numbers of comments/queries for additional information.

b) Participant Flow: Recruitment and pre-assignment details should have more character limits so that data providers are able to provide relevant justification for any specific approaches/reasons for a unique presentation.

c) Time Frame: Increase in character limit will specifically help in pharmacokinetic (PK) endpoints where we are required to provide detailed time frame likes “Treatment Period 1: Predose; Day 1; Hours 0.5, 1,240 hours”. It is sometimes difficult to accommodate the time frame within the available character limit. Additionally, per the recent approach, we have started receiving review comments on the abbreviation used in the outcome measure time frame. Therefore, it would make sense to have character limits increased for the field.

5. If we do not have the data value available for the outcome measures field, PRS only accepts Not available “NA” option. In our experience, “NA” may not be applicable for all cases and sometimes “Not Calculated (NC)” is a better option. Hence, we suggest accepting the inclusion of ‘NC’.

6. Detailed guidance/checklist on redacted protocol and SAP uploads along with the examples of general identifiers that can be redacted by data providers. This will help in harmonizing the redactions and reduce unnecessary additional redactions in the protocol and SAP documents.

7. Inclusion/Exclusion can be split as separate sections for more clarity and ease of readability.

8. Flexibility to edit Statistical Analysis Title manually. This will enable the data providers to provide a proper caption for the statistical analysis for example “MMRM Analysis for PBO versus Drug A” or similar.

9. Providing flexibility to select options in Measure of Dispersion/Precision section. For instance, if the Data is provided in form of ‘Mean’ and ‘coefficient of variation’, there is no drop-down option available to select “coefficient of variation” as “measure dispersion” while reporting “mean” as “measure type”.

10. The data providers should be given flexibility on presentation of the site/facility information, for example - sites that are actively recruiting should be placed on top, then the ones that are going to open soon, followed by the ones where recruitment has ended.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

1. Information on the expected dates for result posting is available in PRS. It would be good if PRS can be used to generate automated email notifications for PRS administrator to flag for any upcoming results submission (for example, sending out notification emails 3, 2, and 1 month before due dates).

2. It would be helpful if PRS would provide a direct hyperlink to some of the commonly used official manuals for cancer staging like RECIST or for Adverse Events like NCI-CTCAE criteria.

3. As per NIH guidance, individual outcome measures should include data from the current study population only. However, generally in PK/PD analysis, there is sparse sampling wherein sponsor collect data from other phases of studies involving the same molecule and perform analysis to reach meaningful results. In such an analysis, sponsors do not summarize data separately for the population of the current study, instead of summarizing for the pooled population (Population from current study + population from other studies). So we suggest including provisions and guidance for these type of results in PRS.

4. There should be more clarity/guidance in Data Elements for Study Start Date and Study Completion Date milestones for observational studies. The current definitions do not justify the scenarios for an observational study or studies where enrollment or LSLV may not be the criteria for study start and completion.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The review criteria, PRS user guide, checklists, auto-validation messages in PRS - all these tools help data providers maintain quality. First draft quality can be further refined if some additional checks within PRS are introduced to avoid known standard comments/queries. Some suggestions are listed below:

a) ClinicalTrials.gov has access to large dataset for outcome titles, descriptions of standard scales or common measurement parameters. It would be good if a link or guidance can be directly provided within PRS to help data providers with the best-preferred approach and acceptable outcome measure title/descriptions based on already available and acceptable information on ClinicalTrials.gov. We already have this feature for the “units of measure” field where PRS gives the option to select common units. We think it would be good if these suggestions are extended to other sections. This will decrease the time and effort of data providers and will also help in decreasing the number of major issues identified in results posting.

b) Auto-validation is a feature that ClinicalTrials.gov currently offers. Our suggestion is to extend this auto-validation feature such that some of the common NIH comments can be addressed before the first submission. For example i) One of the common NIH comments is to provide milestone field for safety population if it is not already a part of participant flow. If PRS can validate that the number in Participant Flow does not match the number “At risk” presented in Adverse Event section - a validation message should pop up requiring the data provided to justify for the discrepancy. ii) There should be a provision for auto-validation to match Actual enrollment in the protocol section with the total subjects started/enrolled in the result section. If the database identifies a difference, a mandatory justification field should be required in order to submit results. This will help in reducing some very common NIH comments/feedback.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

1. Statistics/reports generation for the quality and timeliness would be helpful for the data providers to assess their performance on a real-time basis.

2. Acknowledgement or certification for data providers if they are meeting compliance as per pre-defined criteria (Reports in PRS on compliance status or quality can be used by Disclosure specialist in tracking and accessing performance)

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

1. Increasing PRS character limits for various sections will provide the necessary flexibility to ensure submitted information accurately reflects the study design.

2. Currently, we need to segregate primary endpoints based on individual time points, whereas, we do report multiple time points within a single secondary endpoint. It would be good if data providers are allowed to create a single primary endpoint with multiple time points listed as categories/rows. For example, primary endpoint for plasma concentration or primary endpoint where Blood Pressure is being measured over time can be presented as a single endpoint and there is no need to create multiple primary endpoints.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

1. A consistent approach in ClinicalTrials.gov review: There have been instances in our recent experience wherein the same types of comments are handled differently by different reviewers (e.g. enrollment number discrepancy between “started” milestone versus “protocol registered enrollment” was considered as a major issue in one study and as an advisory issue in another study. Our suggestion would be to have a consistent quality review within the review team as well. This will be helpful in analyzing/assessing future quality standards and maintaining the same.

Submission No.: 169

Date: 3/12/2020

Name: Ivan Zipancic

Name of Organization: Synteract

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Good example of nice working system is Citeline's Trialtrove

Search Criteria improvements:

- 1) Filtering per region would be VERY useful (e.g. Europe, Eastern Europe, Western Europe, North America etc.)
- 2) Age ranges (instead of putting only specific age now, or fixed ranges, it would be useful to include ranges that can be set manually. for example lower than 17 years, such as 0-1 year only, for neonates studies for example)
- 3) Filtering per Therapeutic area
- 4) Filtering per word or "group of words" included in the study title
- 5) Include Planned as a study status (those that are announced in public domain that will start in the near future. would be useful for better assessments of potential competitive landscape - please see below)

Showed Results improvements (additional columns to include in excel download):

- 1) Enrollment Rates (patients per site per month, p/s/m): it would be very useful to calculate estimated p/s/m of the study.
- 2) Enrollment Rate Type (Actual (the most useful one: based on Actual Enrollment Duration (please see below), Actual Enrollment (# of patients) (Target Enrollment if Actual is not available) and # of reported sites), Anticipated (Using Anticipated Enrollment Duration (please see below), Actual Enrollment (# of patients) (Target Enrollment if Actual is not available) and # of reported sites), Predicted (Using Predicted Enrollment Duration (please see below), Actual Enrollment (# of patients) (Target Enrollment if Actual is not available) and # of reported sites). I understand the latest one needs complicated algorithm to be developed, so if Actual is prioritised it would be great)
- 3) Enrollment Duration (months)
- 4) Enrollment Duration Type (Actual (the most useful one: This information would be derived from or found on public domain in journal articles or abstracts, meeting abstracts or presentations, press releases etc.), Anticipated (Forecasted information as disclosed in the public domain by the study sponsor) or Predicted (CT.gov generated predicted information based on your own algorithm that could

analyse Actual data from a set of “similar” trials. I understand the latest one needs complicated algorithm to be developed, so if Actual is prioritised it would be great)

5) Countries: column with participating countries (right now, in the excel download it is difficult to see easily participating countries from “Locations” column)

6) Country/Sites: corresponding number of sites for each of the participating countries

7) Total # of Sites: just simply to include the # of total of participating sites

8) Investigators: name of participating investigators when their name disclosed

9) Age: instead of listing what is stated in the inclusion criteria it would be useful to make 2 additional columns: “Min Patient Age” and “Max Patient Age”. This would facilitate filtering for requested age groups.

10) Inclusion criteria: list of inclusion criteria

11) Exclusion criteria: list of exclusion criteria

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

If you decide to use information disclosed in the public domain (as I suggest above) usually found in journal articles or abstracts (e.g. PubMed), meeting abstracts or presentations, press releases, sponsors' web pages, etc. linking the sources of actual data would be useful if we want to recheck any of them, as well as sometimes updated information can be available and still not reflected on CT.gov. Collected in information from wide range of publicly available data would definitely significantly increase the quality of data provided by CT.gov.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I use CT.gov for a couple of specific functions:

- Enrollment Benchmarking: looking for estimated enrollment rates on studies similar to the one I am currently working on (focused on Completed and Closed studies) --> possible improvements detailed above (i.e. column for p/s/m, enrollment duration, total # of sites etc...)

- Competitive Landscape: looking for similar studies that are currently enrolling similar patient population, hence could impact enrollment of my study (focusing on Ongoing and Planned - including these would be useful to include, as suggested above) --> map function is handy but could be esthetically improved and given possibility to manually untick studies that you don't want to be shown on the map.

- Experienced Sites and Investigators: looking for Sites and PI that have already participated in similar clinical trials --> here several functions could be improved depending on your resources and scope to develop in this direction. If you are interested I would be happy to further discuss

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

(1) a wide range of studies, such as different study types, intervention types, or geographical locations

Several limiting criteria and suggestions for possible improvements detailed in the 1st window above (e.g. Filtering per region, Age ranges etc.).

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Complete, updated and accurate information on:

- 1) Recruiting status
- 2) participating countries
- 3) # of sites
- 4) enrollment duration
- 5) # of patients (for completed studies: # of targeted, screened, enrolled and completed patients)

Submission No.: 170

Date: 3/12/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

-email alerts for recently added/updated trials matching specific keywords
-displaying the relevance of a search hit in percentages
-optimization for mobile device displays OR Android/Iphone apps
-search option for primary and secondary objectives (PK, PD, efficacy, etc)
-search option for biosimilar trials
-suggestion of possible relevant trials (like suggesting similar publications on sciencedirect.com)

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

-
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Searching for competitor's clinical trials, I mainly use search related functions.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

(2) As a clinical research scientist my work is focused on specific therapeutic areas.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

-

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

-

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

-

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

-

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

-

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Submission No.: 171

Date: 3/12/2020

Name: Joseph M. Betz, PhD

Name of Organization: NIH Office of Dietary Supplements

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b.** List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Please see uploaded response letter as well.

Attachment: ODS Response to NLM RFI for ClinicalTrials.gov FINAL.pdf



Formal Office of Dietary Supplements response to NLM RFI for ClinicalTrials.gov Modernization
NOT-LM-20-003

The NIH Office of Dietary Supplements (ODS) appreciates this opportunity to provide NLM with information that will help improve the quality and utility of data included in ClinicalTrials.gov records. As described in NOT-LM-20-003, maintaining ClinicalTrials.gov results in greater public availability of information about clinical trials. This information, when accurate and complete, helps participants, practitioners, decide which clinical trials to participate in. It also enables investigators and funders to identify knowledge gaps and prioritize needed research.

To improve data quality, usability, reusability, and comparability, ODS proposes that researchers using chemically complex and inherently variable dietary supplements and other natural products as interventions be strongly encouraged to cite and follow the relevant guidance documents referenced below. **More comprehensive descriptions of clinical interventions and controls support the validity, comparability, and replicability of clinical trials and enhance the interpretation and generalizability of their outcomes.**

An encouragement for more complete characterization of the intervention is especially advantageous for clinical trials using dietary supplements or other natural products (including, but not limited to, foods, prebiotics, probiotics, and other substances derived from plants, animals, algae, bacteria, or fungi). Unlike the case for approved drugs, the specifications for many natural products used as clinical interventions are typically not defined with physical or documentary reference standards. **By not considering and reporting the identity, source, composition, and stability of dietary supplement and natural products used in clinical trials, the results of a study of an intervention's efficacy or effectiveness—and the generalizability of the trial itself—are limited at best.**

We are not calling for changes to ClinicalTrials.gov underlying policies or requirements. However, **providing guidance on what level and amount of characterization should be reported for different types of interventions will encourage best practices in research. This, in turn, will yield a more informative scientific literature for analysis by all user groups and enable investigators to better design replication or follow-on studies.** Since the creation of a ClinicalTrials.gov record is required prior to patient recruitment, prompting investigators to comprehensively characterize the dietary supplements and natural products used in their trials will increase their likelihood of doing so.

In practice, investigators would still follow the existing steps and rules for creating and updating a ClinicalTrials.gov record. However, the added directions we propose would provide them with resources to guide and prompt more comprehensive reporting (in ClinicalTrials.gov, peer-reviewed publications, and publicly available data repository).

For dietary supplement and natural product interventions, relevant guidance includes:

- NIH rigor/reproducibility guidance: Authentication of key biological and/or chemical resources at <https://grants.nih.gov/policy/reproducibility/guidance.htm>
- NCCIH product integrity policy for clinical trials: <https://nccih.nih.gov/research/policies/naturalproduct.htm>
- Recommendations for Reporting Randomized Controlled Trials of Herbal Interventions: Explanation and Elaboration. JJ Gagnier et al. *J Clin Epidemiol*, 59 (11), 1134-49, 2006. [PMID 17027423](#)
- CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration. C-W Cheng et al. *Ann Intern Med*, 167 (2), 112-121, 2017. [PMID 28654980](#)
- Improving Natural Product Research Translation: From Source to Clinical Trial. BC Sorkin et al. *FASEB J*, 34 (1), 41-65, 2020. [PMID 31914647](#)
- Center for Drug Evaluation and Research. Botanical Drug Development: Guidance for Industry. U.S. Food and Drug Administration; 2016. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry>
- Scientific rigor and credibility in the nutrition research landscape. CM Kroeger, et al. *Am J Clin Nutr*, 107 (3), 484-494, 2018. [PMID 29566196](#)
- Best practices for the design, laboratory analysis, and reporting of trials involving fatty acids. JT Brenna et al. *Am J Clin Nutr*, 108 (2), 211-227 2018. [PMID 29931035](#)
- Considerations for best practices in studies of fiber or other dietary components and the intestinal microbiome. DM Klurfeld et al. *Am J Physiol Endocrinol Metab*, 315 (6), E1087-E1097, 2018. [PMID 30130151](#)

ODS welcomes any questions NLM staff may have on this topic; please contact Dr. Joseph Betz, ODS Acting Director. We always look forward to opportunities to collaborate with our NIH colleagues.

Joseph M. Betz, Ph.D.
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NIH...Turning Discovery Into Health®

Submission No.: 172

Date: 3/12/2020

Name: Sarah Brookhart

Name of Organization: Association for Psychological Science

Attachment: APS Response to NLM RFI 3-12-20.pdf

March 12, 2020

ClinicalTrials.gov Information Team
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Dear ClinicalTrials.gov Information Team:

The Association for Psychological Science (APS) appreciates the opportunity to respond to “National Library of Medicine Request for Information (RFI): ClinicalTrials.gov Modernization” (NOT-LM-20-003). APS represents over 30,000 researchers who are dedicated to the advancement of psychological science. We appreciate and support the work NLM does to encourage timely reporting of research studies, provide a more complete set of studies to inform medical decisions, and offer valuable insight and recognition to experimental participants, researchers, and those who fund science. However, we are concerned over recent NIH policy changes, some related to ClinicalTrials.gov, which have created additional confusion and burden for our members.

As you know, NIH’s classification of basic experimental research with humans—called BESH by NIH—as clinical trials means that BESH studies must be registered and reported on ClinicalTrials.gov. APS agrees with NIH on the importance of registering and reporting BESH studies; in fact, psychological scientists have been the leaders in science-wide efforts to advocate for open and transparent research practices and products. However, APS and its members believe that the requirement to register and report BESH studies on ClinicalTrials.gov specifically is a significant and unnecessary regulatory burden on the area of basic behavioral science and neuroscience. As you may know, the behavioral science community strongly opposes NIH’s expanded definition of clinical trials and its associated policies. Over 3,500 individuals from research universities and institutions across the country have written in criticism of the change, as have 35 current and former members of NIH Advisory Committees. A range of scientific organizations, universities, and research coalitions also oppose the change. Moreover, the inclusion of these types of studies on ClinicalTrials.gov may draw attention away from true clinical trials posted on the site and impede patient and scientific access to applied studies directly advancing medical knowledge.

As experts in research reporting and registration, you know that there are numerous options for providing access to the findings of federally-funded basic research. We would welcome an opportunity to work with you to find an agreeable reporting and registration arrangement for BESH that does not involve classifying this research area as clinical trials or registering and reporting this science only on ClinicalTrials.gov.

Thank you for your consideration,

Best,



Sarah Brookhart
Executive Director

Submission No.: 173

Date: 3/12/2020

Name: Rachel Bent

Name of Organization: Dana Farber Cancer Institute

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

NA

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

NA

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Use of Public Clinicaltrials.gov website

1) This is a centralized source for regulations including FDAAA-801, Final Rule, NIH Policy, How To's, Frequently asked questions, and a search function for Clinicaltrials.gov record numbers.

2) Improvement:

- a) Increased character limits on search engine field for "Title field"
- b) More dynamic usability interface in "Submit Studies" and "Resource" sections of public view of the Clinicaltrials.gov.
- c) A Search "Key Word" Query Field in Resources and Submit Study Sections.
- d) More Defined Sections in the Submit Studies and Resource Sections to increase readability of text. Unable to search in the Resources or Under Submit Studies> Why should I Register and Submit Results> Add other Requirements, FINAL Rule, ICJME etc for a quick link to requirement
- e) Create further filtering function linking to grid of all regulations.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Primary use is to locate cancer relevant trials on Clinicaltrials.gov.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Increase Search and Review Function capability from Record List View of the PRS

a. Ability to select multiple records at one time for review in the “Record List” view

b. Ability to download multiple trials by “Protocol ID” or NCT number from the PRS.

2. Add all 39 Planning Report “Elements” fields to the “Record List view” Show/Hide Columns

3. Specific Protocol Design Investigators and PRS administrators identify difficulty with accurately reflecting specific protocol designs in registration and results reporting modules. Specific study designs include:

a. Master protocols

iii. Adaptive trials

iii. Social behavioral research

iv. Observational studies

v. Observational Trials with a nested Interventional arm.

4. Extension of the Glossary Function from the Public PRS view

a. On the ClinicalTrials.gov public site, the Glossary is accessed by clicking an information “i” link next to a data element. Clicking this link opens a panel on the right which contains only the definition for that data element. Links are provided so the user can easily access complete set of definitions, if desired.

5. Increase ease of use with the Data Element Definitions

a. It is helpful that clicking the Definitions link takes the user to the beginning of the part of the definitions page that corresponds to the section and module currently being edited, but the definition being sought is often quite a bit further down the document, often not visible until the user scrolls down the page.

b. “Hover” feature over the term

c. Having a function similar to the public site Glossary, or a “What’s this?” link by each data element would improve the ease, speed, and quality of information entry because it is more likely that the user can quickly get to the needed information

6. Planning Report Increased Functionality

a. Add the following elements under the ‘Show/Hide Columns’ in order to allow this information to be included in the Planning Report:

- i. Ability to schedule when report will run and sent via email as csv or excel format
 - ii. A 'Select All' element (rather than having to select all 39 options)
 - iii. 'Other funders'
 - iv. 'Access list'
 - v. The corresponding answer to 'anticipated/actual' option associated with study start date
 - vi. Separate Field for Record owner email address
 - vii. 'Problems' added to the list of options
- b. Under the Custom Filter, allow the user to define date ranges upon which to generate the Planning Report.
- i. Standardize the date format. The dates for "Results Expected", "All Results Expected", "Study Start Date", "Primary Completion Date" and, "Study Completion Date" are a mix of MMM-YY (e.g., Jan 21) and MM/D/YYYY (e.g., 1/1/2021). This causes problems trying to analyze data. "Update Expected" and "Verification Date" always appears as MMM-YY (e.g., Jan 21) and "Last Update" and release dates always appears as MM/D/YYYY (e.g., 1/1/2021).
 - c. Have the default Planning Report be for "All records" and/or switch the positions of the tabs. On the Planning Report screen "Action Expected" is the tab on the left and "All records" to the right. On the Home screen "All Records" is the tab on the left and "Problem Records" to the right.

7. Spelling Feature:

- a. The spelling feature is very helpful but this has to be accessed separately from the Record Summary page.
- b. Spell check tool that identifies and highlights spelling error within the document, i.e. similar to a word document. Currently, the spelling tool only identifies the word and section the error is in, it does not highlight the word in question.

8. Text Block Errors

- a. Ex. ERROR: Textblock contains an invalid character at position: 3696. It would be helpful to have the text causing the error to be highlighted within the record.

9. Bullets Feature:

- a. 3rd bullet indent which corresponds to 3 dashes (---) in the PRS does not work consistently and will post as 3 dashes instead of bullet point

10. Increase Character Limit in Inclusion/Exclusion Criteria

- a. We have had a number occasions where the inclusion/exclusion criteria 15,000 character limit has proved an issue. My team with the Principal Investigator spends time carving out the IRB approved Inclusion/Exclusion criteria to fit the 15,000 text limit.

Trials that have an extensive inclusion/exclusion criteria as follows.

- b. Platform-basket-umbrella trials with a with extensive Inclusion/Exclusion Criteria
- c. Multi Arm basket platform screening protocol, that has an inclusion/exclusion criteria for the screening part of the trial and then an inclusion/exclusion criteria for each treatment on the protocol.

11. Ability to increase actual “width” of “Time Frame” field in Outcomes section.

12. Tracking Feature:

a. A tracking feature within the PRS that enables Investigators and PRS Administrators to see what revisions were made as a result of QC comments. Currently, anyone reviewing the revised document prior to release to ClinicalTrials.gov has to compare word for word to verify adequate changes have been made. It is only in the Approve Stage that the submitter can see the changes made. A possible solution is a side by side view of what was changed since the last update versus the last updated version. This would allow the PRS administrator to see the changes that were made. This would be similar to using the QA review comments window against the actual changes made in the record after they've been addressed. For example, if a study team makes a modification to the inclusion criteria for a study, it would be helpful to see where the changes were made. This is especially important when verifying against the research protocol that has been updated. In addition, a NLM enable hyperlinking within the QC comments to link directly to data element that received the comment.

13.NIH Flag and PCORI Flag Results Requirement, similar to ACTs or pACTs that are flagged and add “Results expected date” for these NIH or PCORI funded studies.

ii. Results Reporting

1. ClinicalTrials.gov has previously published a number of “Example Studies for Results Data Entry” and note that Investigators and PRS Administrators find these to be helpful tools. It would be helpful to develop guidance/best practices on both registration and results reporting submission.

2. Allow upload of graphs (e.g., JPEGs) to accompany data tables.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

An upload tool in a standard format (CSV for example) so that we can import study information from virtually any system.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

NA

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- 1) Useful documentation: Definitions provided in the PRS, Protocol Review Criteria document.
- 2. Additional Documentation Requested

- a) ClinicalTrials.gov QC Reviewers encounter many errors during their review of the Registration and Results Reporting modules. The creation of common QC comment scenarios with responses of best practices and solutions would be helpful. The scenarios could be posted on the Clinicaltrials.gov website.
- 2. The Brief Summary located in the Study Description section of the Registration module should be, as stated in the ClinicalTrials.gov Data Element Definitions, “written in a language intended for the lay public.” It would be helpful if the NLM worked with experts in the field to develop guidance and tools to assist submitters in developing a brief summary that clearly communicates the purpose of the research. Examples of summaries would be helpful as well.

3. Out Come Measure Help Section:

- a)The brief overview and then the more through explanation of Outcomes in the Protocol Review Criteria document is a very helpful resource. It would be helpful to have a table of contents in the Protocol Review Criteria document. This would make it easier to locate the guidance information.
- b) It would also be helpful to have examples (screen shots) of acceptable and unacceptable Outcome Measures in their entirety.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Consider track record of compliance when awarding NIH funds and give compliant organizations a competitive advantage when seeking funding

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

NA

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

NA

Submission No.: 174

Date: 3/12/2020

Name: [Not provided]

Name of Organization: Novartis

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Novartis will sometimes provide a link within the ClinicalTrials.gov registration to the public Novartis Clinical Trial Results website, for example, when we want to provide study results that may not otherwise be required by FDAAA, e.g. Phase 1 trials.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

a) With regard to Website Functionality, we propose that character limits be increased, in particular, for recruitment details, description fields, footnotes and limitations and caveats. We have gotten back comments from NLM QA review requesting that we add more detailed information and description of scales when there is not space to do so. We spend LOTS of time word-smithing

Some studies with complex designs, require a longer explanation for the reader to understand how patients were enrolled, and into which arms (e.g.; coming from a core trial into an extension trial).

b) For studies with similar designs and outcome measures, it would be helpful to have the ability to duplicate one study over to a new one to populate with new data, or duplicate sections of a study to another results record.

c) Uncontrolled and single-arm Pre-FDAAA trials should not be marked as Late. We have about 127 studies with this misleading designation. Our recommendation is to tag these as pre-Final Rule as an easy denotation for rapid exclusion when reviewing for new/outstanding NLM QAs.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Novartis utilizes clinicaltrials.gov to publicly disclose a wide range of studies with varying study types, intervention types and with sites in varying geographical locations. Novartis also registers non-interventional studies utilizing primary data collection or secondary use of data.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Novartis has identified steps in the clinicaltrials.gov registration and results Information Submission process that could benefit from improvement.

1. With regard to the IDP Data Sharing section, we provide a statement of our Data Sharing policy and a link to request data. We do not use the other fields. It is far more efficient to provide the information in one field.
2. With regard to Participant Flow, we request the ability to have different arms for multiple periods. We currently have to add all arms for all periods and input zeros for counts. EudraCT already has this functionality to remove arms within a period
3. With regard to Statistical Analysis:
 - We request the ability to duplicate statistical analysis section within and across endpoints.
 - With regard to outcome measures results, we would like the ability to combine different units in one table. For example, clarity would be improved if we have the ability to have units (e.g.; PK parameters, Summary statistics such as mean, median, min, max etc.) apply to categories, not to an entire table
4. With regard to Adverse Events reporting, Novartis has oncology trial results for which we are not aligned with the NLM reviewers on how the all-cause mortality table is to be completed. The NLM reviewers note the total number of deaths listed in the trial record being greater than the number of deaths listed in the “All-cause mortality safety” table. The NLM reviewers are requesting that total trial deaths in the oncology trials be added to the “all-cause mortality safety” table.

Novartis endeavors to submit clinical trial results according to FDAAA 801 Final Rule Jan 18, 2017. In the Adverse Event information section, there are three tables required, All-cause mortality, SAEs and Other AEs. The time-frame, i.e. the specific period of time over which adverse event data were collected, must also be reported.

In the majority of Oncology studies, adverse events are systematically collected until the end of study treatment + 30 days or end of study treatment + five half-lives, specified in days for a particular treatment, whichever is longer. Adverse Events and deaths occurring in this on-treatment period are reported in the Adverse Event Information Tables in the Clinical Study Report.

During the survival follow up period the subject is not on study treatment and the deaths collected are reported as part of an Overall Survival (OS) outcome but not as adverse event information. This reporting format is approved by the FDA, reference 312.32(c)(5), and is represented in the study protocol. In most cases, the Oncology Overall Survival outcome will contain more deaths than those reported in the adverse event all-cause mortality table. For studies where there is a survival follow-up the disposition/study flow may report the reason for end of study as ‘death’.

In reviewing, the NLM comments to oncology trial result submissions, We recommend that NLM add clarity instructions as follows: The time frame for Adverse Event information, which is the same time

frame for the All-cause mortality table, will be reported clearly from the patient perspective for e.g. "from enrollment to end of treatment + 30 day post treatment follow up" as specified by each protocol.

In Oncology there is not always a pre-specified treatment length. The study duration may be more driven by the Overall Survival events. However, it should be possible at the reporting stage to give a number (e.g. up to 24 months) that gives an indication of the treatment time-frame in question.

An Overall Survival table of total subject deaths during the trial, specifically deaths on-treatment plus deaths occurring during the post-treatment survival follow up will be provided in a table. This table of total deaths will correspond to the Overall Survival outcome measure represented in the unit of time.

See the Figure attached for a visual explanation.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Clinicaltrials.gov needs to be held accountable to review non-ACT study records in a more timely manner. Study teams at Novartis are disbanded very soon after results are posted or even before. Too much time is being spent on our end to recall what was done 3 to 6 months ago.

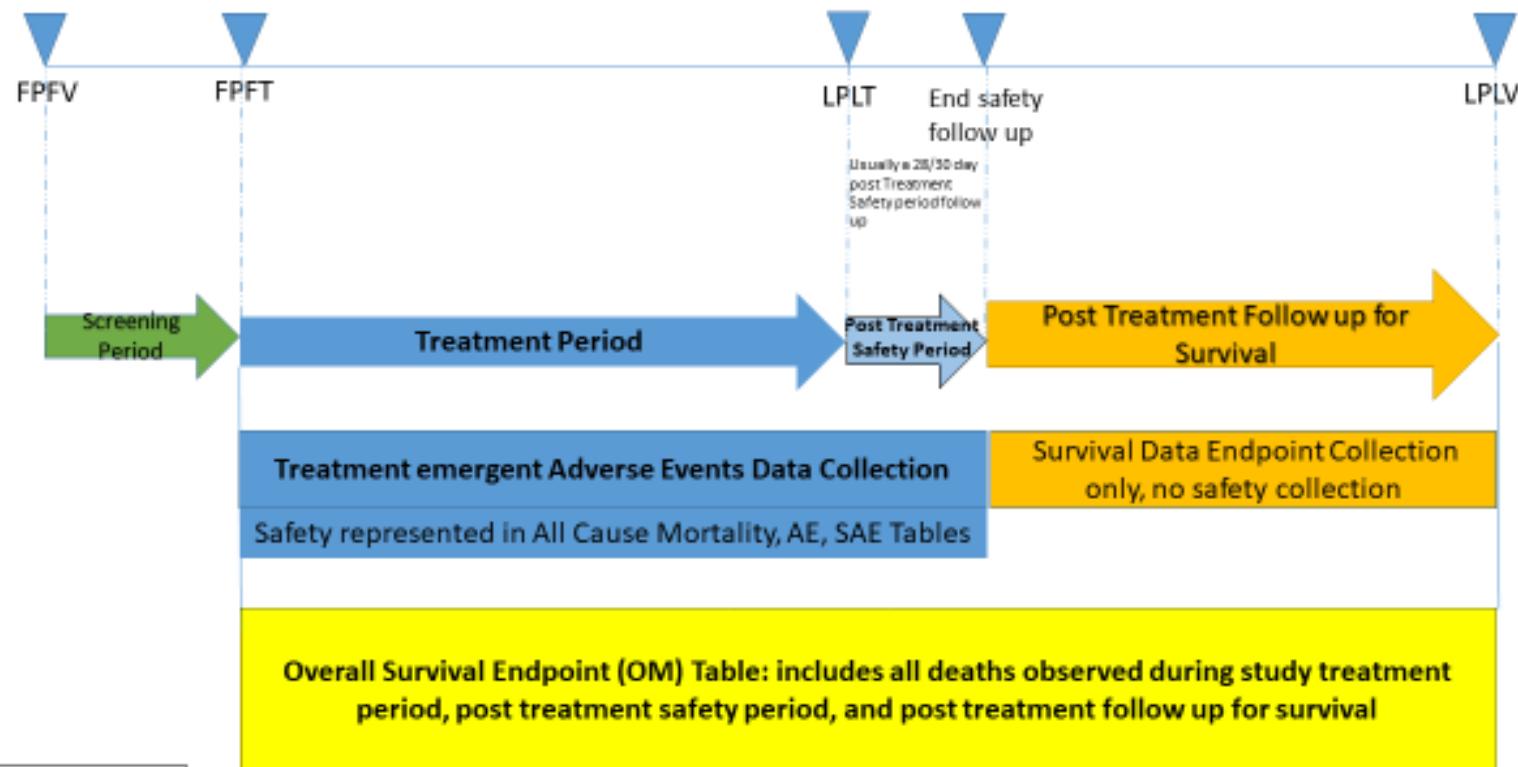
2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

With regard to NLM QA review comments:

- Different reviewers find different problems
- All problems are not identified at one time
- We propose that one reviewer be assigned to do all QA review for a given trial.
- Also, Novartis does not find that making QA review comments public (e.g.; cycle times), or showing publicly how many rounds of review took place adds to the usability or ease of understanding of these record, particularly for patients. We do think these metrics could remain in PRS and be useful for sponsors and for NLM.

Attachment: Oncology Study Overview of Safety Reporting Period and Post Treatment Survival Collection Period_Novartis.pdf

Oncology Study Overview of Safety Reporting Period and Post Treatment Survival Collection Period



FPFV: First Patient First Visit
 FPFT: First Patient First Treatment
 LPLT: Last Patient Last Treatment
 LPLV: Last Patient Last Visit

Submission No.: 175

Date: 3/12/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Global harmonization of regulation and registries would be ideal (EMA at minimum). It would cut down on resourcing, ensure consistency across registries, and make tracking and maintaining compliance much easier.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I work for a small sponsor company that specializes in rare disease areas. It can be somewhat difficult to find ways to have our data fit within the system limitations (ie. composite endpoints) at times.

We typically work with small patient populations in highly competitive disease areas. This can also be tricky as we have to include certain information to fulfill reporting requirements while trying to maintain competitive intelligence. One issue I've come across is sites that appear to be duplicates in the PRS do not both show up in the site list on CT.gov. For competitive intelligence reasons we do not provide the sites names, but we feel that it is still important to show that we have two sites in the same country/city/state/zip.

I also think increasing character restrictions in some fields would be helpful such as outcome measure descriptions and analysis population descriptions.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

For now our trials have a more limited range based on study design, but they are generally run in many countries. Some sort of global harmonization between registries would be ideal.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The method of submission is straight forward, but I find the QA review process to be inconsistent in two ways. First, different reviewers seem to use different criteria, so there have been times where one reviewer accepted a study, and then a almost exact replica of the study was not approved due to major comments. It came back twice and cause us to come very close to being out of compliance. Second, we have had results come back with major QA comments, resubmitted, and then come back again with different major QA comments. This may not be so much of an issue anymore since studies are now being posted with comments, but in the past it has caused significant delay in getting results posted and the delay was due to multiple rounds of QA comments that were not brought up in the first round.

It would also be great if questions sent to the CT.gov mailbox could be answered better. As I mentioned above, we sometimes have tricky scenarios that we have to fit into the limitations of the system. It is not always helpful to have a question answered with a reference to a regulation or FAQ. It would be great to receive more specific answers sometimes.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

As mentioned above, sites that appear to be duplicates in the PRS do not both show up in the site list on CT.gov. For competitive intelligence reasons we do not provide the sites names, but we feel that it is still important to show that we have two sites in the same country/city/state/zip.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Results Review Criteria is helpful, but it could be more detailed. In the data element definitions, I find some of the “conditionally required” fields to be somewhat confusing, as it is not always clear what the conditions for requirement are.

Submission No.: 176

Date: 3/12/2020

Name: Ashley McKhann

Name of Organization: Center for Biostatistics in AIDS Research

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Our current use of the website consists of checking the records for our center's studies or for other clinical trials with similar disease types and outcomes. The search features work well for identifying our own trials. One feature to add is the 'Applicable Clinical Trial' information on the public record of a study as a reference. Another useful feature would be a note to the Adverse Events table if a study has submitted its primary results but the study has not closed, informing the public that the Adverse Events summary results are not finalized and will be updated at study closure.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

-The main submission process to improve is the statistical analysis sections. Having these sections separated from the Data Table is inconsistent with current standards where p-values or confidence intervals are next to the data they are describing. The Statistical Analysis can then be limited to describing the statistical methods and related information. Further, while there can be multiple p-values to enter on a Data Table, generally the same methods are used for all comparisons within an outcome measure. For example "change in blood pressure from baseline to weeks 6, 12, 18, 24, 30 and 36" may be compared between treatment and placebo at each of the weeks (6, 12, 18, 24, 30 and 36). However, 2-sided p-values from Wilcoxon Rank Sum Test and a significance level of 5% would be used across all in this case. With the current set up, 6 separate Statistical Analysis blocks would have to be entered, with most of the information repeated in each of them. Having the statistical analysis results as part of the Data Table accompanied by a single Statistical Analysis Description on methods and related information will shorten records with many outcomes and comparisons, make it easy to connect summary results and their corresponding p-values, and greatly improve readability.

-Inclusion of a process to request a delay for secondary outcomes. There are occasions when the majority of the results are ready for submission but there are delays in secondary outcomes. In these cases currently, the record appears incomplete when a delay could be requested and shown to be approved in the record.

- There is an issue with the current submission process for Adverse Events via spreadsheet. After the spreadsheet results are uploaded, the total numbers of participants affected and at risk in each Reporting Group must be entered manually which defeats the purpose of automating the process.
 - A Results Module that could be automated via spreadsheet upload (similar to the Adverse Events section) is the baseline characteristics table since it is a standard table and certain baseline characteristics are required across all submissions.
 - It would be useful if Reporting Groups and their descriptions could be edited in one place and updated throughout the record. Once the Results Section is started, any edits to the Reporting Groups and descriptions must be made within each individual outcome measure, even if the same Reporting Groups were used throughout, carrying over from the Protocol Section or Participant Flow. Since Reporting Groups can vary across outcome measures, a separate editable section with all Reporting Groups and descriptions that have been defined would be helpful and time-saving.
 - Time to event outcomes could benefit from having the ability to upload a figure for the results. For example, having to use a numerical result such as median time to event may not be an accurate representation of the results of the trial, while a figure displaying the Kaplan Meier curves would more appropriately describe the data.
 - It would be helpful to have a way to respond to the PRS QA/QC review comments within the PRS study record, particularly in cases when a Major Comment or Advisory does not apply or is inappropriate and no changes are made.
- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**
- The Data Element definitions provided with each section are helpful when working through record submission.
 - The comments provided as part of PRS QA/QC review of a record can be hard to understand, especially since they must fit inside the major comments options (which themselves are very vague).
- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**
- Study Phase would benefit from expanding the options. A number of our clinical trials do not fit any of the options available. For example, PK/PD studies of drug interactions for drugs already approved, pilot studies, or studies with multiple cohorts where phase can vary across cohorts (e.g. NCT04193189 which is a phase III/IV study, as determined by NIAID, DAIDS). In those instances, the phase entered into ClinicalTrials.gov differs from that specified in the study protocol document which is uploaded at the time of results submission.

- The requirements for Outcome Measure Titles are not consistent with the definition of outcome measure. Outcome measures are measures – they are evaluated at the participant level and do not include summary statistics or analysis information. However, the PRS review comments consistently require specification of a summary statistic in the Outcome Measure Title, particularly for categorical outcome measures. For example, an outcome measure is “Hepatitis C virologic suppression” while “Proportion of participants with Hepatitis C virologic suppression” is an aggregate summary statistic used for analysis of this outcome measure. In our study protocols, outcome measures are correctly specified at the participant level. However, due to the ClinicalTrials.gov requirements the Outcome Measure Titles have to be edited for ClinicalTrials.gov purposes only. As a result, the Outcome Measures in the trial record differ from those specified in the study protocol and statistical analysis plan, both of which are posted on ClinicalTrials.gov. Please consider allowing the outcome measures to be entered as is in the Outcome Measure Title field, with further details on the analysis information or summary statistic used (e.g. “proportion of participants with Hepatitis C virologic suppression is shown in Data Table”) entered into the Outcome Measure Description field.
- The Results Section features and data elements would benefit from review to ensure they are adequate for early phase trials. The NIH policy that went into effect in January 2017 requires results reporting for all clinical trials fully or partially funded by NIH. This includes PK and phase I trials. The analysis methods for these trials can differ from higher phase trials. For example, they could include descriptive, by-participant, or graphical results which are challenging to fit in the PRS Data Table.
- Statistical analysis details for all secondary outcomes may not be necessary or of scientific value. An example is outcomes related to biomarker data (e.g. NCT02706717) where the protocol specifies comparing a large set of biomarkers between arms. Currently, a statistical analysis section is required for each individual biomarker and time point. This overly complicates the study's record, and the scientific value of all these comparisons in lengthy repetitive Results Outcomes is questionable.

Submission No.: 177

Date: 3/12/2020

Name: Jennifer Dexter

Name of Organization: National Health Council

Attachment: NLM ClinicalTrials.gov Modernization Comments Final.pdf



NATIONAL HEALTH COUNCIL
Celebrating 100 Years

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March 13, 2020

BY ELECTRONIC DELIVERY

Patricia Flatley Brennan, RN, PhD
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

RE: Request for Information (RFI): ClinicalTrials.gov Modernization

Dear Director Brennan:

The National Health Council (NHC) appreciates the opportunity to comment on the National Library of Medicine's (NLM) Request for Information on ClinicalTrials.gov modernization. Clinical trials are a vital part of the medical-product development process and often serve as the point of access to treatments that give people with chronic diseases and disabilities their best chance to treat their conditions. The NHC recognizes that ClinicalTrials.gov is a valuable resource to patients, providers, and sponsors, but improvement is much needed to ensure it serves that purpose. This is why we are pleased that NLM has requested information from the stakeholder community, and we urge the NLM to focus modernization efforts on making the tool more understandable and usable for patients.

Created by and for patient organizations 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, sustainable health care. Made up of more than 140 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses representing biopharmaceutical, device, diagnostic, generic drug, and payer organizations.

Our comments focus on making sure ClinicalTrials.gov is designed in a way that supports our goal of ensuring that all Americans, particularly those with chronic diseases and disabilities, have access to the health care they need. We

recognize that actively participating in clinical trials can serve as the best health care option for many of the patients we represent, and we want to ensure that the restructure of the site enhances patients' ability to understand the information about clinical trial availability to ensure patients and families make the best decisions possible.

Patient Engagement in Development and Oversight of ClinicalTrials.gov

This opportunity to provide input into the modernization of ClinicalTrials.gov is a positive first step in engaging patients, caregivers, providers, and advocates in ensuring the site serves as a beneficial tool for patients. However, there is a need for ongoing, dynamic input from patients and caregivers before, during, and after the redesign to make sure the modernization is truly effective for patients in the long term.

To ensure that the site will serve as a useful and effective tool for patients, **the NHC strongly recommends that the NLM create an advisory group of patients, caregivers, and providers**. This advisory group should be convened early in the process of the modernization and should continue to be active following the modernization to ensure that ClinicalTrials.gov continues to operate optimally for these stakeholders. The three core functions of the advisory group should be:

- Provide input and insights on the redesign and modernization of ClinicalTrials.gov;
- Help determine the best way to present and populate information for the target audiences; and
- Exercise a governance role in the development and utility of the site (i.e., not a tokenistic role).

We encourage the NLM to use best practices for patient engagement from other Federal agencies and the private sector. For instance, the Patient-Centered Outcomes Research Institute (PCORI) has changed their research paradigm to engage patients and caregivers. To encourage the spread of these patient-engagement practices, PCORI has assembled a repository of engagement-related tools and resources developed and used by PCORI awardees¹.

This kind of patient and family involvement has resulted in positive outcomes in other sectors of the Department of Health and Human Services. For instance, the Food and Drug Administration's (FDA's) Patient-Focused Drug Development program provides a good example of convening patients to learn how their conditions and treatments impact their daily lives. Many of the learnings from these convenings have included how to modify language to ensure the information on the site is understandable to greater numbers of individuals.

Similarly, there are examples of private sector initiatives to engage patients to design care delivery and programming. The NHC conducted research² to identify real-world examples of patient engagement in the health care delivery setting. The study showed that a consistently successful strategy that hospitals and health care systems employed to engage patients was

¹ <https://www.pcori.org/engagement/engagement-resources/Engagement-Tool-Resource-Repository>

² [https://nationalhealthcouncil.org/wp-content/uploads/2019/12/meaningful%20Patient%20Engagement%20in%20Health%20Care%20Delivery%20\(2018\).pdf](https://nationalhealthcouncil.org/wp-content/uploads/2019/12/meaningful%20Patient%20Engagement%20in%20Health%20Care%20Delivery%20(2018).pdf)

the development of Patient and Family Advisory Councils (PFACs). PFACs were initially introduced in 2006 by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to offer a structured and formal framework for the collaboration of patients, families, and health care professionals in decision-making, forming a mutually beneficial relationship where patients have a voice to become active participants in their own care. Patients are able to provide input on what matters most to them throughout their experience with the health care system, as well as recommendations on strategies that health systems can use to improve patient-centered care. Adopting a similar approach to patient engagement throughout the development and lifespan of ClinicalTrials.gov would result in a more user-friendly site that benefits patients and their family caregivers.

Usability of ClinicalTrials.gov

The formation of ClinicalTrials.gov is based in the Food and Drug Administration Modernization Act of 1997 (FDAMA). Section 113 of FDAMA³ states that information on ClinicalTrials.gov “shall be in a form that can be readily understood by members of the public.” **The NHC urges the NLM to continue working to ensure that information on ClinicalTrials.gov is presented using patient-friendly language.** Specifically, we recommend tools such as such as a glossary of terms and plain-language summary documents for each study to make the information understandable to patients and their families. We also recommend that the site is routinely tested with patients, family members, and front-line care providers to ensure the site is approachable, understandable, and lay-public friendly. The advisory group referenced above can serve as a useful tool in advising the NLM on whether information is presented in a patient-friendly way.

In addition, we understand that providers play an important role in the process and are often the key to connecting patients with clinical trials. In order to facilitate this shared decision-making, **the NHC recommends that the NLM also seek regular and ongoing input from providers beyond this comment period** to ensure that the information is presented is also usable to front-line care providers.

Finally, we also recommend that the NLM leverage the expertise of patients, caregivers, providers, and information technology experts to assess the platforms that interact with ClinicalTrials.gov to make sure they are most usable by those audiences. For instance, would an app that helped navigate the site be preferable to users? How could ClinicalTrials.gov share data with platforms and sites that patients and others are already using to facilitate access? Given the advances in technology, these questions are worth asking during this modernization.

Conclusion

The NHC believes that the recommendations above are crucial in ensuring the effectiveness of a ClinicalTrials.gov modernization.

³ <https://www.govinfo.gov/content/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf#page=16>

March 13, 2020

Page 4 of 4

Please do not hesitate to contact Eric Gascho, our Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable by phone at 202-973-0545 or via e-mail at egascho@nhcouncil.org.

Sincerely,



Marc Boutin, JD
Chief Executive Officer National Health Council

Submission No.: 178

Date: 3/12/2020

Name: Dr. Ting-Chao Chou

Name of Organization: MSKCC/PD Science LLC

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Date: March 12, 2020

Input Report in Response to RFI of March 6, 2020 Webinar

From NLM/NIH and SBIA/FDA Regarding the Modernization Program

Functionality, Informatics and Standard [modernizingClinicalTrials.gov]

Notice Number: NOT-LM-2-20-003

Input Report Submitted by Ting-Chao Chou*, Memorial Sloan-Kettering Cancer Center, New York, NY 10065 [*Present address: PD Science LLC, 599 Mill Run, Paramus NJ 07652-1754] Tel: 201-251-8812 (O), 201-561-2576 (C) E-mail: dtchou99@gmail.com

"The ClinicalTrial.gov Modernization and How to Provide Input" presented in the Webinar on 3.6.2020, summarized by Dr. Rebecca J. Williams of NLM, NIH was insightful and extremely important for governmental regulatory affairs and public information. This is a welcome event for the major coordinated efforts between NIH (via NLM) and FDA (via CDER-SBIA) to update, improve, modernize the drug-evaluation and development. The FDA announced of "Modernizing the New Drugs Regulatory Program: Reorganization Approved" on 9.26.2019, was also a great major initiative.

Looking into the modernizingClinicalTrial.gov, the concerned issues are much broader than the administrative framework, and far beyond described in the present RFI by NLM/NIH and by previous FDA Announcements and SBIA's, CDER's RFIs. However, they are all inter-connected. This Input Submitter like to make this Input Report in a broader spectrum to include the very basic fundamental issues, as indicated in the followings:

In Slide No. 35 of the 3.6.2020 NLM Webinar indicated that the RFI is not intended to modify the existing legal and policy requirements for clinical trial registration and results submission. In this juncture, this Input Submitter respectively request that Dr. R. J. Williams NLM/NIH forward this Input Report to the FDA's SBIA, CDER, BDER, OCP Officers and Advisory Committee Members of FDA and NIH, for a broader review and discussions for the ongoing Governmental Innovation and Modernization or Reorganization Programs.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. The ClinicalTrials.gov web site functionality and API are well designed and working properly. However, the modernization initiative for enhanced efficiency and transparency is limited by extrinsic factors such as NIH's specific-project for specific-aims policy, while, unintentionally, neglecting general fundamental biologic principle; and FDA's PK-ADME-oriented approach for drug-evaluation with numerous, disconnected, specific-guidelines, while neglecting basic drug dynamics for efficacy and toxicity determination that is common to all drugs. For drug evaluation research, a general quantitative algorithm-based e-analysis and indexed conclusions should be established. In the absence of clear central guiding scientific principle and doctrine, and without the clear and exact Scientific Definitions of key scientific terms, such as "PD", "synergy" and "additive effect of two drug" and "minimum number of dose-data points for clinical trials". To collect/receive large number of clinical trials protocols, and dealing with big volumes of data/results with ambiguous definitions or guidance, are not necessarily, useful to public, and even un-analyzable by professional bio-medical experts. For example, it is impossible to determine synergy if using single-dose of any drug, in vitro, in animal or in clinical trials, regardless of how accurate is the assay, how many time has repeat the study, and how much time or resources has spent. Therefore, "Design" is a serious matter and "Theory" is critically important for data analysis. For another example: All single-dose clinical trials are disqualify for PD analysis. PD explicitly requires two or more doses. If we use 2- or 3- dose-data points for clinical trials, it is important to know exactly, how to conduct data analysis with automated computer simulation, to achieve quantitative/indexed conclusions.

Therefore, this Input Submitter proposes a unique remedy using the innovative new approach of emphasizing the fundamental functional dynamics and informatics first, and then deal with endless of individual cases later. The central scheme present here, is the mass-action law based biodynamics, pharmacodynamics and bioinformatics (MAL-BD/PD/BI). This mathematically derived theory/algorithm provides basic parameters and exact definitions that are essential for streaming effective and efficient regulations. The lack of definitions in key scientific terms and the deficiency in providing unifies guidance reduce the overall functionality, informatics and Standard that NLM seeks.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

2. The submitter of this Input Report has been working on MAL-PB/PD/BI functional dynamics theory, algorithm, and computer software for 45 years with over 430 publications, with over 32,250 citations, in over 1,500 journals, encompassing nearly all disciplines of biomedical sciences. The unified MAL theory has proven useful in applications in vitro, in cells and in animal studies, and in clinical trials, for the protocol design and quantitative data analysis/simulation/diagnosis using very small number of dose-effect-data points by automated computer simulations. [General Reviews] Refs: [1]. Chou, Pharmacol. Rev. 58:621-681, 2006; [2]. Chou & Talalay, Adv. Enz. Regul. 22: 27-55, 1984; [3]. Chou, Cancer Res. 70: 440-446, 2010; [4]. Chou, Integr. Biol. 3: 548-559, 2011; [5]. Chou, Synergy 1:3-21, 2014; [6]. Chou & Martin, CompuSyn software, 2004, PD Science LLC (www.combosyn.com) (Free download upon registration since 2012).

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

3. This Input Submitter is a pharmacologist, theoretical biologist, and cancer researcher, not a ClinicalTrials.gov site user/sponsor for FDA applications. However, this Input Submitter is the MAL-PD theory initiator, developer, who derived the PD-unified Median-Effect Eq. (MEE), and, with P. Talalay, derived the Combination Index Eq. (CIE) which defines synergism ($CI<1$), additive effect ($CI=1$), and antagonism ($CI>1$). The References used the MAL-based clinical trial protocol-design, (including animal studies *in vivo*), with computerized data analysis/simulation are: Ref. [7]. Chou, Leuk. Lymph. 49: 2059-2080, 2008; [8]. Chou, Am. J. Cancer Res. 1: 925-954, 2011; [9]. Mildvan et al. Antivir. Ther. 1: 77-88, 1996; [10]. Fu et al. Synergy 3: 15-30, 2016; and [11]. Chou et al. Synergy 9: 100049, 2019. Using the MAL-CI method, anti-HIV clinical trials, AZT+IFN, used only 10 data-points with 3-doses each drug, and constant- ratio combos, quantified synergy with computer simulation, using only 36 patients [9]. [For ten dose-data-points, A, B, A+B for 3+3+3 (+1 control)].

Similarly, anti-cancer combinations (Taxotere+T607) against colon carcinoma HCT-116 in nude mice xenografts, showed synergism, with experiment using 10 dose-data points, with 66 animals [10, 11].

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

4. The MAL-BD/PD/BI is a proven general theory, obtained following system-analysis that derived (and published) over 300 reaction-rate equations over 15 years. The MAL theory is effective, simple, efficient, quantitative and applicable in general bio-systems, regardless of the followings: (i). *In vitro*, *in vivo*, *in animal* or *in human*; (ii). Drug type: Chemicals, biologics, natural products, or biosimilars; (iii). Drug' Unit: nM, ug/ml, mg/Kg, IU, Rad, multiple-of-infection, oxygen tension, pH, etc. (since all units cancelled-out due to ratio relativity), and (iv). Mechanism or mode of actions of single drug (or drug combination in mixture): Competitive, noncompetitive, uncompetitive; exclusive or non-exclusive; sequential, ordered, or ping-pong mechanisms (see [1-4]).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

5. The general MAL parameters [m and Dm], as the Universal Functional "Identity-Tag", can also be considered as the Bioinformatics BI-Tag, under defined experimental conditions. Thus simplifying and streamlining the regulatory needs to deal with the complex biological variability and diversity. [1, 4, 5, 6].

The unified general MAL dynamics principle, can effectively solve broad spectrum of biomedical problems, including those in clinical trials and clinical sciences, as well as drug synergy

quantification, as indicated tens of thousands of biological papers in over one thousand journals.

The RFI from ClinicalTrials.gov for Functionality, Information and Standard are closely inter-related.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

6. The prevailing sponsored research or grant supported project are for specific subjects for specific aims, thus, most priorities are disease-specific, organ-specific, tissue-specific, drug-specific, but neglect the general fundamental dynamic theory and parameters, as the common denominator, to simplify complex biological system with unified MAL dynamics and informatics.

The single general theoretical article introducing the CI theory, algorithm and computer simulation /quantitation of drug combination synergism [2], has 6,532 citations in 1,287 biomedical journals internationally, as of March 10, 2020, was referred to as “Makes History” (Elsevier News Release, 3.16.2016). However, FDA regulatory guidelines have not yet provided the definition of “synergism” or “antagonism” and the quantitative method to quantify them, although drug combination is widely employed in treating the most dreadful diseases such as cancer and AIDS.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

7. Since 2017, this Input Submitter has voluntarily provided FDA in six Public Comments via Regulations.gov and Federal Register. And presented two Public Hearing at FDA at White Oak Campus on 10.2.2017 and on 5.7.2019, and a FDA Public Meeting on 11.7.2019 “Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA’s Office of New Drugs”. The topic of my presentation was, “Mass-action law Pharmacodynamics (MAL-PD) for Quantitative Biomedical R&D, and Efficient Drug-Evaluation Guidance: Computerized Data Analysis of Single Drug and Drug Combinations in Vitro, in Animals and in Clinical Trials”. All the above details are available upon request with the FDA-Docket ID Numbers and the Tracking Numbers of Comments. The feedbacks from FDA for these subjects are pending.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

8. The contents of this Input Report are open to public. They are not proprietary, classified, confidential, or sensitive information. The pertinent contents, in addition to present at FDA, also presented at JHU, Baltimore (4.8.2019), at USUMS, Bethesda (10.2.2017), and will be presented at EB-2020 (ASBMB and ASPET) in San Diego, and AACR-2020, in San Diego, AI and Big Data in Cancer: From Innovation to Impact, in Boston, and Synergy International Forum, Bonn, Germany. [Some of these Conferences have been postponed or cancelled due to COVID-19 pandemics].

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

9. This Input Submitter is sincerely willing to provide further details of the MAL-BD/PD/BI theory and applications, especially those related to clinical trials protocol design and computerized data analysis. This Input Submitter wish to work closely with the teams of FDA and NIH, for the modernization projects. This Input Submitter is 81 years old, and is in good health. Since retirement and established PD Science LLC, in 2013, there are 13,336 new citations for the scientific work.
THE END.

Attachment: 3.12.2020. ChouTC Input Report. Subm. to RFI. for Webinar.3.6.2020.ClinicalTrials.gov(NOT-LM-2-20-003).pdf

Date: March 12, 2020

**Input Report in Response to RFI of March 6, 2020 Webinar
From NLM/NIH and SBIA/FDA Regarding the Modernization Program
Functionality, Informatics and Standard [modernizingClinicalTrials.gov]**
Notice Number: NOT-LM-2-20-003

Input Report Submitted by Ting-Chao Chou*, Memorial Sloan-Kettering Cancer Center, New York, NY 10065 [*Present address: PD Science LLC, 599 Mill Run, Paramus NJ 07652-1754] Tel: 201-251-8812 (O), 201-561-2576 (C) E-mail: dtchou99@gmail.com

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[Some of these Conferences have been postponed or cancelled due to COVID-19 pandemics].
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Submission No.: 179

Date: 3/12/2020

Name: Dr. Jesse Berlin

Name of Organization: Johnson & Johnson

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

We are interested in voluntarily registering some observational studies that are not applicable clinical trials (ACTs) (i.e., not required by law) to create transparency around this type of research. We have observed the following challenges and would like to submit them for consideration as potential modifications to the platform to better support disclosures that are not required by law. In general, it would be helpful to permit some flexibility in some of the fields for studies that don't fit neatly into the required elements and also provide some consistency in reporting for individuals submitting other similar types of studies. For example, currently:

- For studies based on existing administrative data (e.g., health insurance claims), we must provide a primary completion date, which is obviously irrelevant for research in which individuals aren't being examined or receiving an intervention. The concept of "first patient in" is also irrelevant when looking at an existing database.
- We must provide recruitment status which is not applicable for studies in which participants are not being recruited, and then we have to answer the question on recruiting and provide updates – which is obviously not correct for studies that don't recruit participants.
- We must provide enrollment information. We provide the number of patient records, but no one is officially enrolled in the study and it isn't clear how others who register these observational studies use these fields.
- We must provide the study location including facility name and address – this is presumably the clinical site but not applicable for many types of observational studies. Could this be defined differently for observational studies?
- The study start and end dates are ambiguous for studies currently being conducted from retrospective data. Would it be possible to create a definition for these types of studies? For example, we've used the dates when the tabulated events occurred.

Many thanks for offering Johnson & Johnson the opportunity provide input.

Attachment: Janssen Letter - NLM [12 March 2020].pdf

March 12, 2020

Notice Number: NOT-LM-20-003

Re: ClinicalTrials.gov Modernization

Dear Sir/Madam:

Janssen Research & Development, LLC (Janssen), one of the Janssen Pharmaceutical Companies of Johnson & Johnson, appreciates the opportunity to provide input on efforts to modernize ClinicalTrials.gov. ClinicalTrials.gov is a critically important resource for stakeholders involved in all aspects of drug development and the product management lifecycle.

Janssen has significant experience submitting information to ClinicalTrials.gov and utilizing ClinicalTrials.gov to find valuable information for learning and research. We have provided some comments in the drop-down response options to help inform the modernization initiative. However, we believe that there are additional modernization issues that pertain to technical and policy aspects of ClinicalTrials.gov. We would be happy share these experiences and perspectives with National Library of Medicine in order to provide useful insights that may further support the modernization initiative.

We are available to discuss these topics with you in more detail, at your convenience. Please reach out to us for any additional inquiries or to set up time for additional discussion.

Sincerely,



Rebecca Lipsitz, PhD
Director, Global Regulatory Policy & Intelligence
Global Regulatory Affairs
Janssen Research & Development, LLC
Tel: +202-450-9718,
Email Address: rlipsitz@its.jnj.com

Submission No.: 181

Date: 3/13/2020

Name: Elke Hausner

Name of Organization: IQWiG

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

- perform complex search strategies (as in Pubmed)
- quick access to expert search
- Enable export of all data fields (including link to further documents like study protocol and statistical analysis plan)
- Add another search field for update searches: data entry field
- Implement a new section (e.g. similar LinkOut in PubMed) with all further documents like study protocol, etc.) At the moment these links can be found in different sections and could easily be missed.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

1) systematic reviews from HTA agencies, e.g. NICE or IQWiG. Reason: could contain data that are not freely available elsewhere.

2) Clinical study reports of the EMA and other regulatory authorities. Reason: contain detailed information on the study

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We use CT.gov to identify study data for the preparation of systematic reviews. For this purpose we conduct a sensitive search in CT.gov. The search usually includes terms related to population and intervention. Other limitations of the interface are not applied by default (e.g. study type). The reason is that we are not sure whether these limitations “work” reliably. Afterwards the export is done in XML format. For Endnote we have created an import filter for this format.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

For the preparation of systematic reviews, we search very comprehensively for studies on a specific topic. We would like to apply limitations such as study type. In practice, however, we do this extremely rarely, as we are not sure how reliably these could be applied.

3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Introduce MesH and Automatic term mapping functionality as this would increase recall.

Submission No.: 182

Date: 3/13/2020

Name: Sarah Johnston

Name of Organization: IQVIA

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- Sponsors have asked for their published papers to be linked in the results posting. This may be an important way for sponsors to express their own study conclusions as well as further background for which there isn't any scope in a CT.gov results posting.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- As a team that works on the submission of results only, we use the website to download the protocol registration form for our information. The study start and completion dates, the study phase and also often the study locations and sites can be helpful. The date the protocol registration was last updated is also useful information as this gives an indication of how accurate the protocol registration details are (i.e. if protocol amendments have been incorporated).

- We also use it to download studies that have similar endpoints to look at different ways of presenting this data. Being able to see the outcome measures in the search of result is very useful as is being able to filter by studies that have results.

- As the search results list includes all variants of the search term It would be useful on the search details tab to be able to click on the studies that match specific synonyms rather than just giving a numerical count. i.e. see PRS results search screenshot attached. It would be useful to click on the section circled in red to be given the subset list here.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

- Usually we either look for a specific study based on the protocol code, NCT number, by sponsor or by study drug and indication. Most common or useful function would be by specific term used in an outcome measure or study structure (i.e. multi period/crossover etc)

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Results Submission – Data Input

Participant flow

- When on the Results section landing page the recruitment details are missing from the participant flow section. Not a big deal but would be nice to see this here along with the pre-assignment details.
- If changes are made to the text in the arm descriptions it would be nice if this carried throughout. Or somehow of making the changes apply to the other sections i.e. baseline, OMs etc. This is especially important when these sections have already been input (i.e. post QC or subsequent drafts of the posting) so if we could have the option of editing a full results posting so that the changes to an arm title/description can carry through this would save time.

Baseline Characteristics

- Age, Continuous: Mean and SD are often not provided for the total column in the source documentation. It would be useful if this total column could be able to be left blank. For example, allow the use of NA and a reason added when the Total data value is not available.
- Having ‘Race/Ethnicity, Customized’ could be construed as confusing if you are only planning to show customized Race. The option of having Race customized OR ethnicity customized might be useful.

Outcome measures:

- When adding a new OM it would be useful if any changes to the arm description could be applied to all OMs that are using the same arms. For example when selecting copy the OM from an existing OM (e.g. OM1) these copied OMS would then be linked and therefore making an future edit to OM 1 it should then be asked if you wish to apply the same changes to OM 2,3, 5, and 7 or whatever have used the same arms.
- The ability to copy statistical analysis within each OM would be very handy.
- A title of stats analysis would also be useful and help differentiate between statistical analyses when there are several included in a single outcome measure
- When in the OM data screen it would be useful to edit all the arms in the same place rather than having to click on each arm individually to edit the arm description. Especially if there are a lot of arms – would save a lot of clicks! This is especially useful if there is not the ability to apply changes from the first OM to all other OMs referencing the same arm.
- It could be useful to have the number of participants in the arm (auto-populated) and then the overall number of participants analysed. Typically these numbers may not match and not all subjects will have had data analysed and this could be accepted as expected unless specified. i.e. there would be an optional place to add a comment to explain any discrepancy if needed
- Would it be possible to have multiple units of measure within an Outcome measure. For example a PK table or clinical chemistry analysis may have a lot of different units of measure within the

same source table and these then need to be split out over multiple OMs as they have different units. Could there be an option for an OM to have categories even if it isn't showing a count of participants and for each category to have a different unit applied to them? (i.e. mg/ml, ng.ml, ng*hr/ml, hours etc)

- There is the option to move rows within an outcome measure, but it would be more useful to drag and drop the rows to where you need them to be. If you have a lot of rows it can be very time consuming if you need to make a big change to the order they are presented in, as each row needed to be individually moved up or down row by row.
- When copying an OM it would be very useful to have the option to also copy over any associated statistical analyses (with the actual data entry boxes blank)
- Within the Overview screen the OM it might be useful to have a window that allows a preview of how each OM would look when downloaded to PDF. This is especially true in regard to statistical analyses which look quite different when printed.
- The way the statistical analyses are laid out could be improved. They are often very long and not presented very succinctly, especially if only a p value is used. Could there be anyway to incorporate the analyses into a neater table, or even get the p value into the original results table in order to more closely match the way the results are presented with in the CSR?
- If there is only 1 row of data in an OM then the number of participants analysed may differ from the population as a whole. Could it be added to put participants analysed at the row level when only 1 row is presented.

Adverse Events

- A really useful feature would be to have a button to click to fill in all AE blank data entries with 0 (or a value of your choosing). And then you would only need to go into the ones that have a value over 0 and change it. This would be better as an optional functionality and not as a default to make sure cells aren't filled with 0 in error.
- It would be nice to have the ability to present the AEs in order of frequency or alphabetically by System Organ Class or by Preferred term. I realise there is the option in the data entry screen to sort them into the sorted by alphabetically or by organ class but this is not the same when in preview mode or on CT.gov

Limitations and Caveats

- It would be better to increase the character limit from 250 to 350. Most often it is very difficult for writers to fit the study limitation details suggested by Sponsors within 250 characters.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- It would be useful if the CT.gov registry and the EudraCT registry were more aligned in their validation rules and format.

- Automated email reminders for upcoming deadlines to the sponsor for any upcoming be useful (if this doesn't already happen?)

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- Having the definitions and help sections clickable within the results input system is very useful. As is the character limits of each text box. Being able to validate the results at each stage is also useful to identify errors. I find the FAQ section of the 'submit studies website' very helpful however it is very wordy and often very layered to find this information you need quickly.
- A guide to common QC issues along with recommended solutions would be useful.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

- Implement the fines for a late or non-submission.
- Send out emails to organizations with reminders for studies with upcoming postings needed, or asking if they have a transparency policy in place.
- Could there be an overall leader board for both individuals and organizations for timely submissions or over % of an organization/individuals' submissions that got though QC on first attempt?

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

- There are often discrepancies between what the sponsor has initially planned in the protocol as a secondary endpoint and what they summarize suitably in the CSR. There often are cases when the data does not conform to the registry restriction for presentation but to not disclose the data would be seen as a breach as to what was initially specified in the protocol. In general, sponsors need to be better educated as to what should be included as a secondary endpoint and made it clearer that all results for primary and secondary need to be disclosed and therefore to really nail down what is important as secondary endpoint.
- To aid the presentation of results, it would be useful as stated in answer to 2a above that multiple units could be applied to a results table in 1 outcome measure. This would allow for a more comprehensive presentation of PK results or laboratory parameters.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

- We would suggest referencing standardized questionnaires or tools such as would be used for patient reported outcomes or respiratory assessment (eg. St George's Respiratory Questionnaire) within the CT.gov website, or being able to link to these questionnaires/tools on their own websites. This would provide a complete reference to the tool being discussed though we would still need to include a note on the scale range etc in order to understand the data presented when reading the results posting.
- Another idea could be to link studies registered in CT.gov using the same active ingredient for each sponsor (and not between sponsors)

Attachment: PRS Search Results Screenshot.png

[List](#)[By Topic](#)[On Map](#)[Search Details](#)

Terms and Synonyms Searched:

| Terms | Search Results* | Entire Database** |
|------------------------------|-----------------|-------------------|
| Synonyms | | |
| visual analogue scale | 8 studies | 14,909 studies |
| analog pain scales visual | -- | 1 studies |
| Pain VAS | -- | 400 studies |
| Visual Analogue Pain Scale | -- | 481 studies |
| visual analogue | 8 studies | 15,770 studies |
| scale | 8 studies | 74,765 studies |
| Base Number | -- | 1 studies |
| Race I Init | | 12 studies |

Submission No.: 183

Date: 3/13/2020

Name: Smita Shukla

Name of Organization: GSK

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

- We would like to see improved functionality to support registration and results disclosure of innovative trial designs e.g. basket, platform and umbrella studies
- Can the CTgov search functionality include the ability to search by ‘Study Design’ (e.g. Cross-over, Parallel, Multiple period)?
- Can the CTgov search functionality include the ability to search for “Delayed” Results?
- We would like public disclosure on the study details tab as to whether a study is “ACT”, “pACT” or “non-ACT” and the capability for the advanced search functionality for this information

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- For Protocol Registration, site information is a mandatory field for all studies; however, observational studies might not have specific site information. This will be an issue for “Screening” protocols for Oncology as well. Can NLM consider allowing studies with Phase = “N/A” and without site information to also be registered on CTgov?
- Can the “Hot off the PRS” email functionality be extended to cover for example, other alerts to interested parties such as patient advocacy groups or investigators alerting them of new trials in disease areas of interest?

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- Although the current protocol registration template within the PRS system supports registration of observational studies as well as interventional trials, the same cannot be said about the current results registration template. We would like a new results template for observational studies to be made available within PRS so that we can continue to use ClinicalTrials.gov as our primary registry for registering and reporting results for all of our GSK Sponsored studies.

- For Adaptive Clinical Trials or Multi-phase Clinical Trials, there should be functionality to link studies. A good example that currently works well is the “Expanded Access” record on ClinicalTrials.gov that allows linking of multiple studies.
- For consumer healthcare studies, sometimes the intervention is neither a drug nor a device. We are not able to select “Cosmetic” as an Intervention Type through PRS. We have to select “other” as an option which leads to a warning that Phase 2-4 studies typically have at least one type intervention drug/ biological/ combination product. Examples are 209723 and 212401. We would like to see “Cosmetic” added to the intervention type in PRS.
- Can the current character limit of 999, including spaces, for justifications for good cause extension requests for results submissions and for outcome measure descriptions be increased in PRS?
- Can PRS Show/Hide functionality include the addition of “ACT” and “non-ACT” fields to allow easier searching?
- We appreciate that the FDAAA results template is not in scope of this RFI but we wondered whether certain character limits (e.g. for row titles, timeframes, “on-hold” statements) could be increased? Or are there future plans to review this template?

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- The information provided on the Training Materials page of the ClinicalTrials.gov website is a very helpful resource for results registration. In particular, the Example study records are helpful reference materials for statisticians in ensuring they generate the appropriate outputs for the various different study designs. We would like to see some further examples e.g. results reporting of “switch” studies with multiple periods (add reference to SWORD-1 [201636] and SWORD-2 [201637])?
- Are NLM planning to update QC checklists for Sponsors for Protocol and Results Submissions?
- Are NLM planning to re-visit current advice for multi-part studies which are terminated early to in the future require only results from the parts which were completed and avoid having Sponsors provide empty tables for outcome measures where no data were collected? [Example: 205021 (NCT03358407)].
- It would be helpful if NLM could provide examples of valid justifications language to be used when data cannot be provided for pre-registered outcome measures.

Submission No.: 184

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

The process of entering basic results in the outcome measures and statistical analyses section has been difficult. The definitions and guidance available have not consistently been clear or helpful. It has taken multiple attempts at updating this section before we receive approval and release. It may be helpful to have an assigned, accessible and responsive reviewer who can provide guidance on what is required for approval in real time to shorten the amount of time this process takes.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Guidance tools such as “definitions” and “help” have at times been helpful with submissions. Direct contact with a reviewer may prove even more beneficial.

Submission No.: 185

Date: 3/13/2020

Name: Kristin West

Name of Organization: Council on Governmental Relations

Attachment: CTgovResponse 03122020 final signed.pdf



ClinicalTrials.gov Information Team
National Library of Medicine
National Institutes of Health
8600 Rockville Pike
Bethesda, MC 20894

March 12, 2020

Submitted to: https://nlmenterprise.col.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Re: Request for Information (RFI): ClinicalTrials.gov Modernization, Notice Number: NOT-LM-20-003

The Council on Governmental Relations (COGR) and the Association of American Universities (AAU), two of the leading organizations representing research institutions, are most appreciative that the National Library of Medicine (NLM) is considering making much-needed changes to the ClinicalTrials.gov system, and modernizing and rebuilding the system.

Issues with the use of ClinicalTrials.gov appear to stem from the fact that, at this point, the system serves two different audiences – the public and the scientific community. Registration of studies was initially developed to assist the public in identifying clinical trials of interest, especially studies on life-threatening diseases. At the same time, investigators are required to report detailed research results, which are very technical, and the system was not designed with this in mind. This portion of the system should be more researcher-focused to make the process as efficient as possible. It's not as crucial for this function in ClinicalTrials.gov to be public-facing, since the public is more likely to prefer to read research results in context, e.g., through a publication. We provide the following observations and comments below for your consideration in planning how to serve these two audiences best.

The initial goal of ClinicalTrials.gov was to provide transparency and a mechanism for institutions to report clinical trial data. Specifically, the Food and Drug Administration Modernization Act of 1997 (FDAMA) required that the registry include information about federally or privately funded clinical trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for patients with serious or life-threatening diseases or conditions. The information in the registry was intended for a broad audience, including individuals with severe or fatal diseases or conditions, members of the public, health care providers, and researchers. Since the passage of FDAMA, additional laws and regulations expanded the requirements for the types of trials to be registered and the requirement for the publishing of trial results was also added.

In addition to the federally mandated use of the system, sponsors and journal editors increasingly are requiring investigators to use the system to register and report on other activities beyond trials, such as

observational studies and repositories. Regrettably, the imposition of these additional data points without overhauling the system has left investigators with the sense that they are trying to fit a square peg in a round hole. Because the system is crowded with different kinds of information, there is little transparency for investigators or the public to find the type of information they seek. As a result, system changes and updating are badly needed. We appreciate the NLM providing an opportunity for stakeholders to comment and suggest ways to modernize the system while also reducing the administrative burden for investigators and clinical trial administrative staff.

While our associations are not direct users of the system, a substantial portion of our member institutions are system users. We solicited feedback from them and have also encouraged institutions to submit comments directly to the NLM. COGR and AAU endorse the work of the Clinical Trials Results and Registration Task Force, a national consortium of experts from academic medical centers, universities, hospitals, and non-profit organizations that work towards improvements in transparency in clinical trials registration and results reporting requirements in ClinicalTrials.gov.

We have had many conversations with experts who support PIs in registering and maintaining studies in ClinicalTrials.gov. We have not attempted to summarize their detailed comments. However, several common themes have emerged:

- As stated above, ClinicalTrials.gov was developed in the early 2000s to support the registration of trials conducted under investigational new drug applications. The templates were made to support this activity alone, making it challenging to register the other types of activities that now require registration after the scope of the database was expanded. Examples of other activities include NIH-funded pilot and behavioral clinical trials, certain pilot studies and basic experimental studies with human subjects for which many journals require ClinicalTrials.gov registration.
- Grant project status and the status of the trial within a broader grant may not always align, because awards can begin long before a trial is slated to begin or can be issued for trials that have already started. There are currently insufficient means in either system to account for these situations.
- Journal editors and other stakeholders are increasingly requiring registration of studies in ClinicalTrials.gov to demonstrate that the study is open and transparent, even for non-clinical studies. This is a laudable goal. However, ClinicalTrials.gov, which is currently the primary means for attaining that goal, may not be the best long-term approach for demonstrating transparency.

Given the magnitude of the challenges that the NLM is facing with ClinicalTrials.gov, we suggest that the NLM consider establishing a stakeholder user group, including investigators and ClinicalTrial.gov administrators, to help develop the new specifications and to participate in the initial testing of the

redesigned system. Our associations would be happy to assist the NLM with the establishment of such a group. We offer some additional high-level recommendations for your consideration.

- Provide a public-friendly view for information such as studies for which participants can opt-in, and links to resulting publications (e.g., through Pub Med Central) where the public can access relevant research papers.
- Focus on the investigator's experience, making the system as investigator friendly and efficient as possible for reporting studies and research results.
- Reduce manual data entry. Link to federal funding databases or enable links to institutional databases, so ClinicalTrials.gov is always current and accurate. Add fields so NIH-defined clinical trials may be correctly coded and identified.
- Create appropriate, easily identifiable statuses for reporting research results (e.g., new, in progress, under review, late) to provide the most accurate information possible to research institutions responsible for managing projects.
- Provide automatic feedback from the system to responsible parties to alert them to upcoming deadlines.
- Create helpful indicators for studies, such as "subject to FDAAA", "NIH-funded clinical-trial" or "Other NIH-funded study."
- Consider developing an alternative, simplified method or separate database for registering non-clinical trial studies to support journal requirements and other activities that fall outside the mission of ClinicalTrials.gov.

Again, we appreciate the opportunity to comment. Please contact Kristin West, Director of Research Ethics and Compliance at COGR KWest@cogr.edu, if you would like more information or have questions.

Sincerely,



Mary Sue Coleman
President
American Association of Universities



Wendy D. Streitz
President
Council on Governmental Relations

Submission No.: 186

Date: 3/13/2020

Name: Joshua D. Wallach

Name of Organization: Yale School of Public Health

Attachment: ClinicalTrials.gov Comments 20-03-13.pdf

March 13th, 2020

**ClinicalTrials.gov Information Team
National Library of Medicine, National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894**

RE: Request for Information: ClinicalTrials.gov Modernization

Thank you for the opportunity to provide input to guide the National Library of Medicine (NLM) in planning updates to enhance and better support the users of ClinicalTrials.gov, including efforts to improve the technological infrastructure, public-facing components, and user experience. As group of experts, including an epidemiologist and medical librarian with expertise in meta-research, a bioethicist with expertise in clinical trials, and physician investigators who have experience as peer-reviewers and journal editors, as well as researchers with expertise in clinical trial design, reporting, and evidence summary, we can attest to value and importance of ClinicalTrials.gov. It is a treasured resource for the clinical research community.

In this letter, we (1) provide examples of how we have used ClinicalTrials.gov as a resource for research and research oversight and (2) outline a number of suggestions for improvement.

1. ClinicalTrials.gov as a resource for research and research oversight

Over the past few years, we have used the clinical study registry and results database of ClinicalTrials.gov to inform and conduct a large number of high-impact research projects, as well as to inform our evaluation of others' research. In particular, we have used ClinicalTrials.gov to:

- Locate ClinicalTrials.gov Identifiers (NCT numbers) and 'Other Study ID Numbers', which can be used to match trial registrations, published articles, and other trial data sources.
- Identify clinical trial characteristics, using either the 'Study Details' or 'Tabular View' pages, for both published and unpublished clinical trials (e.g. to determine study sponsors, study design characteristics, study start dates, full study protocols, statistical analysis plans, and results reporting).
- Identify clinical trial patient characteristics, primary and secondary outcomes, and potential adverse events that may not be reported in peer-reviewed publications.

The information available on ClinicalTrials.gov has allow us to conduct dozens of empirical investigations, as well as to evaluate research conducted by others, such as:

A. Obtaining and use of data for systematic reviews and meta-analyses

Trial registries like ClinicalTrials.gov are an important source for identifying additional studies to include in systematic reviews and meta-analyses. Empirical evidence suggests that searching clinical trial registries identifies additional studies and can increase the value of reviews.¹

As one example, our team has searched ClinicalTrials.gov to identify potentially eligible studies and summary results while conducting comprehensive systematic reviews and meta-analyses (e.g. the cardiovascular safety of rosiglitazone²). However, there are countless systematic reviews and meta-analyses that have been conducted and published by the Cochrane Collaboration and others that have made use of data and information available on ClinicalTrials.gov.

B. Evaluating the compliance of studies with registration and results reporting requirements

Meta-research is the study of research itself, which includes evaluations of research methods, reporting practices, and research reproducibility.³ Over the past few years, we have relied on the information available on ClinicalTrials.gov to assess the compliance of studies with results reporting policies. Non-phase 1 trials of Food and Drug Administration (FDA) regulated drugs, biologics, and devices are required to register on ClinicalTrials.gov. Furthermore, the Food and Drug Administration Amendments Act (FDAAA) of 2007 requires sponsors of certain trials to report their study results directly onto ClinicalTrials.gov within 1 year of completion.⁴ The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition of the publication of clinical trials results.⁵ ClinicalTrials.gov can be used to evaluate the compliance of various researchers, biomedical fields, funders, and academic medical centers with various reporting requirements.

Our team has used the data and information available on ClinicalTrials.gov to:

- Examine the completeness of registration within ClinicalTrials.gov among a cross-section of trials.⁶
- Compare trial information and results reporting on ClinicalTrials.gov with corresponding peer-reviewed publications.^{7,8}
- Evaluate the reporting and publication of noninferiority trials in ClinicalTrials.gov.⁹
- Conduct cross sectional analyses of (1) trials funded by the National Institutes of Health and registered within ClinicalTrials.gov and (2) trials conducted by leading academic medical centers in the United States.^{10 11}
- Determine registration and reporting of findings for efficacy trials supporting FDA approval of new drugs for cardiovascular disease,¹² neuropsychiatry,¹³ and asthma,¹⁴ before and after the 2007 FDAAA mandated clinical trial registration and outcome reporting on ClinicalTrials.gov.
- Evaluate registration, reporting, and publication of all clinical trials submitted to the FDA for drugs sponsored by large biopharmaceutical companies.¹⁵⁻¹⁷
- Characterize postapproval clinical trials of therapeutics and devices approved by the FDA, including postmarketing requirements and commitments and the rates and timeliness of registration, results reporting, and publication of clinical studies.^{5,18-23}
- Determine the number of trials and prospective cohort studies with ClinicalTrials.gov identifiers and registration dates prior to study start dates.^{24,25}

All of these studies, and the many others that have been done using the data and information available on ClinicalTrials.gov, have provided a more advanced understanding of the safety and efficacy of medical products and other medical interventions, of the impact of selective publication and selective outcome reporting on the aggregated evidence that informs clinical medicine, and of the impact of FDA, NIH, ICMJE, PhRMA and other government and organizations' policies intended to improve clinical research transparency and reporting.

C. To inform real-world evaluations of drug efficacy and safety

We and others are conducting a number of studies that aim to better understand the use of observational data and research methods ('real-world data to generate real-world evidence') to predict the patient populations and findings of ongoing randomized controlled trials using administrative claims data. In particular, we have used ClinicalTrials.gov to identify and select ongoing trials based on key study characteristics (sample size, endpoints, and inclusion/exclusion criteria). These characteristics can then be used to develop inclusion and exclusion criteria that can be applied to observational data to advance our understanding for how these data can be used to complement traditional clinical trials.

D. To inform peer-review and editorial decision-making

As peer-reviewers and journal editors, we and others make use of data and information available on ClinicalTrials.gov to inform our assessments of research studies submitted for consideration to biomedical journals, including to confirm whether trial enrollment was initiated prior to or after registration, whether the research report conforms to pre-specified trial eligibility criteria, primary and secondary endpoints, and statistical analysis plans, and whether results reported are consistent between ClinicalTrials.gov and the submitted report. Because of ClinicalTrials.gov, every prospective clinical study, particularly those evaluating FDA-regulated interventions, can be "cross-checked" by editors and peer reviewers, either by making use of the information submitted by the trial sponsors, including study protocols, or by making use of the information embedded by NIH/NLM, including links to FDA materials and other resources.

2. Suggestions for improvement

Given our experience using ClinicalTrials.gov for research purposes, we have a number of suggestions that could enhance website functionality.

A. Target audience

ClinicalTrials.gov should resist the temptation of serving all the needs of all parties. While it provides useful information to individuals seeking to identify and enroll in clinical trials, we worry about efforts to make it useful for those individuals to evaluate trial designs and make inferences based on reported results. For this reason, we do not suggest trying to make the 'Study Results' section of ClinicalTrials.gov work for all purposes, with a narrative report of results. If the results from individual studies are not meaningful or are provided without a critical appraisal of the study design characteristics and findings, the information could be misused. The value of the 'Study Results' section of ClinicalTrials.gov is the collection, curation, and display of information about clinical trials, which can be used by various external parties, including those who are interested in further curating the information for use by lay audiences.

If trial sponsors do start providing plain language summaries of trial results, it would be helpful if ClinicalTrials.gov provided a link to where to find them. Furthermore, NLM could consider auto-embedding the abstracts from studies indexed on PubMed on ClinicalTrials.gov.

B. Advance Search

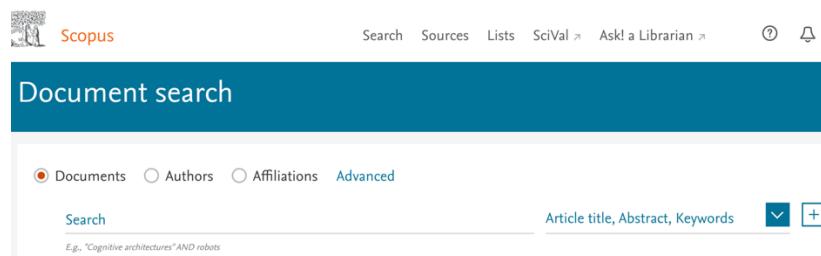
The *Advance Search* feature on ClinicalTrials.gov is incredibly powerful. However, it is unlikely that the full search capabilities are being utilized by the public and the research community. Although the *Advance Search* page includes a link to search instructions, these instructions may not be used by most investigators. We are very experienced users, and yet we have only recently become aware of certain key features (e.g., the "expert search" option). Therefore, many searches may be conducted without search

operators like OR, NOT, and AND. In order to increase clarity, the *Advance Search* page could give a brief example under each search box. This system is used by other search platforms like Scopus.

Example:

Condition or disease: {ENTER TEXT HERE}

*E.g. Immunodeficiency NOT AIDS
(more on how to search [here](#))*



The screenshot shows the Scopus search interface. At the top, there's a navigation bar with links for 'Search', 'Sources', 'Lists', 'SciVal', 'Ask! a Librarian', and help icons. Below the navigation is a teal header bar with the text 'Document search'. Underneath is a search form with radio buttons for 'Documents' (selected), 'Authors', 'Affiliations', and 'Advanced' search. There's also a dropdown menu for 'Article title, Abstract, Keywords' with a plus sign icon to add more fields. A search bar contains the placeholder text 'E.g., "Cognitive architectures" AND robots'.

For each search that is conducted, it should be easy for the search string to be downloaded into a Word/PDF document, including the [Terms and Synonyms Searched](#). It is also important to know the field labels different terms were searched against.

When conducting systematic reviews and meta-analyses, or other meta-research studies where ClinicalTrials.gov searches are performed, it is important to communicate to others the details of each search. Therefore, it would be helpful if there was an easy way to download the search parameters, including “terms and synonyms,” into a format that one can easily rerun (i.e. not requiring the user to re-enter queries).

C. Applicable Clinical Trials

On ClinicalTrials.gov, results reporting is required for any ‘Applicable Clinical Trial’. Although ClinicalTrials.gov provides information for responsible parties to determine whether their study is an ‘Applicable Clinical Trial’, it is difficult for patients and researchers to easily identify which trials had qualified for this designation. We suggest that NLM include an identifier on each registration, clarifying which trials have been designated an Applicable Clinical Trial.

D. Tabular View

We use the *Tabular View* in ClinicalTrials.gov to locate key trial information, including the Tracking Information, Descriptive Information (e.g. Study Design), Recruitment Information (e.g. Eligibility Criteria), and Administrative Information (e.g. Responsible Party). However, the information provided by the Responsible Party for each registration can vary, and it can be difficult to determine which data elements are required. In order to improve this feature, it would be helpful if NLM listed all required and optional elements, noting which are optional and which are required, the response options available to responsible parties, and the response option selected by responsible parties. For instance,

ClinicalTrials.gov current lists:

Allocation: Randomized

Active arm comparator: Placebo arm

To increase transparency, we believe that it would be helpful if ClinicalTrials.gov provide:

Allocation (Randomized, nonrandomized): Randomized

Active arm comparator (Experimental arm, active comparator arm, placebo arm, sham comparator arm, no intervention arm): Placebo arm

E. Results Database

The *Results Database* is an important resource when it comes to evaluating and synthesizing evidence. However, the current display is not particularly user-friendly. In order to facilitate the use of clinical results in systematic reviews and meta-analyses, it would be helpful if there were various download options for the trial results. For instance, investigators may want to download certain study results across intervention arms in Excel or in Word/PDF format. For investigators conducting systematic reviews and meta-analyses focused on adverse events, it would be helpful if an Excel document containing the specific outcomes of interest could be downloaded. This feature will allow researchers to store and share the data that they used to inform their analyses.

Thank you for considering our comments and suggestions for improvement, which we hope can be used to strengthen ClinicalTrials.gov as a resource for the clinical research community.

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Submission No.: 187

Date: 3/13/2020

Name: Eleanor Dehoney

Name of Organization: Research!America

Attachment: Comments on ClinicalTrials.gov Modernization Request for Information.pdf



March 13, 2020

Patricia Flatley Brennan, RN, PhD
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

RE: Request for Information (RFI): ClinicalTrials.gov Modernization

Dear Director Brennan,

Research!America commends the National Library of Medicine (NLM) for launching a stakeholder-informed initiative designed to maximize the utility of ClinicalTrials.gov (CT.gov).

As our nation's central repository of clinical trial information and data, CT.gov plays a pivotal role in advancing medical and public health progress. Given the multi-faceted significance of that progress to Americans and populations across the globe, it is inherently important to ensure the clinical trial information housed on CT.gov is up-to-date and accurate; easily accessible and readily understandable regardless of the audience; and responsive to the variables patients, caregivers, providers, researchers, and the general public consider when exploring whether to participate in a clinical trial and when making use of trial results.

We also believe that optimizing CT.gov should not be a long-term goal, but rather an immediate priority realized through collaborative action.

Over the course of 2018 and 2019, Research!America and partners from across the research ecosystem worked together to surface common challenges that compromise the utility of CT.gov. As part of this effort, we commissioned an in-depth survey of patient organizations and consulted with providers, trial sponsors, researchers, companies working on CT.gov interface technologies, and other stakeholders. We greatly appreciated the opportunity to meet with NLM leadership over the course of this project to review our findings and discuss potential paths forward.

One key finding from this two-year project is that there is strong consensus around the challenges that need to be addressed. As NLM has captured in its Request for Information, commonly identified challenges relate to website functionality, information submission, and data standards. Within these categories, frequently cited concerns include patient/public awareness of CT.gov and the clarity, comprehensiveness, and accuracy of the information it contains. We fully support NLM's interest in hearing from the community about these challenges through this RFI and via the public meeting scheduled for April 30, 2020.

That said, we firmly believe that the initiative NLM has launched can and should quickly segue from gathering stakeholder input on the use of CT.gov today to collaborating with the stakeholder community on concrete, actionable solutions. A sense of urgency around action is fully justified by the crucial role CT.gov plays in the research and development continuum.

We also believe it is incumbent on the diversity of stakeholders that interact with and rely upon CT.gov to assist NLM in making tangible change happen. NLM cannot achieve meaningful change without the support and engagement of patients, trial sponsors, and others who contribute to and benefit from CT.gov.

Finally, we believe patients and caregivers should play a meaningful, ongoing role in assuring that CT.gov fulfills the core, patient-centric role delineated in Section 113 of the Food and Drug Administration Modernization Act of 1997, which established this crucial registry.¹

Our comments below reflect the principles of cross-sector collaboration, timely action, and patient centricity.

Recommendation 1: *Launch a change process within 60 days of the public meeting.*

We fully support NLM's decision to hold a public meeting on April 30, 2020 to share insights and gather additional input. After that meeting, we believe it would be highly productive to plan a kick-off working session and follow-up sessions as needed, during which NLM and FDA collaborate with patients, clinical trial sponsors, providers, clinical research organizations, health IT organizations, and other stakeholders to shape tangible, actionable solutions. We are confident that by rolling up our sleeves as a concerned community, NLM, FDA, and external CT.gov stakeholders can ensure progress is made, and made now, against longstanding challenges compromising CT.gov's utility.

Recommendation 2: *Consult with the patient and caregiver community to frame and stand-up a patient advisory group.*

The advisory group should be convened early in the modernization process, actively inform CT.gov optimization, and remain a permanent part of CT.gov. Patient participation in clinical trials is a lynchpin variable bearing on the nature and pace of desperately needed medical progress. It is both right and smart for patients and caregivers to help evaluate and continuously improve our nation's clinical trials portal.

Functions of the advisory group should include:

- Providing input and insights on the redesign and modernization of CT.gov;
- Helping determine the best way to present and populate information for the target audiences; and
- Exercising a governance role in the development and utility of the site (i.e., not a tokenistic role).

We encourage the NLM to use best practices for patient engagement from other federal agencies and the private sector. For instance, the Patient-Centered Outcomes Research Institute (PCORI) is advancing a novel and important research paradigm that deeply engages patients and caregivers. PCORI has assembled a repository of engagement-related tools and resources developed and used by PCORI awardees.²

Patient and caregiver involvement has also resulted in positive outcomes in other sectors of the Department of Health and Human Services. The Food and Drug Administration's (FDA's) Patient-Focused Drug Development program provides a good example of an initiative that convenes patients to learn how their conditions and treatments impact their daily lives. Insights from these meetings have

¹ <https://www.govinfo.gov/content/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf#page=16>

² <https://www.pcori.org/engagement/engagement-resources/Engagement-Tool-Resource-Repository>

included suggestions of how technical language can be modified to ensure that the information on the site is understandable to greater numbers of individuals.

There are also compelling examples of private sector initiatives that successfully engage patients to design care delivery and programming. For example, the National Health Council conducted research³ to identify real-world examples of patient engagement in the health care delivery setting and determined that hospitals and health care systems successfully employ Patient and Family Advisory Councils (PFACs).

PFACs were initially introduced in 2006 by the Joint Commission on Accreditation of Healthcare Organizations to offer a structured and formal framework for the collaboration of patients, families, and health care professionals in decision-making, forming a mutually beneficial relationship where patients have a voice to become active participants in their own care. Patients provide input on the aspects of care that matter most to them throughout their experience with the health care system and recommend strategies health systems can use to improve patient-centered care. We believe that adopting a similar approach to patient engagement throughout the development and lifespan of CT.gov is a high impact strategy for assuring that this critically important asset continuously meets its mission and objectives.⁴

Again, we commend and thank NIH and NLM leadership for launching this stakeholder-informed initiative and appreciate your consideration of our comments.

Sincerely,

Eleanor Dehoney
Vice President of Policy and Advocacy, Research!America

³ <https://nationalhealthcouncil.org/wp-content/uploads/2019/12/meaningful-patient-engagement-in-health-care-delivery-2018.pdf>

⁴ <https://nationalhealthcouncil.org/national-library-of-medicines-nlm-request-for-information-on-clinical-trials-government-modernization/>

Submission No.: 188

Date: 3/13/2020

Name: [Not provided]

Name of Organization: Memorial Sloan Kettering Cancer Center

Attachment: ClinicalTrials.docxmonderization.docx

ClinicalTrials.gov Modernization

- Tweak the format for the registrations of non-interventional protocols especially the objectives -e.g., quality of life, epidemiology, psychosocial, integrative medicine, survivorship and exercise oncology protocols
- Add more characters in the arm description especially for BMT protocols -Arm/Group Description must have no more than 999 characters.
- Add track changes for amendments when editing
- Show where the errors are in the document especially in the eligibility criteria not what line the error is on -**ERROR: Text block contains an invalid character at position: 8656**
- Button for disregard changes
- Make the PI's email address optional instead of mandatory

Submission No.: 189

Date: 3/13/2020

Name: [Not provided]

Name of Organization: MIRACUM (Part of the Medical Informatics Initiative)

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

We use the ClinicalTrials.gov to search for studies ongoing at certain sites. We use this information to populate and update local study registries based on ClinicalTrials.gov's XML export.

Currently the search for studies is somewhat complicated because the search function does not allow for searching based on the recruitment status at a specific site. Additionally the information to a site is sometimes ambiguous if there is more than one clinic in a city and the clinic is not named.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

(2) Our primary use of ClinicalTrials.gov relies on a limited range of studies. We select all studies running on a specific site regardless of its type. It would help to be able to search for a specific site by a consistent identifier as the name can vary if stated. Second, it would help if the search function would not only address the overall recruitment status but also the status at a specific site.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Fast Healthcare Interoperability Resources (FHIR) are gaining more and more popularity as a data transfer standard in healthcare. We would like to be able to exchange data with ClinicalTrials.gov using FHIR (see <https://www.hl7.org/fhir/researchstudy.html>). This would be applicable for imports and exports to or from ClinicalTrials.gov.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Submitting a study with an automated tool would reduce human made mistakes and increase data quality. To automate study registration it is of utmost importance to provide correct specifications to all data elements. Unfortunately the Data Element Definitions (<https://prsinfo.clinicaltrials.gov/definitions.html>) and the xsd. don't always match: It suggest a fixed list

of terms (“Chose one”) where a free text is used in the registration form (e.g. “Primary Purpose”). Other fields don’t exist in the form (Secondary ID Type). A complete overview of all fields necessary, with exact field types and information on the field’s context would be helpful.

3. **Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. **Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

We would prefer more structured fields to input data. To maintain the balance between structure and flexibility we suggest to implement the option to chose “other” which opens the possibility to enter free text wherever necessary. This would be particularly useful for the field “Secondary ID”. Here its origin is (sometimes) shown on the web page but it is not exported to XML. Without this context information it is hard to work with the data.

FHIR also often provides a way to use free-form alongside structured input.

Eligibility criteria are currently presented as unstructured text on ClinicalTrials.gov, while there is a significant body of existing research attempting to formalize criteria (either via NLP, manually, or both), we believe there’s a need to provide them in a structured, standardized way to support automated patient-to-trial matching.

- 3b. **List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

The FHIR standard for data exchange is growing increasingly important and it would help to unify the data transported and reduce the need of data transformation and the potential loss of information associated with it.

Another standard that would improve the data quality is the use of OIDs to identify the study sites. Currently it is ambiguous which site is meant, especially if there is only a city mentioned and there is more than one possible site. This also prevents the search for studies at a specific study site - it only works for locations where no possible other study sites exist. When used in conjunction with HL7 FHIR, OIDs can be used as identifiers to the “Location” resources which reference study participation sites.

Submission No.: 190

Date: 3/13/2020

Name: Jessica Cohen

Name of Organization: Vertex Pharmaceuticals Inc.

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

1. ClinicalTrials.gov has separate tabs which capture information on “What's New, Trends, Charts” etc. If these features are made more visible directly on the homepage, it would be really useful. Many users may not go to specific sections or tabs unless they are aware of where to look for the information. Therefore, having the information on homepage will make these features that ClinicalTrials.gov already offers more visible/accessible for general public. For example: something in line with the home page for National Institute of Health Research UK (<https://www.nihr.ac.uk/>).

2. The presentation on ClinicalTrials.gov can be made more user friendly by use of graphics or lay language. If we can have a lay language presentation for information on ClinicalTrials.gov in addition to how the information is presented currently, it would make it easier for general public to understand the information. For example: protocol information can be categorized in to 2 sections - one which is currently available and a simplified version of the same information with public friendly headings/captions for patient and patient families. (For Reference:
<https://bepartofresearch.nihr.ac.uk/trial-details/trial-detail?trialId=2969&location=&distance=>)

3. On the search results page, there should be an option to sort the studies based on study dates (like first submitted, study start date or first results submitted dates). This will help in easily identifying the studies which are latest and can be viewed for reference by data providers.

4. There should be a Live-chat option available on the ClinicalTrials.gov website. There are many CROs and teams worldwide who can support in this area. ClinicalTrials.gov can connect with various disclosure specialist groups who was well versed with both ClinicalTrials.gov and PRS and can help the public with their queries in real-time. Kinapse would be willing to help and support if ClinicalTrials.gov is interested to explore this option.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. We have observed that ClinicalTrials.gov is not listed as primary registry in WHO International Clinical Trials Registry Platform (ICTRP). Considering the bulk of studies that are registered through ClinicalTrials.gov, it would be good if we have ClinicalTrials.gov listed as one of the primary registries for WHO ICTRP. This would help in repeating the similar information on multiple registries. Anyone who has registered on ClinicalTrials.gov would be compliant with WHO standards.

2. It would be good to have a feature of hyperlinking the parent studies with extension studies. If NCT number for parent studies appears as a hyperlink in the extension study, it can be used to directly navigate to the parent study if user/viewer wants to.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

1. Search/Advance search option is something that we use very frequently while visiting the website. It would be very helpful if this feature is further refined and more specific advance search options are added to further enhance the user experience. Some of the suggestions are cited below:

- a) We often try to search similar type of studies on the website for reference and example. This helps the data provider to maintain consistency within sister studies (for example, studies with same type of allocation method/units of measure/intervention model etc.).
- b) It would be good if the advance search option is updated to include additional filter options on the basis of studies of studies with Delayed certification filed.
- b) It would also be helpful if there is a feature so that the public can select the option to either have the exact match based on their criteria if they want targeted search results.
- c) It would be good to have the option to add/search based on Sponsor Name directly from the Homepage itself rather than going to advance search option.
- d) In advanced search option for observational studies, it would be good to have further search options for “Prospective” and “Retrospective” studies to get more refined search results.
- e) Data providers may also use the website to perform different type of analysis (For example, how many studies had major issues identified when the results were first time submitted or no NIH issues within a given duration). Therefore, it would be helpful if we have some filters for “Study Results Posted in First Attempt”.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our primary use is a wide range of studies, such as different study types, intervention types, or geographical locations.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- 1) In Participant Flow, there should be a facility to create or delete different arms in different periods. If ClinicalTrials.gov can align with EU results format for multi-period studies, it would be helpful for data

providers. This will help us to only create arms which are applicable for individual periods. Also, this would make US and EU results more in alignment with each other for such multi-period studies.

2) While working on PRS, there should be an option to apply the changes in reporting arm title and description to all the successive sections. Also, there should be an option to automatically update arms in protocol section to match the results section for consistency and overall alignment in the record. This will make the drafting less tedious.

3) When safety is not collected/not assessed for a study, we currently need to report number affected as "0" and number at risk as "0". Ideally in such cases, there should be an option to select "NA" and then provide justification in a comment box.

4) Character limit should be increased for Pre-assignment, Analysis population and Time frame sections:

a) Analysis Population: Data providers are expected to include different type of relevant information in analysis population section like definition of analysis set, reason why data is not provided for all arms, clarification on any pre-specified intent of a study, reason why there is a change in overall population etc. Therefore, it becomes difficult to capture the complete information under the provided section due to character limit constraints. An increase in character limit will help us to capture the information more clearly and can also help in limiting or avoiding comments/queries for additional information.

b) Participant Flow: Recruitment and pre-assignment details should have more character limits so that data providers are able to provide relevant justification for any specific approaches/reasons for a unique presentation.

c) Time Frame: Increase in character limit will specifically help in pharmacokinetic (PK) endpoints where we are required to detailed time frame like "Treatment Period 1: Predose; Day 1; Hours 0.5, 1,240 hours". It is sometimes difficult to accommodate the time frame within the available character limit. Additionally, per the recent approach of ClinicalTrials.gov, we have started receiving review comments on the abbreviation used in the outcome measure time frame. So to avoid such kind of comment and explain the outcome measure time frame more clearly, increased character limit will be really helpful.

5. If we do not have the data value available for outcome measures field, PRS only accepts Not available "NA" option. In our experience, "NA" may not be applicable for all cases. Sometimes, "Not Calculated (NC)" is better option for the data field. Hence, we suggest to accept inclusion of 'NC' for the field if not providing actual value.

6. Detailed guidance/checklist on redacted protocol and SAP uploads along with the examples of general identifiers that can be redacted by sponsors. This will help in harmonizing the redactions and also keep a check on unnecessary additional redactions in the protocol and SAP documents.

7. Inclusion/Exclusion can be split as separate sections for more clarity and ease of readability.

8. Flexibility to edit Statistical Analysis Title manually. This will give the data providers to provide a proper caption for the statistical analysis for example "MMRM Analysis for PBO verses Drug A" or similar.

9. Providing flexibility to select options in Measure of Dispersion/Precision section. For instance, if the Data is provided in form of ‘Mean’ and ‘coefficient of variation’, there is no drop down option available to select “coefficient of variation” as “measure dispersion” while reporting “mean” as “measure type”.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

We use Prime from Xogene to manage our study and posting statuses and make ACT assessments.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

1. Expected dates for result posting is available. Flagging for posting timelines on PRS will be more helpful. (sending out notification emails 3, 2, and 1 month before due dates.) Observation studies, closure status, free text NA option.

2. To introduce feature of Hyperlinking: It would be helpful if PRS would provide direct link path for some of the commonly used official manuals for referring the cancer staging and Adverse events (i.e. NCI-CTCAE criteria or AJCC manual etc.)

3. As per NIH guidance, individual outcome measure should include data from population of the current study only. However, generally in PK/PD analysis, there involve sparse sampling wherein sponsor collect data from other phases of studies involving the same molecule and perform analysis to reach the meaningful results. In such analysis, sponsor do not summarize data separately for population of current study, instead summarize data for pooled population (Population from current study + population from other studies). So suggest to consider accepting results for measures for which analysis generally done by using population from other studies.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The review criteria, PRS user guide, checklists, auto-validation messages in PRS - all are very helpful tools that support data providers to maintain quality. First draft quality can be further refined if some additional checks within PRS are introduced to avoid known standard comments/queries. Some suggestions are listed below:

a) ClinicalTrials.gov has a huge access to data in terms of outcome titles, descriptions of standard scales or common measurement parameters. It would be good if a link or guidance can be directly provided within PRS itself to help data providers with the best preferred approach and acceptable outcome measure title/descriptions based on already available and acceptable information on ClinicalTrials.gov. We already have this feature for “units of measure” field where PRS gives the option to select common units. We think it would be good if these suggestions are extended for other sections as well. This will decrease the time and efforts of data providers and will also help in bringing down the number of major issues in results.

b) Auto-validation is a feature that ClinicalTrials.gov currently offers. Our suggestion is to extend this auto validation feature such that some of the common NIH comments can be addressed before the first submission. For example: i) One of the common NIH comment is to provide milestone field for safety

population if it is not already a part of participant flow. If PRS can validate that the number in Participant Flow does not match the number at risk presented in Adverse Event section - a validation message should pop up requiring the data provided to report justification for the discrepancy. ii) There should be a provision for auto-validation for matching Actual enrollment in protocol section with the total subjects started/enrolled in the result section. If the database identifies a difference, a mandatory justification field needs to be filled in order to submit results. This will really help in reducing some very common NIH comments/feedback

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

1. Statistics/reports generation for the quality and timeliness would be helpful for the data providers to assess their performance on a real-time basis.

2. Acknowledgment or certification for data providers if they are meeting compliance as per pre-defined criteria (Reports in PRS on their compliance status or NIH quality metric which can be used by Disclosure specialist in tracking and assessing their performance)

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

1. PRS Character limit enhancement for various sections will help in providing the needed flexibility to ensure submitted information accurately reflects the study design.

2. As per previous review criteria guidance, we need to segregate primary endpoints on the basis of individual timepoints, however we do club them for secondary endpoints. It would be good if data providers are allowed to create single primary endpoint for a particular outcome measure with individual timepoints being listed as separate categories/rows (for example endpoints for Plasma concentration or safety endpoint where BP is being measured over time can be presented as a single endpoint with individual timepoints being reported in categories)

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

1. Consistent approach in ClinicalTrials.gov review: There have been instances in our recent experience wherein same type of comments are handled differently by different reviewers (e.g. enrollment number discrepancy between "started" milestone and "protocol registered enrollment no." was considered as Major issue in one study and advisory in other study. Our suggestion would be to have a consistent quality review within the review team as well. This will be helpful in analyzing/assessing the future quality standards and maintaining the same.

Submission No.: 191

Date: 3/13/2020

Name: Christine Hodgdon

Name of Organization: Storm Riders Network

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Currently the database from which clinicaltrials.gov links to produce search results is severely limited because information is entered at random by the study investigators. For example, when searching for metastatic breast cancer trials, the data may be entered as “metastatic solid neoplasm,” “advanced solid tumor,” or “advanced breast cancer,” which means that if a user does not include ALL terms, the trials for which they may be eligible will not appear in the search results. The user is essentially left guessing what terms the investigators may have entered when registering the trial.

A solution would be to create a database similar to Amazon or Zappos which has drop down menus so that all the information is entered uniformly, making the user experience much more efficient and effective. One option that would improve search capabilities is if there was a condition labeled “all metastatic cancer.” Metastatic cancer patients are the most vulnerable cohort of patients and there are many phase 1 advanced solid tumor trials for which a metastatic patient would qualify, but are very difficult to find based on the condition and disease entered by the investigators.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Metastatic Breast Cancer Project: <https://www.mbcproject.org>

Metastatic Breast Cancer Alliance has a registry and clinical trial matching application called MBC Connect: <https://www.mbcconnect.org>

Storm Riders Network: <https://thestormriders.org/science-research/clinical-trials/>

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I currently use the website daily to update a trial database I created which can be found at TheStormRiders.org and which specifically identifies trial for which metastatic breast cancer patients will qualify.

I have several suggestions for improvements of the current system:

Updates to registered trials:

Often times trials are not routinely updated, so for example the recruitment status may say “Recruiting,” but is in fact “Active, not recruiting,” or sometimes the trial is closed. I experienced this problem when attempting to list all the trials for metastatic breast cancer patients living in the Seattle area and was unable to do so because the information provided on clinicaltrials.gov was painfully outdated. A solution would be to implement a system that requests frequent and consistent updates to registered trials, and perhaps some kind of penalty for failure to report updates.

Another feature that would be very helpful to users is to allow users to view what kind of updates have been made. For example, was there an update to the type of drug being studied, the exclusion criteria, the inclusion criteria, or the recruitment status? What would be especially helpful is if users could be notified when the status of a trial changes from “Not yet recruiting” to “Recruiting.”

Notification functionality:

Currently there is no function that allows users to input their data (e.g. subtype, drug preference, mutations, criteria that would exclude them) and receive a notification when a new trial becomes available for their type of cancer, or to be notified when a trial that was “not yet recruiting” or was “active, but not recruiting” has actually begun recruiting.

Improve Filtering Functionality

a. Filter by Mutation

Another limitation is that there is no efficient means to search for trials by genomic mutations. With advancements in precision medicine and next generation sequencing, cancer is increasingly treated by the mutations it expresses, rather than by its site of origin. And for something as common as hormone mutations, there should definitely be an option to choose which hormones a patient’s cancer expresses. A drop-down menu that allows the user to choose mutations expressed by their cancer, would greatly increase the number of trials that appear in the search.

b. Filter by Exclusion Criteria

Patients often know which criteria will exclude them from a trial (e.g. metastatic disease, brain metastases, leptomeningeal disease, no measurable tumor, unable to provide biopsy, performance status, etc.) A filter that allows patients to enter their exclusionary information which would automatically remove any trials from the search results for which they do not qualify.

c. Filter by Site of Metastasis

Patients are often searching for trials that will address the site of their metastases whether it be bone, liver, lung, skin, or brain. Patients with brain metastases or leptomeningeal disease are often excluded from clinical trials and face a poor prognosis, so it is imperative this vulnerable cohort of patients have access to the trials currently recruiting and for which they may qualify.

d. Filter by Intervention and/or Drug Category

The type of intervention is also very important to patients searching for trials and a filter that allows users to choose what type of intervention they are willing to undergo would provide more tailored search results. For example, a patient may prefer to take pills as treatments for their cancer. In this case, the user should have the capability to filter out the interventions that use antibodies and require

infusions. On my website, I have identified 10 different classifications of interventions or drug treatments including chemotherapy, immunotherapy, therapeutic antibody, endocrine (hormone) therapy, miscellaneous inhibitors (e.g. PARP, HDAC, Proteasome), serine-threonine kinase inhibitors, tyrosine-kinase inhibitors, radiation therapy, surgery, and other (e.g. imaging, immunopheresis, neurotoxin, photodynamic therapy, steroid, therapeutic peptide, ultrasound therapy, antibiotic, engineered toxin bodies (ETBs), radiosensitizers). The ability to select trials that use interventions the patient prefers will provide a more tailored search.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My primary use of CT.gov relies on a more limited range of studies- those for which metastatic breast cancer patients will qualify. Having the capability to narrow the search fields to focus on cancer->breast cancer-> metastatic breast cancer would be very impactful for patients seeking a clinical trial.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

N/A

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

N/A

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

N/A

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

N/A

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

N/A

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

In general, the site requires a standardization of language across each data point of entry. I highly recommend creating a working group comprised of patients and advocates to provide input.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

N/A

Attachment: CT.gov Feedback.pdf

Christine Hodgdon
Metastatic breast cancer patient & advocate
Founder of TheStormRiders.org

1. Database Overhaul

Currently the database from which clinicaltrials.gov links to produce search results is severely limited because information is entered at random by the study investigators. For example, when searching for metastatic breast cancer trials, the data may be entered as “metastatic solid neoplasm,” “advanced solid tumor,” or “advanced breast cancer,” which means that if a user does not include ALL terms, the trials for which they may be eligible will not appear in the search results. The user is essentially left guessing what terms the investigators may have entered when registering the trial.

A solution would be to create a database similar to Amazon or Zappos which has drop down menus so that all the information is entered uniformly, making the user experience much more efficient and effective. One option that would improve search capabilities is if there was a condition labeled “all metastatic cancer.” Metastatic cancer patients are the most vulnerable cohort of patients and there are many phase 1 advanced solid tumor trials for which a metastatic patient would qualify, but are very difficult to find based on the condition and disease entered by the investigators.

2. Updates to registered trials

Often times trials are not routinely updated, so for example the recruitment status may say “Recruiting,” but is in fact “Active, not recruiting,” or sometimes the trial is closed. I experienced this problem when attempting to list all the trials for metastatic breast cancer patients living in the Seattle area and was unable to do so because the information provided on clinicaltrials.gov was painfully outdated. A solution would be to implement a system that requests frequent and consistent updates to registered trials, and perhaps some kind of penalty for failure to report updates.

Another feature that would be very helpful to users is to allow users to view what kind of updates have been made. For example, was there an update to the type of drug being studied, the exclusion criteria, the inclusion criteria, or the recruitment status? What would be especially helpful is if users could be notified when the status of a trial changes from “Not yet recruiting” to “Recruiting.”

3. Notification functionality

Currently there is no function that allows users to input their data (e.g. subtype, drug preference, mutations, criteria that would exclude them) and receive a notification when a new trial becomes available for their type of cancer, or to be notified when a trial that was “not yet recruiting” or

was “active, but not recruiting” has actually begun recruiting.

4. Improve Filtering Functionality

a. Filter by Mutation

Another limitation is that there is no efficient means to search for trials by genomic mutations. With advancements in precision medicine and next generation sequencing, cancer is increasingly treated by the mutations it expresses, rather than by its site of origin. And for something as common as hormone mutations, there should definitely be an option to choose which hormones a patient’s cancer expresses. A drop-down menu that allows the user to choose mutations expressed by their cancer, would greatly increase the number of trials that appear in the search.

b. Filter by Exclusion Criteria

Patients often know which criteria will exclude them from a trial (e.g. metastatic disease, brain metastases, leptomeningeal disease, no measurable tumor, unable to provide biopsy, performance status, etc.) A filter that allows patients to enter their exclusionary information which would automatically remove any trials from the search results for which they do not qualify.

c. Filter by Site of Metastasis

Patients are often searching for trials that will address the site of their metastases whether it be bone, liver, lung, skin, or brain. Patients with brain metastases or leptomeningeal disease are often excluded from clinical trials and face a poor prognosis, so it is imperative this vulnerable cohort of patients have access to the trials currently recruiting and for which they may qualify.

d. Filter by Intervention and/or Drug Category

The type of intervention is also very important to patients searching for trials and a filter that allows users to choose what type of intervention they are willing to undergo would provide more tailored search results. For example, a patient may prefer to take pills as treatments for their cancer. In this case, the user should have the capability to filter out the interventions that use antibodies and require infusions. On my website, I have identified 10 different classifications of interventions or drug treatments including chemotherapy, immunotherapy, therapeutic antibody, endocrine (hormone) therapy, miscellaneous inhibitors (e.g. PARP, HDAC, Proteasome), serine-threonine kinase inhibitors, tyrosine-kinase inhibitors, radiation therapy, surgery, and other (e.g. imaging, immunopheresis, neurotoxin, photodynamic therapy, steroid, therapeutic peptide, ultrasound therapy, antibiotic, engineered toxin bodies (ETBs), radiosensitizers). The ability to select trials that use interventions the patient prefers will provide a more tailored search.

Submission No.: 192

Date: 3/13/2020

Name: Melanie Chladny

Name of Organization: University of Michigan Medical School

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

University of Michigan Medical School, with input from other University units and the community, has prepared a response to each question along with some introductory and concluding remarks. While we tried to answer each question individually, there are structural discussions and cross-references among the different answers. Therefore we felt it would be most appropriate to submit this response as a single document, uploaded as a PDF file attached below.

Attachment: NLM RFI ClinicalTrials.gov Final.pdf

Comments on the Request for Information (RFI): ClinicalTrials.gov Modernization

Notice Number: NOT-LM-20-003

Issued by: National Library of Medicine (NLM)

Response Date: March 14, 2020

Name of Organization: University of Michigan Medical School, with input from other University units, and the community.

The University of Michigan Medical School applauds this initiative and appreciates the NLM's efforts to enhance the efficiency and utility of ClinicalTrials.gov. To prepare this response, we obtained input from a broad range of community groups to ensure that we understand and represent many perspectives: persons with medical conditions or their family members, prospective clinical trial participants, community physicians, academic medical researchers, and the many staff members that support their efforts working with ClinicalTrials.gov. A core committee prepared these comments, including a health science information specialist and six experienced ClinicalTrials.gov administrators. The administrators are members of the national Clinical Trials Registration and Results Reporting Taskforce, and collectively oversee over 1400 ClinicalTrials.gov records.

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Regarding new uses for ClinicalTrials.gov, we believe that research transparency would be enhanced if ClinicalTrials.gov records could automatically link to other electronic NLM systems such as PubMed Central to reference all related articles authored by the Principal Investigator and Co-Investigators. This would improve accessibility to publications, and more detailed trial results. Research transparency and comparative research would be further enhanced by linking similar or related trials in ClinicalTrials.gov in much the way PubMed Central has “Similar Articles” and “Articles that Cited this Article” appear automatically on the side.

Beyond its value as an information source for the public, ClinicalTrials.gov may be underutilized by grantors, IRBs, and feasibility or protocol review committees. ClinicalTrials.gov could facilitate feasibility reviews and grant application assessments by revealing important information details to reviewers about similar or nearby research. Details such as recruitment feasibility, outcome feasibility, completion rates for particular interventions, and achievement of objectives could enhance the review process. We heard from staff that if NIH modeled such considerations in its own review sections, universities would likely follow suit.

It would be helpful for users to be able to search the database by outcome measure titles, units of measure, or trial design type, ideally with the ability to overlay some of these characteristics. Administrators and study teams search ClinicalTrials.gov to identify details about similar trials such as how a device is classified, an outcome measure is described, or arms are set up. Administrators would appreciate improved searchability in both internal and public sites, including the ability to concurrently search multiple accounts at the same institution.

We received many suggestions about the “Search and Advanced Search” functions on ClinicalTrials.gov. The addition of more variables, with simultaneous layering, without having to open the “advanced search” window would improve searchability. For example, users seeking information about local trials want to search or sort by keyword, location, and recruitment status. It is currently difficult to locate studies in a specific geographic region other than by state or city. ClinicalTrials.gov has a map view of studies, but the information is only detailed to the state level. Ideally users could identify all trials taking place at a given institution, or within a given radius of a zip code, as people can with sites like Zillow, Carfax, Expedia, or Red Cross. Both physicians and lay people would appreciate the ability to search by institution, condition, and even department, medical specialty, and geographic region. It would be more convenient for users if NLM could overlay health conditions and other search criteria on an updated map search function. To make the search function more useful, NLM could introduce ways to sort by other variables such as distance, disease, and age criteria. For example, when searching for a flight on Expedia, users can filter or sort by cost, time of day, and duration for travel on a certain date. It would also be helpful if autofill suggestions would appear for the “other” categories, as well as for conditions. User testing would help identify the most important search or hierarchy features.

b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

We appreciate that there is already the capability to link to publications and de-identified individual participant data because it enhances research transparency and contributes to the advancement of science. For the lay public, connection to a well-reputed medical dictionary would be helpful. On other NIH websites, such as the NCI website, underlined terms open up such a glossary in real-time for the user.

Given that ClinicalTrials.gov, PubMed Central, and PubMed are administered by NLM, we believe that the three systems could be interconnected so that all research conducted by an investigator is easily linked to resulting publications. For example, if an article with a PubMed ID lists an NCT number within it as relevant to the findings in the article, PubMed could “push” this ID into the ClinicalTrials.gov record or “push” an email to the Responsible Party, who could then accept and submit that change with a click or two.

Social Media

Social media branding and engagement could advance the reach of clinical research. Given the ever-increasing prevalence of social media, ClinicalTrials.gov could be modernized to accommodate linkages to social media sites including Facebook and Twitter, as many other NIH and FDA webpages do. ClinicalTrials.gov has been, and should always be, available to the entire public, but whether it should stay focused on its original statutory mission of being a source of truth for a wide swath of trials, against which to check publication or data submitted to FDA, and a real-time database for ongoing research, or whether it wishes to enhance its approach to become a mechanism for trial recruitment may determine whether or not and what sort of social media usage is advisable. One approach would be for NIH to further fund the expansion of one or more CTSA-funded recruitment platforms such as [UMHealthResearch.org](#) or [ResearchMatch.org](#). We would expect that links to

social media sites on ClinicalTrials.gov would involve multiple warnings that one is leaving a governmental system.

To be effective, a recruitment site should be social media friendly with linkages to social media recruitment pages, support groups, and health information. Tweets and posts can be automatically generated using study titles, direct URL, and specific hashtags to assist with advertising the trial and improving recruitment. Social media enables study teams to reach more followers, tag people or groups, and share articles. Multi-site trials could publicize across the country and better reach target audiences based on trial location. Some of the social media campaigns for studies listed on UMHealthResearch.org have reached more than one hundred thousand people.

Data Scraping

Some of our peer institutions “scrape” data from ClinicalTrials.gov to populate local registries. Data scraping can entail copying hundreds of fields from an application program interface (API). We welcome more guidance from ClinicalTrials.gov on how organizations might implement or use API. Information could be posted on the public site to extend this capacity to smaller organizations that may not currently have the resources to implement API. ClinicalTrials.gov staff or web functionality contractors might be well served to go out into the field to interview health research institutions of various sizes and foci and investigate options that already exist for data integration.

c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Currently ClinicalTrials.gov is a convenient public source for research protocols, results, informed consent documents, and data sharing examples. Some of the people we spoke with have used ClinicalTrials.gov to look for trials for themselves, clients, or patients to participate in. Some see it as a source of trial information. But many felt that it currently doesn’t meet their desires as well as other sites. Below, we offer several suggestions for potential improvements to ClinicalTrials.gov based in part on the desires we have heard from healthcare providers and the lay public.

Appearance, Accessibility, and Function

ClinicalTrials.gov has been in use for twenty years. We recognize that there were significant resource constraints on its initial development and even its expansion to include results reporting after FDAAA was enacted. Similarly, we appreciate that during the last decade multiple efforts have been made to seek feedback from academic and industry users, as well as to provide reports and iteratively improve functionality to enhance the public’s ability to use the system. Nonetheless, some stakeholders think that the site has not kept pace with user needs and evolving expectations about how the site could be used. They would like to see ClinicalTrials.gov introduce new features and functionality.

The best websites offer simple and user-friendly navigation. Our stakeholders revealed that ClinicalTrials.gov users would appreciate a more user-friendly interface. Site visitors should be able to quickly and easily locate everything they need. For example, the ability to select a geographic

location from a map and type in a condition or key word would allow for a frustration-free search for studies about a topic in a specified urban area.

A good user interface should be designed for all audiences, including colorblind and disabled users.

To improve the user experience, ClinicalTrials.gov should become more appealing and easy to navigate. There is such a vast amount of information on the site in text-heavy format that lay or occasional users find it difficult to locate what they are searching for.

Among government websites, the FDA, CDC, and NCI websites could serve as models for the modernization of ClinicalTrials.gov. Like ClinicalTrials.gov, these sites house enormous collections of resources, databases, and regulatory information. Yet they are welcoming, navigable, organized, and easy to use.

Several enhancements would improve the ClinicalTrials.gov user experience. We offer the following recommendations:

- Modernize font type and size with more consideration of visual impairments
- Update the logo
- Beautify and contemporize the webpage design
- Make the interface more user-friendly
- Increase the use of visual content
- Implement a scroll-over function for specific terminology so users can understand definitions
- The public site could offer more fields in the advanced search to improve searchability:
 - ACT
 - Investigator Name
 - NIH Policy
 - Funder
 - Outcome Measure
 - Interventions
 - Study Design
 - Location
 - Trials with Data Sharing Plans
- Please facilitate a more nuanced demographic search capability to support the NIH and FDA's expressed desires to facilitate more inclusive representation in clinical trials.
- The ClinicalTrials.gov public records could highlight or emphasize the recruitment status and links to external recruitment pages to help participants locate those important details, like the NCI site does.
- Improve and share more discrete analytics about users. Beyond current data about the number of visitors to ClinicalTrials.gov each month, it would be helpful to know more about who is using the site so ClinicalTrials.gov could update infrastructure accordingly. Are the same people visiting the site each day? What proportion of users are administrators, academic researchers, media, regulators, lay public researchers, and people seeking trials?

The ClinicalTrials.gov website says it is “a web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions” (<https://clinicaltrials.gov/ct2/about-site/background>). If the intention is to really support participant recruitment, our stakeholders felt that some improvements can be made to ClinicalTrials.gov in

terms of its utility as a recruitment resource. Stakeholder feedback revealed that the information on ClinicalTrials.gov about clinical trials is overwhelming, hard to distill down, and that it is difficult to understand which study might be the most suitable for a prospective participant.

We consulted with a team of clinical trial recruitment specialists, some of whom use ClinicalTrials.gov. One individual, despite having a graduate degree and decades of research experience, encountered difficulty using the ClinicalTrials.gov advanced search function because it wasn't iterative or user friendly. Over time, she learned how to use basic system functions, but it took time and patience, and perhaps more knowledge than the average participant might have when seeking clinical trials. We encourage NLM to consider that people seeking to participate in trials are often in crisis, overwhelmed, and may not have a university education. As written, ClinicalTrials.gov records might create additional barriers for people seeking information about clinical trials. Our recruitment professionals noted that organizations that pull language directly from ClinicalTrials.gov aren't as successful in reaching participants or recruiting as those that adopt more participant-friendly language.

When potential participants are seeking opportunities to participate in a clinical trial, they want a bi-directional experience. Instead of reading and analyzing long eligibility lists, they would like to answer easy questions about themselves and have the system show them which trials match. Conversely, ClinicalTrials.gov is one-sided, not interactive, and difficult for people to easily gain access to comprehensible information about trials.

A health research recruitment site has a fundamentally different mission than a trial registry. To be truly useful as a recruitment site, trial details should be geared toward prospective participants. Information should be presented in a user-friendly platform with lay language, inviting interaction, and engaging questions.

ClinicalTrials.gov could be more straightforward about what it is, and who it's geared toward. We appreciate that ClinicalTrials.gov was created to meet regulatory and policy obligations to provide information, and it does that very successfully. Perhaps rather than trying to be all things to all people, there should be a deliberate separation between a site that is primarily focused on the public users' needs and the need to meet statutory, regulatory, and policy obligations. If NLM is committed to achieving a participant-friendly format, it could link to an external trial registry or a separate tab on ClinicalTrials.gov connecting this audience to a more lay-friendly user platform. Well short of that, it could also make contact information more prominent, including instructions for people who are interested in learning more about a trial.

To better understand the needs of the public, we convened a focus group to obtain feedback about people's experience with, and overall perception of, ClinicalTrials.gov. The participant group was comprised of patients with chronic health conditions and caregivers or loved ones of patients undergoing treatment for disease. Several participants had previously been involved in research studies and clinical trials involving rare disease, chronic disease, cancer treatment, cardiac rehabilitation, diabetes, liver disease, and transplants. Even though several people had been previously involved in clinical trials, only four of twelve convened were aware of ClinicalTrials.gov before participating in the focus group, three of whom had previously used ClinicalTrials.gov to search for a trial for the purpose of enrollment. Almost all participants had previously searched for a clinical trial on sites other than ClinicalTrials.gov.

When asked their first impression of the ClinicalTrials.gov website, respondents stated that it seemed "imposing", "overwhelming", "confusing", "dated", and "bureaucratic". It appeared to

participants that the site is not geared toward the general public. Focus group participants generally felt that the site contained a vast amount of potentially useful information, but that language was difficult to understand, and considerable time would need to be invested to find what they were looking for. One respondent asserted that for people who aren't familiar with ClinicalTrials.gov, "...it would be challenging to weed through the site to find what's important", while another stated, "I am an experienced user of computers, and would have given up on this site long ago [if focus group moderators didn't explain how the site worked]".

When asked what they liked best about ClinicalTrials.gov, focus group participants appreciated access to information about clinical trials. When asked what they would like to change about the site, several respondents indicated that navigability and accessibility should be improved. Participants overwhelmingly felt that the site should be more user friendly. User feedback showed that the front page was extremely difficult for some users to navigate. Some participants could not figure out how to find the search field, let alone search for a trial. Another user observed that if the site is supposed to be geared to the public, the "Learn More" link for Patients and Families should not be hidden on the bottom left part of the site page, and only accessible by scrolling down. Although Brief Descriptions are supposed to be written in lay language, several participants did not understand the information. One user who searched a trial on her own disease could not understand the trial after reading the Brief Description. Commonly used clinical trial terms may not be understandable to the general public (e.g., "exclusion criteria", "arm", "outcome measure" and "adverse event"). Several participants felt that recruitment status and contact information should be much more explicit and visible. Many respondents raised concerns about accessibility. Focus group participants were concerned about ensuring that ClinicalTrials.gov is accessible to all users, including those who are not tech savvy, the elderly, and people with disabilities.

Focus group participants were given the task of searching ClinicalTrials.gov for a subject they were interested in (e.g., health condition, drug name, keyword). Less than half the users were able to find what they were looking for. One participant stated that while she was able to find a trial that interested her, the record lacked information that would be meaningful to a potential participant, nor did it answer any questions she had about the trial. When the group was asked to search for a trial with results, one experienced user of ClinicalTrials.gov stated that despite finding nine trials on the drug they were searching, none had results posted on ClinicalTrials.gov, whereas when that person searched medical journals, they found scores of articles providing much richer information on the drug than ClinicalTrials.gov. Most respondents did not find the registration or results information posted on ClinicalTrials.gov easy to understand. Everyone felt that ClinicalTrials.gov should share information in a manner that's easy for the public to understand.

Participants had several suggestions to make ClinicalTrials.gov more accessible and understandable. Several people commented that users need a manual to use ClinicalTrials.gov. One respondent suggested the addition of vignettes geared toward patients. Others suggested that they would appreciate having a video overview of how to successfully navigate the site. Another person suggested that a 1-page infographic could help the public understand how to use the site.

When focus group participants were asked what they thought the primary purpose of ClinicalTrials.gov was, they answered that it was to meet a legal requirement to share details about drug and device clinical trials and share the results of completed clinical trials with scientists. When asked to answer from a patient's point of view what ClinicalTrials.gov's primary purpose *should* be, participants thought the site should help people find clinical trials to participate in and understand information about clinical trials. When asked to answer the same question, but from a taxpayer's

point of view, participants commented that the purpose of ClinicalTrials.gov should be to help people understand information about clinical trials and ensure that companies and researchers are transparent about changes to clinical trials. Their responses suggest that citizens are not uncomfortable with the notion that a site to ensure transparency is a reasonable goal – and that that information may not be the same information or packaged the same way as information that would help people understand information about Clinical Trials. But they also want information that is readily accessible and understandable. The underlying gap between scientific language and meeting the regulatory requirements and translating the material into accurate, readily available knowledge remains substantial and not inexpensively or quickly soluble, as enormous amounts of additional writing, editing, and vetting would be required and would impose still more burden on either research teams, the government, or both. That said, making the search functions more robust, using algorithms to make suggestions and look for good fits, and then more immediately sharing contact information to refer people to potential trials they would be interested in on the registration side, and ready links to articles that explain results more completely on the results side, could go a long way toward usability.

Many users were concerned by the fact that they - as people who know more than the general public about clinical trials - were nonetheless unaware of ClinicalTrials.gov's existence. Several participants were especially concerned about whose job it should be to make patients and prospective participants aware of ClinicalTrials.gov. Whether it should be researchers, community physicians, or the government itself who promote the site, the public should be better informed that this wealth of information is available to the public, especially once it is modernized. Lay users also shared very different opinions about whether they could bring the information they found in ClinicalTrials.gov to their physicians, ranging from, "They're all too busy and wouldn't have time to look at this," to "My doctor already knows or thinks they know everything they need to," to "They would rather read articles, so how would this help them?"

One participant, involved in PCORI research, said that this entire system needs to "wise up" to get participants involved in trial design. If participants or patients were able to rate trials for whether they would be willing to participate in them, or whether they found the outcomes meaningful to them, or comment on what outcomes they would find more meaningful, then the public would truly have a voice in shaping research.

Over the course of NLM's multi-year modernization initiative, we strongly recommend more public engagement and user testing of planned enhancements to ensure that ClinicalTrials.gov meets the needs of the public and is truly a source of meaningful information for patients and prospective trial participants. The following example illustrates how a site could meet the needs of prospective research participants.

In 2005, the University of Michigan Institute for Clinical and Health Research, in part supported by CTSA funds, created a robust participant-centric recruitment site. After several iterations and more than a decade of user testing and redevelopment, the site, which has become UMHealthResearch.org, now offers a much more dynamic search and user experience. Throughout the site's development, it has kept pace with technology and consulted with users to understand how people find research studies and what users want in terms of the experience. Each trial recruitment page contains a title, purpose, description, and contact information. Optional help text can be used to assist people in navigating to the information sought about trials. Trials are presented in a lay-friendly, engaging, and informative manner. The site can suggest a match based on user

profiles and trial recruitment details; users can search the site for any posted study; and study teams can search its registry of prospective participants.

In [UMHealthResearch.org](#), trial details are populated by study teams themselves, because they know their studies best and are motivated to reach enrollment targets. Study teams put a lot of effort into drafting the registration, using non-scientific lay language to make it easier for participants to understand what would be involved in participation and the study purpose. Formal scientific titles may even be turned into lay language questions that asks the underlying question a researcher seeks to answer. The portal allows for confidential batch messaging to everyone who expresses interest in participating in a particular study. Currently, this platform is being expanded to multiple other research institutions in large metropolitan areas.

Just as a participant recruitment site should be lay-friendly, it should also be manageable for study teams. We have heard from some study teams who, after registering their trial on ClinicalTrials.gov, received hundreds or thousands of inquiries from potential but ineligible participants. In one instance, a third party site had “scraped” ClinicalTrials.gov and shared details about a trial to a large group of people who didn’t even qualify to participate. This was overwhelming for the small study team who had to field the many inquiries. As a thoughtfully structured recruitment site, [UMHealthResearch.org](#) automatically filters interested participants to ensure that they meet the eligibility requirements. The platform also has filters to prevent people from flooding the system, screening questionnaires to filter eligible and ineligible candidates in and out, respectively, and auto-responses and response timing requirements so that potential participants hear back promptly.

We wish to flag one specific drawback to having a separate participant-facing page: for it to be effective, it further increases the burden on the study team to develop the right sort of language to engage participants. Therefore, if a separate participant recruitment page function were to be introduced in the ClinicalTrials.gov modernization efforts, the participant recruitment component should not become a requirement for Responsible Parties. It should only be offered as an option so that Responsible Parties can choose to capitalize on recruitment benefits. Principal Investigators and study teams already have an incentive to recruit participants; so by making recruitment easier to achieve, they are likely to use and appreciate this value-added tool.

Whether it is most efficient for ClinicalTrials.gov to develop its own recruitment pages, a massive undertaking, or facilitate links to external recruitment sites is a weighty decision for ClinicalTrials.gov to make. We would recommend first prioritizing the modernization features that enhance efficiency and compliance with its original statutory mandate of providing information, while continuing to gather information about existing recruitment-type options to make that determination.

If ClinicalTrials.gov decides that there is an unmet need for a comprehensive national research registry or network geared toward recruiting participants, it presumably faces three basic options: create a whole new platform at taxpayer expense, provide multiple links to public or private sources that each perform partial functions, or create active interfaces with recruitment match platforms already developed with NIH CTSA funds. Any of these options might help study teams achieve better recruitment, especially those studying rare diseases.

We also investigated how the site could work best for community or referring physicians, and found that, again, it would require a very different site with different workflows. Referring physicians want a definitive source of trial information, such as a trifold brochure, protocol, and recruitment details so

that they can determine if a trial is suitable for their patients. Physicians are concerned with specific and detailed eligibility criteria, while that level of detail may dissuade potential trial participants.

We also consulted with community physicians across Michigan to ensure that we could better understand how this important stakeholder group uses ClinicalTrials.gov. We learned that physicians use ClinicalTrials.gov differently. One respondent's health system participates in several research studies and clinical trials, many of which are registered on ClinicalTrials.gov. He considers ClinicalTrials.gov to be a great source of information for the public and noted that his practice regularly refers people to the site for information about trials. Another community physician stated that he has never used ClinicalTrials.gov, nor have his peers. Instead, his health system uses national and local research networks such as National Research Network, Arbor Research Collaborative for Health, Michigan Public Health Practice-Based Research Network (MI-PBRN), or Upper Peninsula Research Network (UPRNet), as a source for clinical trials. Yet another community physician was not familiar with ClinicalTrials.gov.

A practitioner told us that although she is familiar with ClinicalTrials.gov, she does not use the site because of her busy work schedule. She felt that any of her patients who might be a candidate for a trial would likely also be under the care of a specialist; so she assumed that the specialist physician would be a more appropriate source of information. Another physician acknowledged that the site can be burdensome, and "one more thing on the to do list" for busy doctors.

One individual acknowledged that, "as a physician, it's not challenging to use ClinicalTrials.gov, but for others, it can be". To successfully navigate ClinicalTrials.gov, he felt that it was important for users to know what keywords and search criteria to use. Another physician stated that while they have used ClinicalTrials.gov to search for a trial, it was for a family member and not for the purpose of a patient referral.

We heard from a few physician-researchers who were not impressed with trial results on ClinicalTrials.gov. Instead, most physicians preferred to review scientific literature to learn about the results of clinical trials and human subjects research: "I'd sooner review results through journal articles than ClinicalTrials.gov. ClinicalTrials.gov results could be more robust, by adding links to published works and data sets. This would be more valuable to researchers and the public." Another practitioner indicated that they do not use ClinicalTrials.gov to find results because the site is not convenient. Instead, she prefers to obtain information from medical journals, the UpToDate software system, and the internet.

One physician commented that industry-owned data sets would be of great value to the physicians and public if they were publicly accessible. More and more companies and independent researchers are posting their datasets to their institutional or general repositories such as Vivli. To help physicians find these datasets, it would be helpful if links to the datasets referenced in the IPD section were prominently displayed in the registration section and also in the results section once results are posted.

Another respondent acknowledged that it can be a challenge to connect with other physicians doing research. One respondent noted that physicians generally reach out to academies such as the American Academy of Pediatrics to join academy-sponsored research projects and suggested that, if ClinicalTrials.gov is motivated to reach more community physicians, they would be well served to develop better linkages and auto-feeds with academies.

d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our research portfolio at the University of Michigan spans single site investigator-initiated trials, large multi-site clinical trials, feasibility and pilot studies, observational studies, and repositories. While most University of Michigan initiated trials are performed in the United States, some are conducted abroad. This broad scope of research is reflected in our use of ClinicalTrials.gov. The University of Michigan both conducts and searches for a wide range of studies, including those that match all the parameters mentioned in the question. More complete and facile searching based on any fields in a study record, including interventions, would make the system more useful for our researchers.

2. Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

We sent a survey to everyone at University of Michigan with a ClinicalTrials.gov account, and heard that submitters want a better user interface, clearer definitions, and help language. We have compiled all of these suggestions, from a range of more or less experienced submitters with varying degrees of experience, into the list below.

General Comments

- Any way the system could accommodate automation of data entry during registration, streamline the process, and make it easier for people to submit information would be most welcome.
- Our stakeholders resoundingly commented that to be truly modernized, ClinicalTrials.gov should accommodate automation wherever possible in order to reduce the administrative burden of manual data entry. Consider the potential cost and productivity savings if the system no longer required all ClinicalTrials.gov submitters to manually enter data that could otherwise be automated. Additionally, there would likely be an increase in data accuracy if information could be imported or automatically entered into the system.
- Help tools should be bigger, bolder, and more visible.
- There could be a direct link to real-time help modules while performing data entry.
- Submitters welcome more useful help language and guidance - more examples, help text, and interactive questions.
- We suggest introducing a “What’s this?” hover function when hovering over a field name.
- Improve searchability
 - It would be nice if the User List could be sorted by user name, first name, last name, or group.

- Our list of users is more than 1000 names long. To facilitate locating a name to be added to an access list, it would be appreciated if the Record Access List could be sorted or filtered (e.g., by group).
 - The User Name list, as it appears when one is trying to add a name to a record, whether in the access field or the Responsible Party field, is not sorted or searchable by first or last name. Rather than having to scroll through a list of hundreds of people without knowing the Responsible Party's user name, the Responsible Party field should be populated by typing first, last, or user name. Much like the current functionality in the Conditions field, a pick list of terms could appear when the submitter begins typing.
- As administrators, the biggest problem we see with quality is that submitters tend to guess definitions of terms without checking to fully understand the meaning and intent. Please offer a variety of help options for people seeking more information or assistance. One model is to adapt the “walk through” functionality of the new NLM NIHMS system. The first time someone uses the system or creates a new record or results submission, an optional “walk through” feature could automatically provide interpretive help and interaction. Remaining a permanent icon in the upper right corner of the interface, the walk through assistant could be easily turned on if a submitter chooses to use it.
- We suggest that the system more explicitly flag fields that are not required.
- For mandatory fields that are not completed, submitters would appreciate a notification, such as a text box that appears to remind them that the field must be populated, and perhaps the reason for the requirement.
- **Definitions**
 - Definitions should be more consistent, clear, and accessible.
 - On the public site, the Glossary is accessible by clicking an information link next to a data element. Clicking this link opens a pane on the right which contains only the definition for that data element. Links are provided so that the user can easily access a complete set of definitions, if desired. Having a function similar to the public site Glossary, or a “What’s this?” link by each data element would improve the ease, speed, and quality of information entry because the submitter could more quickly access the needed information. This would solve the problems noted next.
 - In the PRS, there is a Definitions link at the top of each page, but it becomes invisible when the submitter scrolls down the page, and it is not near the data elements on the page. The Definitions link could be bigger, bolder, and more visible.
 - The Data Element Definitions document is a great resource but is too dense in the current format, driving inexperienced submitters to give up or guess the definition. We appreciate that the Definitions link takes the user to section of the definitions page corresponding to the section and module currently being edited, but the definition being sought is often quite a bit further down the document, often not visible until the submitter scrolls down the page. Even expert submitters experience difficulty locating the right definition.
 - Some definitions are too vague to be useful to inexperienced submitters. Definitions such as study purpose, primary completion date, and time frame would be improved with the addition of contextual information and examples.
- **Other Quality Control**
 - Please add a personal pronoun detector for the entire study record.

- Improve the ease of error detection. Errors and warning messages should be smarter. We advocate for the display of common fixes to error messages. Sometimes an error shows as a problem in the record, but it is unclear to a study team how to resolve the error. Some errors offer helpful hints as to the problems, but others (title lengths for example) just inform the submitter that something is wrong. Sometimes the errors or warnings are misleading, especially to submitters who are less familiar with PRS. It should be clear which messages will prevent a record from being released and which ones are essentially suggestions.
 - Character or word limits in the platform should be removed unless needed for a technical reason. All information about them should be consistent and accurate. Currently, some fields have warnings that list a character limit much smaller than the actual limit.
 - A spell check should highlight the location of the error and take the submitter to the error in the ClinicalTrials.gov record.
 - Currently, it is not possible to expand text boxes when using Internet Explorer to perform tasks in ClinicalTrials.gov. Please allow all text boxes to be expanded, regardless of which internet browser is used.
- Please include an **internal, temporary, tracked changes view** of revisions in PRS while in progress (only until the update is submitted). There currently isn't a way for submitters or administrators to see revisions to a record that is in progress and has changed since its public posting. A tracked changes view in PRS would allow users and administrators to see what changes were made to the record before a record update is released. There's currently no audit trail of what revisions have been made in the PRS. This feature would be similar to the "History of Changes", but this internal version would only be visible to administrators and submitters with access to the specific record. It would only need to be available to users in PRS until the record is made public, since the public "History" shows all changes from one submission to another.
- There should be an "undo" button in case a record is mistakenly edited by someone with access other than the Responsible Party. This would prevent the imposition on a Responsible Party to approve and release a record that hasn't actually changed and may already be complete.
- When a submitter marks a record "Entry Complete", there should be a pop-up with a link to a real-time quality review checklist or guidance text to facilitate a self-check to identify and fix mistakes.
- Please improve the downloadable registration and results previews. Create previews that are easy to read and easy to edit. The current .rtf preview is editable but has strange formatting and is hard to read (e.g., the line spacing is too crowded and has seemingly random gaps). Conversely, the .pdf preview is easy to read but hard to edit. The .pdf could default to a navigational mode that allows scrolling. Creating a MS Word doc preview would be one straightforward solution.
- Approval and release of records could be easier and more straightforward for Responsible Parties. Often, Responsible Parties click the "Approve" button but don't realize that they're also required to consent to the submission's release by clicking the "Release" button. When Responsible Parties miss this second step, it necessitates outreach from an administrator and/or study staff and further burdens the Responsible Party to log in again to complete the release. The system could offer either a reminder that the check box must be checked in

order to complete the approve and release, guidance text, or a progress bar throughout the release process to communicate that the release is not yet complete.

- It would be helpful to receive more guidance about how to complete each section of the registration and the implications of entered data on results reporting. For example, reminder text could appear when outcome measures are created, including reminders (for ACTs and NIH-funded trials) that results will be required for each primary and secondary outcome measure listed but not for exploratory outcome measures.

Registration

- We believe that non-ACTs could be held to a different standard than ACTs without sacrificing quality. There should be more flexibility with the protocol registration for behavioral trials, especially those using qualitative or mixed-methods methodologies to accommodate studies whose primary objectives may be qualitative or descriptive.
- At the time of registration, the system could identify ACTs and NIH-funded studies based on data entered and issue an advisory notice that they will be required to upload a copy of the protocol and statistical analysis plan at the time of results reporting. For studies that do not appear to be required by law or federal policy to register and report results, the system could issue an advisory reminder to consider whether the any other funder of the study requires results to be reported, and what that reporting obligation might entail.
- Once an ACT or NIH-funded trial is ready to be released, the Responsible Party could be required to click an attestation that they understand and acknowledge their continuing obligations to maintain the ClinicalTrials.gov record and report results.
- We recommend the introduction of system notices advising likely next steps, even for records that have been successfully released and published. For example, “Next step: if your study is ‘Not yet recruiting’, please remember to update this status to ‘Recruiting’ within 30 days of the date when your first participant signs the informed consent document.” These could appear both on the front page of a particular record and in a “Likely Next Steps” column, next to the “Problems” column. Further, these could be sent out by email to Responsible Parties at regular intervals.
- Please introduce algorithms based on the NIH policy and start date to identify results reporting obligations for compliance monitors and Responsible Parties.
- Please introduce algorithms based on the Common Rule obligation to upload the informed consent document based on start date and Collaborator or Sponsor.

Title

- The system should remove the requirement to include a Brief Title, and leave it as optional. There should be an optional check box that indicates that the Brief Title is the same as the Official Title.
- The note that appears when a title may not be sufficiently descriptive is not helpful because the title may have already been established and approved by an IRB. We suggest eliminating it.
- The system could allow entry of an acronym in the middle of the title rather than at the end. Similarly, some brief study titles contain lower case and upper case letters. However, the

system automatically capitalizes certain words. A submitter might type something as lower case and save it that way, but the system automatically capitalizes letters. This is problematic. The system logic should be reformatted so that it can flag, but not prevent, registration of a study that has an unconventional title.

Study Status

- It's unnecessary to be required to manually update the Record Verification Date each time a record is revised. This field could be automatically updated to reflect the date when a record is updated.
- Submitters find it difficult to differentiate between the many different date types in the Study Status module. Additional terms such as "Record Verification Date" confuse submitters who have difficulty differentiating between the many different date types in the Study Details module.
- Study teams have difficulty understanding the meaning of "Primary Completion Date" and "Study Completion Date". The system should be programmed to flag these fields with a more explicit definition, or create an algorithm to auto-populate the estimated "Primary Completion Date" and "Study Completion Date" based on the time frame of outcome measures, although this might require additional smart logic regarding those time frames. ClinicalTrials.gov could offer examples, prompt questions, or provide formulas that submitters can use to understand the meaning of an estimated completion date. We suggest the introduction of a calculation box with interactive questions about the anticipated start date, duration of accrual, primary and secondary outcome measure time frames, and possibly other factors such as duration of treatment. The fact that many submitters do not understand the meaning of time frame is problematic. The system could also generate text confirming the data entry to ensure that the submitter understands how completion dates impact the trial record. For example, after the submitter enters data in all required fields, the system could generate text such as: "You've stated that your primary outcome time frame is 2 months. Does that mean 2 months from enrollment, or from the start of treatment?" Despite that this term is apparent to an experienced submitter or administrator, it is not intuitive to everyone.
- Please clarify the difference between "Active, not recruiting" and "Suspended". The current definitions are too ambiguous. ClinicalTrials.gov defines "Active, not recruiting" as "Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled", and "Suspended" as "Study halted prematurely but potentially will resume". However, to some, "Active, not recruiting" might mean that a study is on hold, but will definitely resume (which is a distinction from the "Suspended" definition). Given that "Suspended" implies that all study activity has ceased, "Active not Recruiting" is the best definition for studies that cease some activities, (e.g., enrolling new participants), but continue with other activities (e.g., collecting data from already enrolled participants). System logic could clearly indicate that "Suspended" is to be used only if trial is expected to reopen, or allow submitters to provide details about the reason for the suspension (e.g., Study Suspended for Safety Reasons). Likewise, when "Active, not recruiting" is selected, a prompt could appear to remind Responsible Parties that this term cannot be used once all data is collected. An optional text box could appear to allow the Responsible Party to explain why the study is active but not recruiting (e.g., waiting for IRB approval for additional enrollment).

- Inconsistency between government departments adds to the confusion about the true meaning of terms. While ClinicalTrials.gov records use the term “Active, not recruiting” to demonstrate that study participants continue to receive an intervention or be examined but no new participants are recruited or enrolled, the NCI term for this status is either “Closed to Accrual” or “Closed to Accrual and Intervention” (<https://wiki.nci.nih.gov/display/CTRPdoc/Trial+Status+Values+in+the+CTRP+and+ClinicalTrials.gov>). However, there may be some scenarios when the two sources do not align, as described above. Likewise, ClinicalTrials.gov uses the term “Suspended” to indicate a temporary closure for any reason (financial, safety, planned interim analysis, etc.), while NCI uses the term “Temporarily closed to accrual”.
- Another concern about the term, “Active, not recruiting” is the regulatory risk of misinterpreting this term to mean “continuing to collect exploratory data”, “continuing to follow patients” or “still open with the IRB”. We’ve come across several cases where Responsible Parties got this term wrong. It puts the onus on administrators to pore over trials listed as “Active, Not Recruiting” and cross-reference other aspects of the ClinicalTrials.gov record with their clinical trials management system and IRB management system to ensure that the status is accurate. If ACTs are incorrectly listed as “Active, not recruiting” when they should be listed as “Completed”, institutions are exposed to the risk of regulatory noncompliance and resultant consequences. A warning should appear with the definition and regulatory implications of the selection. Perhaps when the submitter selects the “Active, not recruiting” status, they should be required to check a box to attest that the study has not yet completed data collection. Again, given the consequences for noncompliance, it’s important that the system provide clear definitions that are not subject to interpretation.
- A study may be on hold for anticipated reasons (e.g., funding, recruitment challenges, staffing, etc.). Submitters may be uncomfortable using the term “Suspended” because it implies a safety or regulatory issue necessitating the hold, or suggests wrongdoing or noncompliance. We suggest replacing “Suspended” with a similar term, such as “Temporarily stopped” which is similar to the NCI’s term but possibly more easily understood by lay people.

Sponsor/Collaborators

- The “Collaborators” field should not have a note stating that it has a limit of 80 characters. Some Collaborator names are legitimately more than 80 characters, and not all submitters understand that the Data Element Definitions provides the true character limit of 160 characters.
- It would be extremely helpful to be able to differentiate “Collaborators” in the research process from financial sponsors or “Funders”. One of our community members noted that she prefers to participate in government sponsored trials over industry sponsored trials.

Oversight

- We suggest that to help submitters accurately answer whether a trial is studying a US FDA-Regulated drug, the system could pose interactive lay language questions which would help determine the applicability of section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

- We suggest that to help submitters accurately answer whether a trial is studying a U.S. FDA-regulated Device Product, the system could pose interactive lay language questions which would help determine the applicability of sections 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.
- Some ClinicalTrials.gov submitters have requested improvements to the ACT device question. Interpretation of a device can be difficult, especially for radiation-emitting device products and devices that are used in clinical trials but are not the intervention studied. Perhaps ClinicalTrials.gov can offer interpretive support for identifying whether a trial is studying a device. For example, in similar fashion to the NIH case studies that identify whether NIH would consider a research study to be a clinical trial, NLM could develop some examples to address the regulatory ambiguities of device trials. Similarly, the Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial should be much more palatable, so that someone without access to sophisticated regulatory or legal support can identify whether their study qualifies as an ACT. We believe that the checklist should be written in a manner that any member of the lay public can read and understand the content. We would appreciate it if details from the checklist were incorporated as guidance and interactive text into PRS, rather than asking the reader to pore through pages of fine print. If a “smarter” checklist was built into the system itself, better answers may ensue, which ultimately would lead to better transparency and compliance.
- In the “Human Subjects Protection Review” section, please introduce a field that would identify multicenter trials.
- Please offer corresponding fields to identify a Single IRB that might be different from the Principal Investigator’s institution.
- We believe it would be helpful to allow more than one IRB to be listed when necessary.
- For new protocol registrations, please remove questions from the “Oversight” module that no longer apply (i.e., FDA Regulated Intervention).

Study Description

- We welcome a “Best Practices” guidance or help link for both the “Brief Description” and “Detailed Description” sections. If either section is intended to have a readability score, then a tool that would assess readability and provide warnings and suggestions would be extremely helpful.
- Add an in-text citation detector for the “Study Description” section.

Conditions

- Differentiation between conditions and key words can be tricky. Submitters would welcome coaching language, examples, or clearer definitions.
- Not all study words are in the dictionary. Although the “Search MeSH” tool is quite helpful, it does not offer an exhaustive list of terms. When a term can’t be found in the MeSH search, the system triggers a note. One submitter gave the example, “Note: ‘head’ is not a recognized condition”. We question the value of this sort of notice, since the system allows us to enter a term that is not in the MeSH.

- We would appreciate the ability to easily move the position of “Condition” or “Keyword” in a list. Currently, to re-arrange the order of the text, words must be deleted and re-added in the desired order. It would be helpful to have priority arrows to move the words up or down in the desired order.

Study Design

- As noted earlier, the biggest quality problem we see is that submitters tend to make their best guess of terms without checking to fully understand the meaning and intent. For example, “Study Purpose” is confusing to submitters. The list is vague and open to interpretation, which increases the risk of error (with potential regulatory implications). Case examples provided by NLM would be helpful. Real-time or live chat services could be useful to help submitters interpret a field like this.

Arms and Interventions

- The system could accommodate customizable and separate inclusion and exclusion criteria for each arm. Recruitment status could also be separated by arms: a three arm study may have one or two arms enroll by invitation-only, while another arm is open to the public. Because trials have such variability, we advise against making these proposed new fields mandatory.

Outcome Measures

- We suggest introducing a dropdown menu of standardized time frame types (e.g., time point, time-to-event) to facilitate the registration of outcome measures with help language and case examples to help submitters enter the amounts and units of time. These could also facilitate the Primary Completion Date calculations requested above.
- It is currently very difficult to enter or edit outcome measures in the PRS system. Submitters find it more convenient to create a Word document and then copy and paste into ClinicalTrials.gov. Please improve data entry features in the outcome measures module by introducing larger field views, a more facile data entry structure, and pop-out windows.
- The outcome measure time frame cannot be expanded, which makes it difficult for the submitter to see all text if the time frame description is uncharacteristically lengthy. Please enable an expand function similar to other text boxes.
- Many submitters have trouble with the rule that multiple time points for the same outcome measure must be listed as separate outcomes. We suggest introducing a function to group outcome measures that use the same measurement at different time points.
- When outcomes measures involve assessment tools, currently each submitter must type in a description of the scale, its range, and interpretation. If the PRS developed an ongoing pick list of standardized assessment tools (as it does for Collaborators), this would save immense amounts of time for institutions across the nation. For example, a search for the term “PROMIS” on ClinicalTrials.gov generated more than 1,600 records that listed the Patient-Reported Outcome Measurement Information System assessment tool, which means that

more than 1,600 times submitters drafted unique text to describe the same standard assessment tool.

Eligibility

- The Eligibility section could be improved. Some survey respondents expressed confusion about whether the eligibility section should be drafted in a technical or lay format. Clear guidance could provide clarity and improve consistency.
- The Eligibility section could accommodate listing different eligibility criteria for different arms. A question could be posed at the beginning of the Eligibility Criteria module: “Are there different eligibility criteria for different arms?” If so, the number of arms listed could prompt the number of eligibility criteria sections.
- The system is programmed to create bulleted inclusion and exclusion lists using dashes, which is not intuitive to submitters and increases the likelihood of formatting errors that result in PRS comments. Manual data entry of inclusion and exclusion criteria is labor-intensive and the fields are cumbersome.
- Inclusion and Exclusion lists should be separated.
- Please remove character limits in the Inclusion/Exclusion Criteria section.

Contacts/Locations

- It would be helpful to have an option to auto-populate contact information. The “Central Contact” person is often the “Site Contact” person. It is burdensome to have to manually enter first name, last name, phone, and email for a contact person in both the “Overall Contacts” and the “Location” sections. A check box asking if the information is the same would reduce the burden of manual data entry.

Challenges and Opportunities Regarding the Potentials for Interoperability

- Occasionally, when an FDA-approved trial (e.g., under an Investigational New Drug or Investigational Device Exemption) is ready to be registered on ClinicalTrials.gov, the approved protocol contains outcome measures that do not align with ClinicalTrials.gov standards. This creates difficulty completing the ClinicalTrials.gov registration, especially for outcome measures. Ideally, ClinicalTrials.gov, the FDA, and NIH would endorse one or several widely accepted clinical trial protocol templates, and further develop the “smart” features in them to facilitate protocol development in line with ClinicalTrials.gov standards, and flag when outcome measures are not clearly delineated in a specific, measurable format.
- We would like to see ClinicalTrials.gov interact more smoothly with internal academic medical center and other government systems. For NIH-funded studies, considerable resources could be saved if the system allowed for data entered into a NIH Forms E or upcoming Forms F application to auto-populate a new draft ClinicalTrials.gov registration.
- If status changes in an organization’s clinical trial management system could be automatically uploaded to ClinicalTrials.gov, the administrative burden and manpower required to update ClinicalTrials.gov would be greatly diminished, and the number of problems records would decrease.

Results

- The NIH advises study teams to budget for approximately 40 hours of manpower to report results in ClinicalTrials.gov. This is a lot to ask of study teams, especially for small scale studies. Productivity would be greatly improved if ClinicalTrials.gov could decrease the amount of time required to report results. This can be accomplished by making the system easier to use, reducing the dependence on manual data entry, and offering more system flexibility overall.
- Our submitters have told us that results reporting is very challenging for any study design beyond a typical randomized controlled trial. The system is not well set up to accommodate facile results reporting for pre-post, cluster randomized controlled trials, factorial design, adaptive trials including Sequential Multiple Assignment Randomized Treatment (SMART) trials, platform trials and behavioral trials. We encourage NLM to introduce more system flexibility to accommodate other trial designs so that results can be reported more easily and that those results will be more meaningful to the public.
- When baseline characteristics or outcome measures are based on scales and scores, growing pick lists should be available to reduce manual entry, as discussed under outcome measures above.
- While we acknowledge the legal requirements that dictate results reporting in tabular format, some investigators have experienced difficulty converting their data into the allowable tables. At least for non-Applicable Clinical Trials, submitters would like to be allowed to upload their data in whatever form they have it (manuscript, Excel, etc.) rather than conforming to what might be perceived as an unnecessarily rigid structure.
- The results reporting process could be significantly simplified if submitters could upload fully built data tables, at least with a methodology similar to that used in the download/upload feature already available in the Adverse Events module.
- To maximize the utility of results tables, the system could additionally permit the ability to upload graph images or jpegs to accompany data tables. This would improve the public's understanding of the data. Graphs could be accessed by clicking a link next to the data table. This would enhance understandability of results, especially for types of data that actually represent graphical information (e.g., area under a curve) and for users who understand visual images better (bar graphs, line graphs, pie charts). This function is available in the EU Clinical Trial Register.
- Please add a feature that enables submitters to copy statistical analyses, similar to the way outcome measures can currently be copied. In the statistical analysis module, it would be helpful to be able to copy an existing analysis. This would reduce the burden of manually duplicating each entry.
- We also believe that the statistical analysis could be relocated to the actual outcome measure page. This way, p-values could be entered in the outcome measure data table, either as an additional column or as footnotes, similar to the way they are shown in typical journal articles.
- Submitters tend to be frustrated by the inability to tailor the results to the analysis in ClinicalTrials.gov. The system only allowed for a standard analysis approach without the ability to comment on the results. For example, if a p-value was borderline, or required additional testing due to initial findings, there is not a sufficient place to provide that background information. The results reporting setup (dropdown menu and fields) discourages sharing complex analyses. Perhaps a brief results and/or conclusion section to

explain the findings would be helpful to both the investigator and the public user. Or, lacking those, it would be helpful at least for submitters to create a direct reference and link to a particular article or other source of further information once it is published.

- PRS reviewers appear to be focused on sample sizes. If the numbers differ between the analysis and the overall sample size (which they often do for a multitude of reasons), an immediate hard stop identifying unequal sample sizes would be ideal. If this stop were accompanied by a prompt that would require the submitter to identify and explain the sample size differences, it may help to eliminate multiple QC review cycles.
- While we appreciate the download/upload features available only in the Adverse Event module, further time saving features could be developed. Since many, if not most, data collection systems are event-based, Responsible Party staff often have to manually calculate the number of subjects affected by each adverse event (which is time consuming and prone to human error). It would save Responsible Parties considerable time nationally if ClinicalTrials.gov could provide a tool or software that Responsible Parties could use offline to translate or concatenate the data from a standardized event-based data collection system such as REDCap (with participant identifiers) to automatically produce the “participant based” data structures that ClinicalTrials.gov requires. Then, the reformatted data could be directly uploaded to ClinicalTrials.gov.
- Please remove the character limits in Caveats and Limitations.

System Improvements

We heard from our Responsible Party and study team stakeholders that resolving small problems or making small changes in PRS is administratively burdensome. A Principal Investigator’s main career focus might be patient care, teaching, or research. For institutions that delegate Responsible Party status to the Principal Investigator, it would seem reasonable that a Principal Investigator could grant “release authority” to someone on the access list for a record, at least for ongoing updates. We encourage NLM to consider creating such a delegation of authority function to alleviate the administrative burden on Principal Investigators. A delegation of authority function need not negate the fact that the Principal Investigator is responsible for the accuracy and veracity of the record, or their overall responsibility to supervise and oversee all aspects of the trial.

Both the internal and external sites are quite slow. We encourage NLM to consider that speed impacts user experience. Making the site quick and responsive would enhance usability.

Another stakeholder commented that the ClinicalTrials.gov PRS system would be easier to use if it were designed like TurboTax. Like ClinicalTrials.gov, TurboTax is a platform people use to meet a complex regulatory requirement (paying taxes). Yet TurboTax provides a personalized platform that creates a seamless and intuitive user experience. It’s widely accepted in the software development world that users dislike manual data entry. TurboTax addresses this fact by offering automated data entry and data syncing from a variety of sources. Users make selections that automatically populate fields. TurboTax software is infused with personality to develop rapport, enhance comfort, and improve what could otherwise feel like a frustrating user experience.

It would be ideal if every field from PRS were searchable in the public site. We welcome greater consistency between the internal PRS site and the public site. For example, if “Detailed Description” is positioned at the top of the PRS registration it could be found in a similar location on the public

site. Similarly, it would be helpful for submitters if all fields that will not face the public were clearly labeled as such.

Just as the system flags Applicable Clinical Trials at the top of a record, it would be very helpful if the system could also flag federally funded studies (particularly NIH). This function would enable submitters and administrators to identify and monitor trials that are subject to the Common Rule and would also remind study teams of the obligation to upload Informed Consent documents within the required time window. Once a study status is updated to “Completed”, the system could flag the study or send automated reminders to the study team that an Informed Consent document upload is due. Perhaps a smart logic question could follow a status update of “Active, not recruiting” to remind users that the time for posting a Consent document is now open. Additionally, when a submitter changes the study status to “Completed” and enters a completion date, a system-generated message could appear, reminding the submitter of the requirement to upload the Consent document within 60 days of the last participant visit.

Ultimately, flagging studies based on algorithms rather than single fields (similar to the ACT determination) for the NIH results reporting requirement, the consent posting requirement, and the IPD plan requirement (ICMJE policy) would be extremely helpful, especially if displayed in the “Record Status” area. For example, to help Responsible Parties to comply with the NIH policy for results reporting, the system could flag studies that identify NIH funding and any start date after the policy effective date (“study start date” is currently the only related field in the registration record and it would include more trials than are actually in scope rather than fewer trials). Likewise, to identify studies that are required to upload Informed Consent documents, the system could employ an algorithm based on federal funding and any start date after the Common Rule effective date. For studies required to disclose data sharing plan details, the system could employ an algorithm that applies to all records with any start date after the ICMJE policy went into effect.

Perhaps NLM could link ClinicalTrials.gov to ERA Commons so that federally funded work by a Principal Investigator could be listed on a pick list for the submitter to select from.

Many ClinicalTrials.gov users log in only a few times a year and forget how to navigate the system or perform tasks. The University of Michigan has developed many instructional tools for submitters to perform small tasks in the system (e.g., how to approve and release an update, how to grant access to another user, how to modify a record, how to upload a document, how to change a password). Our ClinicalTrials.gov submitters find these very helpful and a good reference. Other organizations may not have the same resources available to develop their own tools. This is another example where we believe that consistency across the system would benefit all parties. Ideally, ClinicalTrials.gov would develop such tools so that all users would benefit from the same universal, clear, and easy to understand instructions. We recognize that one hindrance to such development in the past may have been that ClinicalTrials.gov recognized that different submitters might have different business processes, but with some outreach, there are ways to identify what aspects need specialization so that templates could be developed and institutions could adjust according to their specific needs. All submitters should have equal access to clear, simple instructions about how to use the system. Ideally such tools or help would be accessible within the system itself so just-in-time training could be available to submitters.

PRS Review

We understand that ClinicalTrials.gov staff review a large number of submissions, and we are very appreciative of the care and attention given to every record review. We acknowledge the importance of PRS review and the difficulty of the task, given the enormous range of clinical trials and research studies in the world. We appreciate that for years ClinicalTrials.gov has worked to improve consistency among their reviewers. Nonetheless, we have occasionally experienced inconsistency between PRS reviewers during the quality review with other recent reviews and with the stated website guidelines. At times, one reviewer has returned PRS QC comments for an entry that would not generate comments from another PRS reviewer. We have also experienced significant inconsistencies in the time taken to review submissions.

With adequate staff, we believe that the review queue could be shortened, and the review delay could be minimized. There have been times when a new registration submission took more than a week for PRS to process when it typically takes a day or two. Results submissions almost always take longer than a month, and some submissions have taken several months for the PRS review to begin. One submission in 2018 waited more than eight months, while another in 2019 took almost six months before being reviewed.

In addition to resolving the review queue, the amount of help available to submitters for resolving PRS comments should be improved, especially considering the reputational and regulatory stakes associated with ClinicalTrials.gov posting results and PRS comments within 30 days for Applicable Clinical Trials. One Principal Investigator shared, “It took me 10 months of back and forth with the ClinicalTrials.gov team to get it done. They need to make it so that ALL data can easily be entered.”

We recognize the constraints of the law requiring ACT results to be posted within 30 days, but we would be grateful if ClinicalTrials.gov staff could prioritize assistance to study teams to reduce the likelihood of results being posted with major comments still unaddressed. If more pre-submission consultations or live help were available to submitters, these sorts of problems could be avoided.

Please improve the ease of locating, understanding, and correcting PRS comments. In order to resolve comments, submitters first need to know where to find the PRS comments, review history, and submission date; that comments are formatted differently from the rest of the text; and understand that the PRS comments link will generate an un-editable screen shot of the record with the problems.

Improve Planning Report

The planning report is used extensively and greatly appreciated by our ClinicalTrials.gov administrators. We offer several suggestions to improve the planning report.

- Include all registration data fields in the planning report rather than a select number of fields (e.g. include “IPD” field).
- While administrators have access to all records, it would be nice to be able to filter the planning report by any field (e.g., problems, location, IPD) in order to conduct monitoring and outreach effectively.
- Regarding the “Show/Hide Columns” tab, there should be a “Select all” option rather than having to manually select all 38 columns. There should be a “Select all” column in both the problems report and the planning report.

- Record Owner names are organized by user name, which makes it difficult for administrators to manage compliance outreach without knowing each individual user name in an organizational account.
- The planning report webpage could default to “All Records” rather than “Action Expected”, or one should at least be able to set one’s own preferred default setting that does not have to be reset at every log in.
- It would be helpful to be able to download only certain sections of the planning report (e.g., all trials due to report results in the next year, all active studies created in the past year, all studies that are due for an annual update within the next month).
- It would be easier to search or filter records based on applicable regulations and federal policy rather than just by date.
- The planning report could contain a funder category (NIH, Other federal, Private funder, other, etc.) and flag which studies are subject to the Common Rule.
- The planning report could differentiate between anticipated and actual start date, as it does for primary and study completion dates. It would be ideal to be able to sort by anticipated or actual start date.
- The planning report could offer the capability to filter date ranges rather than action expected.
- The planning report could contain details such as access list, problems, and status.

Notices & Communication

A significant proportion of the work that’s currently done by ClinicalTrials.gov compliance professionals across the country could be alleviated if the system provided more automated outreach and the site offered more information and support to submitters. Across the country, institutions have invested considerable resources into ClinicalTrials.gov support personnel who manage the registration and results reporting obligations of institutions. If ClinicalTrials.gov were to send automated notices, it could at least reduce, if not prevent, non-compliance and alleviate the burden on organizations to provide administrative support for the vast majority of basic monitoring tasks and compliance outreach. Less frequent submitters tend to forget when an update is due. Many submitters struggle with keeping track of the timelines and expectations of ClinicalTrials.gov for each active study in their portfolio. It would be ideal if the PRS would send pre-emptive notices or reminders directly to Responsible Parties, Record Owners, or other individuals on the access list about impending problems and deadlines (e.g., annual updates, errors based on the passing of anticipated dates, records that have not been released, etc.) and step by step instructions on how to resolve those problems. It would be especially helpful if notices would include links to the system log in page, because many people forget the web address to the PRS. Also useful would be the ability for submitters to opt in to proactive email reminders about a given record in advance of problems. For organizations that delegate Responsible Party status, compliance monitors and administrators would appreciate a function to send email to everyone on a record’s access list, including Record Owner, Responsible Party, and others, ideally with one click.

We acknowledge that ClinicalTrials.gov is required by law to post results for ACTs 30 days after submission. We greatly appreciate ClinicalTrials.gov’s decision to confine its implementation of this provision, as the statute created it, to ACTs. There are hundreds of organizations across the country that use ClinicalTrials.gov and strive to comply with regulatory and policy obligations, but they range in experience, ability, and manpower. Under the newly implemented system, QC review comments

noting errors, deficiencies, or inconsistencies which are posted will remain on the historical archive forever, potentially negatively impacting a Principal Investigator's or institution's reputation. Further, whatever incorrect or inadequate information prompted the comment will also be on the website. While we appreciate that the comment is supposed to prevent someone from relying on the problematic portion of the results, that risk remains. Therefore, rather than posting the results to the public site as soon as the first PRS QC review is completed, ClinicalTrials.gov should develop a means to review quickly enough that if Responsible Parties respond to comments efficiently, the posting of the corrected results reporting would still remain within the 30-day window the statute allows. We support adequate staffing of ClinicalTrials.gov's QC team to allow quick turnaround of initial and revised ACT results submissions, thereby protecting the public from erroneous, deficient or inconsistent information.

Commentary published in January suggests that some companies use "poor submissions" as a way to delay registration or results posting (<https://www.sciencemag.org/news/2020/01/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law>). We cannot speak to what others may do, but it has been our experience over years of work in this area that researchers universally want to share their work in a compliant and effective manner but find the system challenging. The system is challenging structurally because of the interface and challenging conceptually in that the records sit at the crossroads of "public accessibility" and "detailed science". It is our belief that the intent behind having a statutory requirement for posting results within 30 days was to prevent data from gathering dust in a hidden archive, not to have problematic results that represent a system-based learning curve posted on a public website forever.

Under the proposal described above, only if a Responsible Party didn't adequately respond efficiently within the allotted time frame would the study as originally submitted need to be posted publicly with comments. This would greatly reduce the number of substandard results submissions that would become part of the permanent record. An alternative approach would be to create an option to submit "draft" results to a preliminary PRS review team well ahead of the 12-month deadline and/or to more readily offer consultative appointments, which could resolve most major problems prior to submitting final results. This latter option would improve the quality of what gets posted, incentivize teams to prepare their results even earlier, and more collaboratively teach teams how better to use the system.

While results for non-Applicable Clinical Trials are not currently subject to the 30 day posting rule, submitting draft results or having access to consultative appointments would also be particularly useful for behavioral trials where meaningful results depend on analysis to reduce confounding variables. This would have been helpful in the case of NCT01499173, which took three rounds of comments, and one or more extensive conference calls with ClinicalTrials.gov staff to be able to adequately explain why the outcome measures were written as they were.

System Flexibility

At least in part, ClinicalTrials.gov was created to help researchers meet the regulatory requirement to register and report results of clinical trials of US FDA-regulated drug, devices, and biologics. Today, we see increasing expectations toward transparency for all types of scientific research. Given this shift, the system should be revised to accommodate this greater diversity of study designs, especially for studies and trials including social and behavioral research that are not Applicable Clinical Trials. Many investigators and institutions have struggled with this. The system could either offer more tools

or allow more flexibility for behavioral studies. Perhaps the system could introduce a smart logic branch with two separate data entry systems and corresponding rules: one for ACTs and another for non-ACTs (which would include behavioral studies). The system is not currently well structured to accommodate behavioral health interventions, especially mixed methods research, making it difficult to accurately fill in all of the required fields. We believe that the system could accommodate sharing details about behavioral research with more flexibility than trials that are required by law or NIH policy to register and report results. For behavioral research, there could be better interoperability/flexibility/functionality in the system outside of ClinicalTrials.gov's standard tables (e.g., scales and scores).

Many behavioral studies which are now considered trials have a qualitative component even as part of a primary or secondary outcome measure, but because the system is not built for non-numeric data, such outcome measure submission becomes nearly impossible. Our users reported that the registration process is especially difficult for behavioral studies that do not fit the standard medical model, especially for outcome measures and arms and interventions.

We do not believe that FDAAA, even as explained under *Seife vs. HHS* prohibits such a bifurcated approach as the statute confined its reach to Applicable Clinical Trials. The Court points out the statute's distinction between basic and expanded results, and confirms that basic results (that is the completion of the four modules, Participant Flow, Baseline Characteristics, Outcome Measures and Adverse Events) are required for all Applicable Clinical Trials, and that no Applicable Clinical Trial between the period of enactment and effective date of the final rule could be exempt, but neither the statute nor the court decision require that all the same modules in the same format apply to non-Applicable Clinical Trials. Nothing in the court's decision implies that the terms of basic or expanded results must be identical for non-Applicable Clinical Trials. We appreciate that other parties, ranging from the International Committee of Medical Journal Editors (ICMJE) to the NIH, through its Policy on the Dissemination of NIH-Funded Clinical Trial Information and various other funders, legitimately encourage or require results reporting which covers the same basic categories as the four results modules, but we believe that overly rigid application of a structure built for one purpose (drug and device trials) to a much wider swath of human subjects research, could end up reducing the quality and breadth of such research, rather than helping it as intended. If the current constraints remain, without robust and widely varied exemplars for adapting complex research to these forms, Responsible Parties familiar with ClinicalTrials.gov structures may opt for narrowly designed projects to facilitate "fill in the box" results, rather than engage more deeply with community members and emerging experts to consider a wider, more qualitative and humanistic approach to behavioral research. This in turn may deepen entrenched concerns of a gap in understanding between academics and researchers and the very public they are trying to understand and serve, working against rather than in the direction of, Patient Centered Research. We believe that further careful thought and substantial consultation should occur with leaders in the fields of Psychology, Sociology, behavioral and mixed methods research as well as patient and participant advocacy groups and leaders, to consider how to build a more flexible outcome measure reporting system for studies and trials that are not Applicable Clinical Trials. With all the improvements in technology and search capabilities in the last two decades, we believe that a more flexible structure could still be highly searchable. Even if ClinicalTrials.gov chooses to shy away from an option that would flex the Outcome Measure tables, we believe that such consultation would still be highly advisable to create and provide better guidance and case examples for how to put complex, qualitative, and nuanced information into the modules effectively.

b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Currently, study teams report that there is too much duplication of effort to enter the same or similar trial information into multiple systems, which takes a lot of time that could otherwise be spent on research or patient care. For a single clinical trial, study teams are required to enter the same or similar information into several electronic databases, including clinical trial management software, REDCap or other database, IRB Management System, grant application systems, etc. Consolidation or interoperability of some of these systems would be ideal.

One of the huge challenges with interoperability is the assumption or expectation that all audiences are or should be served by a single product. While study teams find multiple entry into different systems to be frustrating, grant proposals serve a different purpose often preceding detailed protocol development, which in turn is different from the language most suitable to recruitment or informed consent documents, etc. A second challenge is that data elements will need to be compared and aligned to ensure accuracy. For example, “sponsor” in a clinical trial management system might mean funder but that it’s not necessarily the same as “sponsor” in ClinicalTrials.gov or FDA regulations. While we share some of the desires we have heard below we ask that extreme care and thoughtfulness be used when considering the creation of interoperable systems to avoid losing important nuance or audience adaptation.

For registrations, it might be worthwhile for ClinicalTrials.gov to review a number of major electronic IRB systems, to look for common data fields for which API pushes could be built from the IRB systems to populate parts of ClinicalTrials.gov registrations. Even if these were limited to basic information such as study title, team, phase, and collaborators, this would still save thousands of work hours nationally.

For NIH-funded studies, we encourage continued improvement of interoperability with NIH. If NIH protocol templates and forms were harmonized more extensively with ClinicalTrials.gov, sections of them could be made able to populate ClinicalTrials.gov, particularly for eligibility, arms and interventions, and outcome measures. That said, some of these would require electronic templates with some additional options within the templates, for example, making clear whether any eligibility criteria should be publicized and or need to be masked from potential participants. We recommend mapping data elements in the Protocol Section of the ClinicalTrials.gov record to the NIH/FDA e-protocol writing tool and protocol templates. While ClinicalTrials.gov Data Element Definitions clearly describe what information is expected for a given element, users report that interpreting that definition and locating the corresponding information in a protocol document is a challenge. Inclusion of a feature to display the sections in the NIH/FDA protocol template where the information is most likely to be found would reduce entry burden by assisting in interpretation of the data element meaning, and indicating where the information to populate the data element may be found in the protocol source document. Ideally, such a feature could be displayed as links near the data elements, with pop-up window or pane that display that element, with the likely sources within the NIH/FDA protocol templates. Helping users correctly interpret and identify the correct information for a data element would have the effect of improving the quality of the submitted information.

University of Michigan faculty and staff would benefit from ClinicalTrials.gov interoperability with OnCore and REDCap. Some would like to be able to import information regarding any changes to a record. For example, a study status change that's reflected in OnCore could be imported into ClinicalTrials.gov. But given that OnCore is used for externally sponsored trials for which the

Responsible Party is not at the University, as well as for investigator-initiated trials for which the Cancer Center or the Principal Investigator is the Responsible Party, there would need to be easy ways to designate which records should export and which should not, as well as mechanisms to alert the Responsible Party to “release” these updates into the record. Therefore, we do not advocate fully automated interoperability, as a manual “release” function provides a good opportunity for quality assurance and accuracy.

It should be noted that private corporations creating products, such as OnCore, to feed into ClinicalTrials.gov may periodically run “behind” in updates to ClinicalTrials.gov data fields. This was true in 2017 when the ClinicalTrials.gov fields changed in response to the newly promulgated regulations. A significant modernization would be likely to invoke such a cycle again. While that is not a reason to avoid modernization, it suggests that clear and widely publicized announcements of specific planned changes and likely time frames would be helpful, and direct collaboration with relevant companies would be even more beneficial.

ClinicalTrials.gov registration and results reporting are independent processes, and we have to pay multiple full time employees at the University of Michigan to manage and interpret interactions with ClinicalTrials.gov. Any modernization effort must include releasing training documentation well in advance of a new site going live. There should also be a transition time to help all users become familiar with the new system before being required to use it. Otherwise, it’s likely that there will be delays in activities that require using the site.

c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

It appears that the utility of ClinicalTrials.gov is broadening beyond the registration and results reporting of Applicable Clinical Trials. Federal regulation 42 CFR 11 is specific to Applicable Clinical Trials. The system structure could become more flexible for studies that are not required by law to register and report results. This basic concept has already begun in as much as observational studies open different questions than clinical trials. Similarly, behavioral trials that are not ACTs could open some additional alternative options for reporting. Because the system already effectively identifies Applicable Clinical Trials, it could use branching or smart logic to open certain options to non-ACT trials.

d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Within the Protocol Registration and Results Reporting System (PRS), University of Michigan ClinicalTrials.gov administrators appreciate the ability to use the planning report to augment monitoring and compliance efforts. We use the planning report to identify potential problems, which enables us to conduct outreach before problems occur, as well as the PRS to identify and resolve problem records. The list of major PRS comments is helpful for administrators to better understand reviewer expectations and to educate research teams about the characteristics of acceptable submissions. The PRS User Guide and Protocol Review Criteria are useful resources for administrators and study teams alike. The spell check (including possible unexpanded acronyms), preview, .pdf maker, definitions, and help features are widely used among both administrators and

research teams. Both administrators and responsible party and staff users appreciate the convenience of the immediate password reset link on the PRS login page.

We would appreciate if NLM could organize outcome measure type and units of measure to create a bigger model bank and improve searchability. Outcome measures could be more searchable and sortable in order to provide users with good examples of outcome measures. The outcome measure library could identify when outcome measures were written or reviewed so that out-of-date examples would not be shared.

Many research teams find it difficult to identify time frames that must relate back to a specific event in ClinicalTrials.gov when grant timelines and schemas and protocols may have been written from a different perspective. Providing a standardized library of baseline characteristics, outcome measure titles, descriptions, and time frames would give them a ready reference to understand the ClinicalTrials.gov expectations.

A library of assessment tools, scales, and scores would also be very helpful, going beyond the pick list discussed above, to simply reduce manual descriptions of assessment tools. If the library could also cross link to related tools (e.g., all quality of life tools), it could actually allow researchers to better understand when and how different tools have been used in the past and whether they were effective or were not well tolerated by participants. As discussed in our response to question 1, patient advocates felt this would be particularly effective in creating an iterative process of more patient centered and designed trials.

More guided tutorials on different outcome measure types and use of arms for sophisticated trial designs (step trials, platform trials, adaptive trials, SMART trials) would be useful. The Clinical Trials Registration and Results Reporting Taskforce (CTRRR Taskforce) Slides on Results Reporting are an example, but as the PRS reviewers see every trial's results, they could build such a library far more efficiently than a small group of ClinicalTrials.gov administrators.

We would benefit from the creation of a best practices library for rare or complex study designs and advanced analyses. Social and behavioral research examples would also be useful. It would be great if ClinicalTrials.gov could identify good example registrations and results reports.

e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

ClinicalTrials.gov could implement an honor roll on its public site to recognize stellar Sponsors, either for particularly well-written information, or results submitted prior to the deadline.

A library of particularly well-written results modules or descriptions, highlighting recognition of contributors, could incentivize care in the production of these tables.

More significantly, we believe that if there were a series of pre-submission dates or goal/deadlines that would entitle one to be able to obtain a preliminary PRS review without immediate posting on the public website, Responsible Parties would have a huge incentive to submit their results in a timely, well-written fashion. This could be calibrated to the complexity and the quality of the draft submitted. For example: for every three outcome measures presented, the draft results would need to be submitted one week earlier than the 11-month "pre-submission review deadline", proposed earlier. If a Responsible Party did so, and received the equivalent of major comments, they would still

have the time and ability to fix them; but if their submission was without any problems, not only would they have the inherent benefit of it posting sooner, but they could be awarded points, awarded for submissions (or per outcome measure) that did not invoke major comments. These points could be included in NIH grant submissions, or could be acknowledged in mentoring or tenure choices. Or they might be traded in for consultation priority on a future registration or results reporting.

ClinicalTrials.gov could provide badges or "achievement icons" that would appear in the trial record for each milestone accomplished (e.g., "results submitted within 1 year of trial conclusion" or "IPD plan submitted upon registration").

Another option would be to somehow grant compliant researchers a five-star rating or a seal of approval for timely trial registrations or results submissions that funders would be aware of and could consider this sort of compliance success when deciding on future award funding. Timely registration and results reporting would be even more beneficial to Principal Investigators and institutions if ClinicalTrials.gov recognized good compliance. ClinicalTrials.gov could also issue standard metrics that Principal Investigators can use when applying for grants (NIH, PCORI, Gates foundation, etc.).

If results reporting were given a unique data identifier and if grants or bio sketches offered a field to include such identifiers, academic institutions would have an easier means of giving credit to faculty for posting their results.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

While we encourage the use of data standards and links to external data standards, we find these goals – submission, management, and use of information content – to be very broad. There are different standards for each stated goal. We would like to better understand the NLM's priorities in order to thoroughly answer this question. Given that ClinicalTrials.gov is a resource that is used internationally, we recommend that ClinicalTrials.gov adopt or endorse the use of internationally accepted data standards. We acknowledge that even with such standards in place, not everyone will associate the same meaning with a term; so we ask NLM to consider including a data dictionary to help people fully understand the language used in ClinicalTrials.gov.

a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

We appreciate that the NLM is seeking input from the public, but would prefer if NLM could first recommend specific standards and contexts for their use and then seek public input at that point. There are myriad acceptable data standards. Similarly, there are different standards for different types of research (e.g., FDA-regulated, NIH-funded, behavioral research, etc.).

Which standards could be recommended ultimately depends on the NLM's stated goals and priorities. Standards could be domain-specific, but ClinicalTrials.gov could consult with and obtain

buy-in from relevant scientific communities in order to adopt anything specific. Perhaps specific standards could be applied for specific groups, or be unique to smaller research fields. Data standards for FDA-regulated trials could accommodate more structure, while other trials and studies could have fewer restrictions.

At any rate, consistent adherence to data standards should be encouraged throughout a clinical research study. Consistent practices and language could be used, starting with the grant proposal and continuing through to the protocol, pick list, analysis and results reporting. The interoperability discussed earlier would support such consistency.

The University of Michigan Medical School believes that creativity and innovation should be fostered in clinical research. We encourage NLM to keep in mind that while useful at times, standardization is not always compatible with creativity, innovation, and accommodating new developments in a field. The value of standardization may not be as significant as envisioned for studies that are more innovative than others, and standards here would not provide the efficiency or user-friendly experience they may be seeking. NLM should carefully consider which registration and results fields might require the use of data standards.

b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

While we are in favor of incorporating ontologies into the registration process whenever possible to facilitate the accurate identification of all trials with data matching certain criteria, we are reluctant to recommend a specific standard because we recognize that the implementation of standards can further increase the administrative burden of research (harmonization, implementation costs, training costs, time, etc.). We want to encourage innovation in clinical trials and are concerned that requirements to use a limited set of standards would end up restricting creativity.

Some units within University of Michigan have already adopted the Clinical Data Interchange Standards Consortium (CDISC) standards for data collection. Clinical Data Acquisition Standards (CDASH) terminology is already required for FDA submissions, so those standards for Applicable Clinical Trials only might be a logical first step to consider after further consultation with the relevant communities. ICD10 or Systematized Nomenclature of Medicine (SNOMED) could be used to indicate specific diseases and/or disease states. Perhaps the Unified Medical Language System (UMLS) would be an appropriate tool to incorporate many health and biomedical vocabularies and standards to enable interoperability between computer systems.

Again, we wish to thank the National Library of Medicine and the ClinicalTrials.gov staff for their decades of hard work and their courage, adaptability, and ethos of service represented by this broad-ranging Request for Information. We remain happy to work with ClinicalTrials.gov and can be reached for any further clarifications or questions about the comments posted here at UMMS-RegAffairs@med.umich.edu.

Submission No.: 193

Date: 3/13/2020

Name: Michael Vaughn

Name of Organization: TransCelerate BioPharma Inc.

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

“High Priority – Short Term” - Item related to patient friendliness that can implemented without significant database or regulation updates

1. User specific web interface – allow user to identify their purpose for visiting site and tailor the UI (User Interface) dependent on the needs of the users e.g. a researcher is likely to want different forms of information than a member of the public looking for a trial to participate in.

2. Integration of mapping application programming interface (API) such as google maps that allow users to see location of site facility (when available) and driving time from home location. This allows members of the public to more realistically assess the feasibility of being part of a trial.

“High Priority – Medium Term” - Item related to patient friendliness which may require significant database or regulation updates in order to implement

3. Guided search – disease specific guided search that help users get to a result listing that meets requirements

4. Account functionality – so that researchers and members of the public can save searches that they have invested time in tailoring. This can also allow automated updates of new trials within search criteria

a. User can write and save notes about a particular trial that can be shared with an HCP/family member

5. To support the FDA expectations that sponsors enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity (<https://www.fda.gov/media/75453/download>) sponsors could optionally submit trial data in Spanish if the trial is operating at sites that can support Spanish. 12.4% (41 million) of the American population speak Spanish - https://en.wikipedia.org/wiki/Languages_of_the_United_States. This would be a mirror database and may just require an additional data field at the site information level to distinguish they can support Spanish speaking participants. (reference: Improving The Value of Public Clinical Trial Registries to Patients: A Perspective and Call to Action pg8)

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

“High Priority – Medium Term” - Item related to patient friendliness which may require significant database or regulation updates in order to implement

1. Electronic Health Record Systems – This would allow for automated trial matching for patients looking for research options. This will reduce resource burden on HCPs manually reviewing criteria. The time burden on referring HCPs could be significantly reduced. It could make searches more easily filtered and search results understood by patients/caregivers.
2. Patient Advocacy Groups – (mesh terms)
3. Allow CSR synopsis/ results summary as an attachment (to be added as a document type in the Document Section).
4. Linking secondary IDs (e.g. EUDRACT, UTN, any local registry ID) to their source so that people from difference languages will be able to see the information in their native language. The functionality could be the same as it is done for publication automated linking.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

The primary use of ClinicalTrials.gov for members of TransCelerate BioPharma Inc. is to register and post results as required by US Regulation. The patient-focused features listed below come from the collaboration of TransCelerate BioPharma Inc. and a diverse group of patients who co-designed the Clinical Trial Registry of the Future.

- A) ClinicalTrials.gov website / Existing features that work well
 1. SEARCH: basic search function on home page with ability to select not yet recruiting & recruiting studies OR all studies
 2. SEARCH: ability to search on a location & identify studies within a specific radius
 3. SEARCH RESULTS: filter pane on search results page to further refine search
- B) ClinicalTrials.gov website / Potential Improvements

“High Priority – Short Term” - Item related to patient friendliness that can implemented without significant database or regulation updates

1. SEARCH: ability/option to detect location (country, state & city) versus having to manually enter location
2. SEARCH RESULTS: ability/button on top of search results page to enter email to set up automated alerts when there are changes to the search results

3. SEARCH RESULTS: ability to download, print (produce print ready view) and share (ability to enter email or share to social media) search results via buttons on top of search page (all results) and next to study in search results (individual study)

4. SEARCH RESULTS: map view: ability to see exact search results on Google-map with scroll in/out feature with location pins of participating sites/locations

5. COMPARISON PAGE: ability for user to create their own trial comparison page by selecting specific studies, fields and order of fields they are interested in; ability to download, print (produce print ready view) and share (ability to enter email or share to social media) comparison page

6. TRIAL DETAILS: reorganize the current information/fields

a. include/add icons at top of Trial Details screen to provide an at-a-glance view of basic trial attributes: recruitment status, trial type, phase, sex, age

b. add search box in order to search within the specific trial data

c. create/show 4 tabs of data: Overview, Participation, Locations, Resources, Trial

Results

d. add ability to expand/collapse sections of data on each tab of data

7. TRIAL DETAILS / PARTICIPATION: include details on what it might be like to participate in a trial

a. Include icons for participation duration, number of visits, off-site requirements, intervention type

b. Include data: post trial treatment, site services, reimbursement, pay to participate, lay summary

c. Include a visit by visit interactive timeline showing visit, visit duration, activities for each visit

8. TRIAL DETAILS / OVERVIEW

a. visualize/include nearest location on Google-map

b. include all protocol registration information; re-order the information according patient defined importance as shown in the Clinical Trial Registry of the Future.

9. TRIAL DETAILS / LOCATIONS

a. visual (Google-map) and list view of locations; list view includes location name & address, distance & recruitment status, contact name, phone number & email address

10. TRIAL DETAILS / RESOURCES

a. contain all the current resource/links embedded within the CT.gov registration

11. TRIAL DETAILS / TRIAL RESULTS

- a. contain all the current Trial Results data
- b. ability/button to enter email to set up notification when results are posted if no results posted or if results are updated

"High Priority – Medium Term" - Item related to patient friendliness which may require significant database or regulation updates in order to implement

- 12. USER ACCOUNT: creation of a user account for ClinicalTrials.gov public website
 - a. Optional account allows for individual to enter
 - i. general information (name email, phone, password, language, time zone, date/time, measurement units)
 - ii. accessibility information (voice over, zoom level, text size, high contrast, auto speak text)
 - iii. search criteria (age, sex, location (address, city, state, zip), radius)
 - iv. medical condition
 - b. account allows management of
 - i. bookmarked searches (search name, description, filters, ability to delete bookmark)
 - 1. when selecting a bookmarked search the below information/columns of data would appear on bottom half of screen: trial name, condition, intervention, distance, status, ability to delete or indicate as favorite
 - ii. alerts (search name, description, text, email, frequency, ability to delete alert)

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

TransCelerate BioPharma Inc. is a non-profit membership organization whose members are made up of clinical trial sponsor within the biopharmaceutical industry. The primary use of ClinicalTrials.gov for TransCelerate's members is to register and post results of clinical trials in alignment with US Regulation and includes work on a wide range of studies.

TransCelerate BioPharma Inc.'s mission includes collaborating across the biopharmaceutical research and development community. Based on research conducted and results published, the RFI responses also include the viewpoint of patients (e.g. patient surveys, patient advisory boards) health care professional survey, investigational site survey, and site advisory boards.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

“Medium Priority” - Items not considered related to patient friendliness but an important consideration for implementation

1. Automated Record Consistency Check/Validation: Within a registration record, simple automated consistency validations can be added to flag obvious error. For example, the protocol title has Phase 1/2 but in the Design module/Phase, Phase 1 is selected by the user. e.g. 2, Brief title has pediatric patient, but under the Eligibility Criteria minimum age is selected as 18 years. e.g. 3. If primary endpoint timeframe is shorter in comparisons to timeframe of any one secondary endpoint, system can raise a warning flag if primary completion date = study completion date.

2. Like EudraCT system, PRS should give flexibility to define 2 different designs used in the same protocol with 2 different periods, e.g. Period 1 double blind, double masked whereas Period 2 is either single blind or open label.

3. Result module should allow to upload a graph. People who are not scientists/researchers a graph is more meaningful than data.

4. There should be designated field to capture certain information such as exceptional cases like termination date (which does not coincide to the primary or study completion date and creates compliance issues), termination reason with expanded character limitation than what we have now in PRS, protocol amendment # for which the public content is going to be modified.

5. Some type of linking between sister/extension studies, umbrella/basket trials etc. so that data entry can be minimized by transferring similar data from an already existing record to a new record. In the PRS, a field like “expanded access” can be provided to capture the related study NCT# and on the public website it will provide a better opportunity to patients to see related studies that they are searching on a particular indication.

6. Observational study record needs to remove the fields related to Interventional studies for example Observational disease registry study for which there is no drug involvement asking for intervention is misleading. Similarly, asking for primary purpose and giving the option relevant to interventional study but no relation to observational study is also not very helpful.

7. Ability to make modifications or updates to the data sharing statement on clinicaltrials.gov after registration entry has been completed without opening up the record to additional changes since it was submitted. This modification would be useful as this action is not changing the information about the trial itself but simply where to request the study data upon completion.

“High priority, Medium term” - Item related to patient friendliness which may require significant database or regulation updates in order to implement

8. Addition of Study duration, frequency of visits and treatment duration as individual fields in the PRS will give a better search functionality and decision making to participate in a trial

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

“Medium Priority” - Items not considered related to patient friendliness but an important consideration for implementation

1. If NCT #, initial release date, initial public posting date, similar dates for amendment related release, review comments from NIH reviewer can be available through API to be accessed by Sponsor, it will save a lot of time in tracking this information manually in the disclosure system and making manual data entry error.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

“Medium Priority” - Items not considered related to patient friendliness but an important consideration for implementation

1. Content reuse by extracting information directly from the protocol as XML and uploading to PRS. This will ensure content alignment between ClinicalTrials.gov and protocol. (Clinical Protocol template)

2. Use of small intelligent tools which can be embedded to PRS which will help enforcing required data into field. E.g. “clinical registration tool” prepared by TransCelerate enforce the elements required to be mentioned in the brief title and brief summary.

3. An embedded outcome measure library by disease and variable would be extremely helpful to sponsors and will also ensure consistency in outcome measure reporting within industries & academia. This will also reduce the NIH-Sponsor review time and cycles for the record.

4. TRIAL DETAILS: For qualified personal have the full list of inclusion/exclusion criteria. Ideally those criteria would be from a library as done in the TransCelerate’s Common Protocol Template, which offers model inclusion/exclusion criteria.

5. A connection to FDA drug approval site or embedded functionality to flag a drug as already approved in US or not will be very helpful to PRS user.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

“Medium Priority” - Items not considered related to patient friendliness but an important consideration for implementation

1. Existing useful documents: ACT checklist, protocol registration review criteria, result review criteria, voluntary submission flow chart etc.

2. Suggestion for New document:

a) If PRS embedded Outcome library is not possible as suggested in c # 3, an extensive excel spreadsheet of accurately written outcome measure from different therapeutic areas with complex measurement should be prepared.

b) A complete data element definition document in excel format with fields for data type, limitation (character or numerical), suggested values, whether required or conditional or optional etc. would be very helpful to use.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

"Medium Priority" - Items not considered related to patient friendliness but an important consideration for implementation

1. Incentivizing – When submissions pass QC first pass, there could be congratulatory messaging to the sponsor submitting. Automated annual reporting to show metrics, areas of success or weaknesses for sponsor submissions. Annual reporting will allow sponsors to justify additional resources within disclosure departments if performance is not meeting industry standards.

2. Incentivizing – If sponsors can see the registries as a source of value for accelerating research (i.e. reducing enrolment duration + better informed participants), they are likely to invest more resource in submitting complete, accurate, and timely registration and results information. Improvements to the registries that increase ability to connect patients and HCPs to trials of interest will have a clear benefit for sponsors.

3. A recognized yearly email to individual and/or organization for achieving

a) 100% compliance to ACT data submission deadline

b) above a certain percentage (e.g. 95%) of studies disclosed without any comment cycle for registration and result disclosure

4. Helping organization by providing important KPIs related to disclosure activities such as:

a) By Organization: how many studies registered in a year, how many are ACT and how many are non-ACT, how many did not receive any comment, how many 1 or more than 1 cycle of comments, by study what was the duration from submission to publicly posted as a clean record .

b) By Organization: how many studies' results are disclosed in a year, how many are ACT and how many are non-ACT, how many did not receive any comment, how many 1 or more than 1 cycle of comments, what was the duration from submission to publicly posted as a clean record by study.

5. Add a validation in place which sends an alert email and/ or flags a study on PRS home page if any information is past due to be updated (event dates like study start, study completion and primary completion). The flagging or alert should be done or sent out on the day it is past due, so sponsors are alerted immediately, allowing them to update the registry with the most current data.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

“High Priority – Medium Term” - Item related to patient friendliness which may require significant database or regulation updates in order to implement

Inclusion and Exclusion criteria on the registry could be considered on three levels of requirements and may benefit from allowing all separate forms:

1. For public understanding –This is unlikely to cover all the protocol criteria but would help inform a member of the public if they could be eligible to screen. Key criteria should be written in lay language.

2. Per protocol criteria – This should reflect verbatim what is in the protocol. It could be efficient if sponsors submit the per protocol criteria with a type of tag which indicates which criteria are appropriate for public understanding (per point 1).

3. NEW - Programmatic inclusion/exclusion criteria (see attachment labelled EMR_CLINICAL_TRIAL_REGISTRY_INTEROPERABILITY) - There could be new data fields for inclusion and exclusion logic that would have more controlled terminology/standards. These would be a programmatic representation of the inclusion criteria which can be used to query against electronic health record databases (reference: Improving the Value of Public Clinical Trial Registries to Patients: A Perspective and Call to Action pg24).

i) The programmatic language standard used could be selected in consultation with leading EHR vendors to ensure EHR compliance with data field standards (coming from the 21st Century Cures Act) being used. Provision of this extra data by trial sponsors could be optional for a number of years to allow time to demonstrate benefits before eventually becoming mandatory.

ii) Expected benefits – automated screening of patients for trials who consent to learn of clinical research options. Reduced burden on health care professionals who may not have time to review inclusion/exclusion criteria

“High Priority – Short Term” - Item related to patient friendliness that can implemented without significant database or regulation updates

4. Protocol Templates – Various initiatives exist looking to provide template protocols to sponsors that form the basis of new research. Controlled terminologies within these protocol templates will facilitate the beginning of standardization of sections such as inclusion/exclusion criteria. Most of the information for registries exists within these documents so if these templates can be updated with guidance on how/where data should be written for registries, it is likely to increase quality and facilitate

automated processes for trial disclosure. Protocol template versions can be released in line with evolving standards for terminology and structure.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Fast Healthcare Interoperability Resources (FHIR) standards may support interoperability of clinicaltrials.gov with EHR systems

TransCelerate has created a number of videos to highlight the concepts of the Registry of the Future

1. What is the Clinical Trial Registry of the Future:

https://www.youtube.com/watch?v=EVZigj0q_JI#action=share

2. Searching for a Clinical Trial:

<https://www.youtube.com/watch?v=O68tj1GpIKU#action=share>

3. Evaluating a Clinical Trial:

<https://www.youtube.com/watch?v=2c9v4p3l1kk#action=share>

Attachments: References.zip, containing (1) Clinical-Trial-Registry-of-the-eBook.pdf, (2) EMR_CLINICAL_TRIAL_REGISTRY_MOCK_DATA_INTEROPERABILITY.xlsx, and (3) The-Clinical-Trial-Registry-of-the-Future-Proposal.pdf

Clinical Research Access and
Information Exchange Initiative

eBook:

CLINICAL TRIAL REGISTRY OF THE FUTURE

Patient-Focused Features
Proposed for Consideration
by Public Registries




TransCelerate
BIOPHARMA INC.

ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

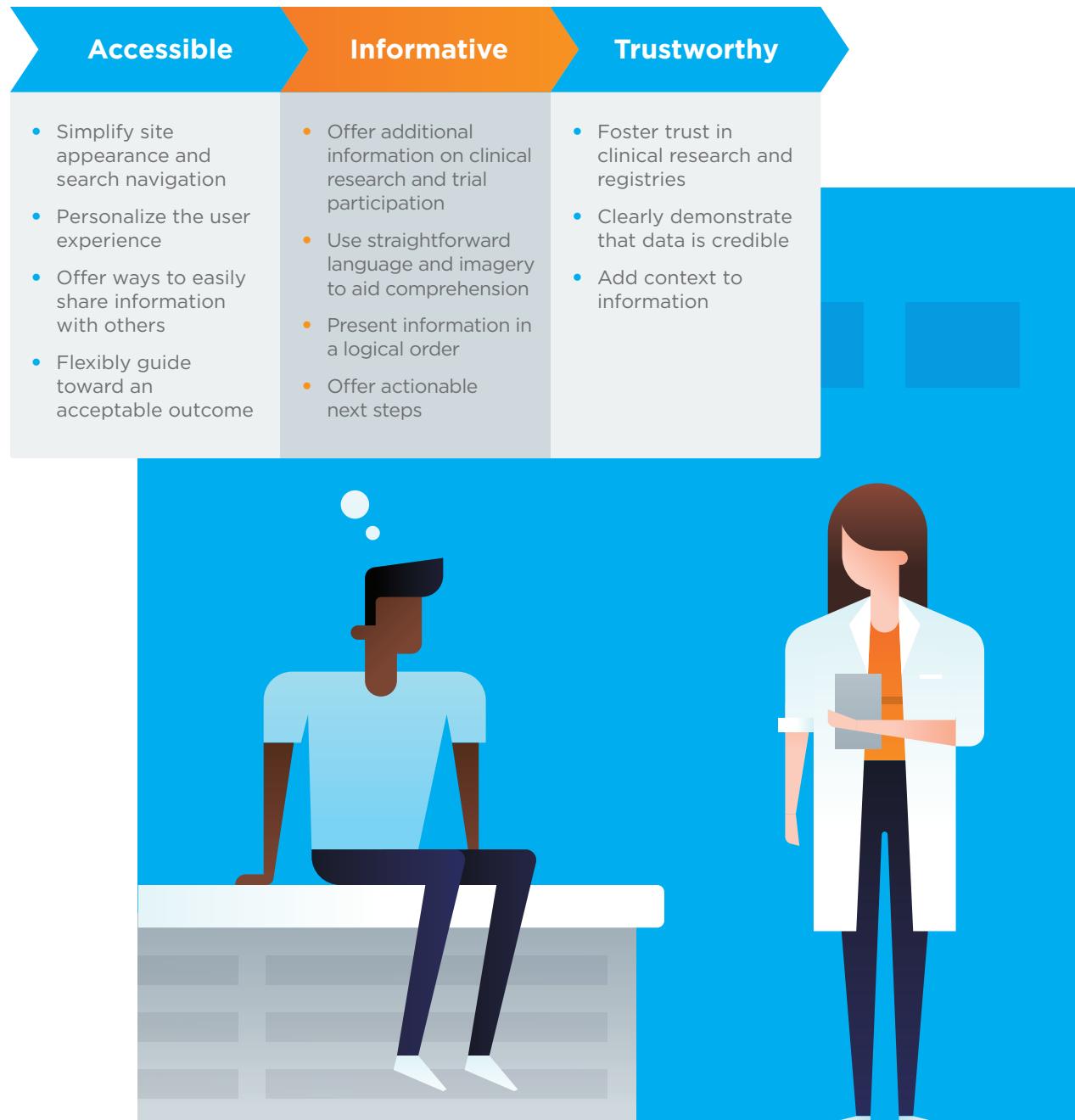
BEGINNING WITH THE PATIENT IN MIND

Beginning in 2016, TransCelerate sought the input of a diverse group of patients on information desired about clinical trials, the user experience of existing public registries and improvement opportunities for future public registry design. Through consultation and collaboration with patients, key takeaways pertaining to the design of a “Clinical Trial Registry of the Future” concept were summarized into three categories:

- Accessible
- Informative
- Trustworthy

GUIDING PRINCIPLES FOR CLINICAL TRIAL REGISTRY DESIGN

It is with these guiding principles in mind that future efforts to enhance, improve or extend the utility of public clinical trial registries should be taken. In order to explore specific features or enhancements which satisfy the above principles, and to initiate broad multi-stakeholder discussion on practical advances toward these goals, TransCelerate co-designed with patients a wireframe proof of concept for “Clinical Trial Registry of the Future.”



CLINICAL TRIAL REGISTRY OF THE FUTURE WIREFRAME HOMEPAGE

Focusing on the desktop user experience as a starting point, the homepage for Clinical Trial Registry of the Future was designed to welcome users into a positive environment and facilitate easy searching of clinical trial information.

1 ROTF

2 Home About Clinical Trials Advanced Search For Researchers Help

3 **4** **5** **6** **7**

8

9 LATEST STORIES [\(View All\)](#)

10 RECENTLY VIEWED

11 COMMUNITY

Social Feed Name 01.01.2017
Lorem ipsum dolor sit amet, consectetur adipiscing elit. Aenean euismod bibendum laoreet.

12 NAVIGATION

Home About Clinical Trials Advanced Search For Researchers Help

13 CONTACT

123 River St Anywhere, PA 555.555.5555 Frame.Lname@email.com

Legal Notices Privacy Policy

14

- About Clinical Trials:** educational content about clinical trials that answers seven commonly asked questions.
- Advanced Search:** access to all possible search criteria from a single page for more advanced users.
- For Researchers:** resource hub for researchers and study record managers including guidance on registration.
- Help:** resource hub for users containing FAQs, glossary of terms, clinical trial education library and tutorials for use of the platform.
- Bookmarks:** access to content previously saved by user for future reference.
- Language Preferences (Globe):** drop-down to select appropriate language/region preference to personalize display (e.g. kilometers versus miles).
- User Account:** access to and/or option to create a personal account enabling additional features and saved preferences.
- Simple Search:** search for trials in three basic categories (seeking participants, completed with results, or all trials) by keyword or condition, with option to specify a base location and radius within which to search. “Smart” features are built in to allow detection of current location, if desired, and type-ahead functionality which automatically pulls suggested search terms as user begins typing.
- Latest Stories:** content of interest to various patient and disease communities, dynamically displayed based on user’s browse/search history.
- Recently Viewed:** easy access to clinical trials recently viewed by the user.

SEARCH RESULTS

The trial search results page provides a comprehensive view of important trial characteristics while allowing the user flexibility to customize additional filter criteria, plot results on a map, build a side-by-side comparison, or take additional actions on specific trial listings.

The screenshot shows the ROTF search results page for 'Colorectal Cancer' in 'Philadelphia, PA (19125)'. The interface includes a top navigation bar with links like Home, About Clinical Trials, Advanced Search, For Researchers, Help, and a search icon. Below the navigation is a search bar with filters for Condition ('Colorectal Cancer'), Distance ('25 miles'), and Location ('Philadelphia, PA (19125)'). A status filter shows 'Status: Seeking Participants'. Action buttons include 'Grid View' and 'Map View'. The main content area has a title 'We have found 22 matching trials' and a 'Help me refine my results' link. It features a 'FILTER BY' sidebar with sections for Status, Trials, Advanced, Distance, Condition, Trial Type, Trial Phase, Intervention, Time Commitment, Placebo Possible, Age & Sex, Accepts Healthy Volunteers, Funder Type, Trial Results, and Hidden Trials. The main grid displays 10 trials per page, showing columns for Name, Condition, Intervention, Distance, Commitment, Status, and Actions. Each trial listing includes a small gold bar indicating new posts since the user's last visit. A 'Compare Selected' button is at the bottom left, and a navigation bar with arrows and page numbers (1, 2, 3) is at the bottom right. Numbered callouts (1-7) point to various features: 1. Top-left location pin; 2. Search bar location pin; 3. Top-right action buttons; 4. Map view button; 5. Top-center location pin; 6. Filter by sidebar; 7. Bottom-left compare selected button.

6. Filter Pane: manually refine results based on additional trial attributes or trial participant preferences, including intervention type, estimated participant time commitment and condition-specific factors (e.g. molecular profile of tumor). Hover over filter categories and individual criteria to reveal glossary-supported term definitions.

7. Compare Selected: after ticking checkboxes for each desired trial listing, users may generate a side-by-side comparison of selected trials containing all attributes on the filter pane as well as select non-structured (e.g. free text) trial attributes. The comparison table may be downloaded, printed or shared via email directly from the page.

- 1. Search Criteria:** view confirms previously entered search criteria and provides option to 'x' out of criteria the user no longer wishes to include.
- 2. Help Me Refine My Results:** open a guided search pop-up window for users wishing to answer a series of optional questions about the chosen condition and/or prospective trial participant.
- 3. Search Results Action Buttons:** bookmark the chosen search criteria to re-visit results at a later date, set an alert to be automatically notified of new results under the same search criteria, and download, print, or share the results table.
- 4. Map View:** alternative to grid view which plots all results on a single geographic map with zoom-in and drill-down capability.
- 5. Search Results Grid:** view key attributes of each trial, including intervention category (indicated by icon) and intervention name, distance from desired search location with hover-over capability to reveal location name, and estimated trial participant commitment in total duration and number of visits. Action buttons for each individual trial listing in the grid allow users to bookmark a single trial for future reference, track trials of specific interest, record or open previously written notes about the trial, or hide a trial from view. Gold bars indicate new trials posted since the user's last visit.

SEARCH RESULTS (OPTIONS), *continued*

“No Results Available” ➤

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help    

Home > Search Results Colorectal Cancer Altoona, PA (16601)      

We have found 4 matching trials [Help me refine my results](#) + Grid View Map View

Condition: Colorectal Cancer × Distance: 250 miles × Location: Altoona, PA (16601) × Status: Seeking Participants ×

No results matched your criteria exactly.
We have found no results that match your search criteria. Please see below for tips & suggestions on ways to improve results that may interest you. If you would like to create an alert for when results are available, [sign in](#) or [register](#).

We have expanded your search radius to **250 miles** from Altoona, PA (16601) instead of 25 miles. You will now see **4 Trials**.

You could also try
[Change search location >](#)
[Change search radius >](#)
[Search another medical condition or keyword >](#)

[Go Back](#) [Continue](#)

Funder Type  +
Trial Results  +
Hidden Trials  +

Additional Resources

| NAME | TYPE | LINK |
|---------------|-----------------|--------------------------------------|
| Group XYZ | Advocacy Group | www.GroupXYZ.com |
| Group ABC | Advocacy Group | www.Group-ABC.com |
| Group 123 | Advocacy Group | www.Group_123.com |
| WebSource ABC | Informational | www.WebSourceABC.org |
| LMNOP Group | Patient Support | www.LMNOP-Group.com |

“Help Me Refine My Results” ➤

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help     

Home > Search Results Colorectal Cancer Philadelphia, PA (19125)      

We have found 22 matching trials [Help me refine my results](#) + Grid View Map View

Condition: Colorectal Cancer × Distance: 25 miles × Location: Philadelphia, PA (19125) × Status: Seeking Participants ×

Refine your search results
Answer a few optional questions to better refine your search results. These are to help get you started. You can always modify them at any time from the filters on the left-hand side of the search results page or by simply returning to this page.

View 22 Results

What is your medical condition or diagnosis?
Colorectal Cancer

[NEXT](#)

Funder Type  +
Trial Results  +
Hidden Trials  +

A study of Drug WWW in patients with advanced solid tumors Colorectal Cancer Drug WWW 18 Mi Months 5 +/- Visits 10 +/- Seeking Participants   

A study of Drug XXX in

SEARCH RESULTS (OPTIONS), continued

“Map View” ➞

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help   

Home > Search Results Colorectal Cancer Philadelphia, PA (19125) 

We have found 22 matching trials [Help me refine my results](#) +

Condition: Colorectal Cancer Distance: 25 miles Location: Philadelphia, PA (19125) Status: Seeking Participants

GRID VIEW **MAP VIEW**

FILTER BY Showing: 14 of 14 trials

A study of Drug ABC in patients...

Status: Seeking Participants, Completed with Results, All

Advanced

Distance: 19125, 25 

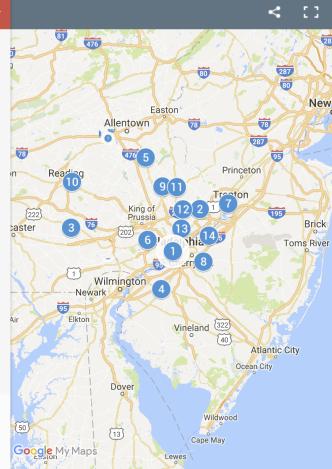
Condition, **Trial Type**, **Trial Phase**, **Intervention**, **Time Commitment**, **Placebo Possible**, **Age & Sex**, **Accepts Healthy Volunteers**, **Funder Type**, **Trial Results**, **Hidden Trials**

Description: A study of Drug ABC in patients with advanced Solid Tumors

Purpose: This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. [Read More >](#)

Address: Location XYZ, 126 S 11th St, Philadelphia, PA 19125

Site Contact: 1800-555-5555 http://iz9r0.axshare.com/#g=1&p=trial_detail



“Compare Selected” ➞

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help   

< Back to Search Results

COMPARE SELECTED TRIALS

| Name | A study of Drug ABC in patients with advanced Solid Tumors | A study of Drug IRX in patients with advanced Solid Tumors | A study of Treatment 123 in patients with advanced Solid Tumors |
|-----------------------------------|---|---|---|
| Purpose | This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. | This is a multicenter, randomized, phase 3 study to evaluate Drug IRX in patients with KRAS mutant colorectal cancer. | This is a multicenter, randomized, phase 3 study to evaluate Treatment 123 in patients with KRAS mutant colorectal cancer. |
| Status | Seeking Participants | Seeking Participants | Seeking Participants |
| Distance | 12 Miles | 13 Miles | 15 Miles |
| Nearest Location | Address: 126 S 11th St, Philadelphia, PA 19125 Get Directions | Address: 857 Main Street, Philadelphia, PA 19125 Get Directions | Address: 333 Lake Street, Philadelphia, PA 19125 Get Directions |
| Contact | 1-800-555-5555 | 555-555-5555 | 555-555-5555 |
| Condition | Colorectal Cancer, Colon Cancer | Colon Cancer | Colon Cancer |
| Type | Interventional | Interventional | Interventional |
| Phase | Phase 3 | Phase 3 | Phase 3 |
| Intervention | Drug ABC | Drug IRX | Procedure 123 |
| Time Commitment | Months 6 +/- Visits 15 +/- | Months 4 +/- Visits 16 +/- | Months 5 +/- Visits 14 +/- |
| Placebo | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. |
| Age & Sex | Age: 18+ Sex: Female & Male | Age: 18+ Sex: Female & Male | Age: 18+ Sex: Female & Male |
| Accepts Healthy Volunteers | No | No | No |
| Funder Type | Industry | Academic | Government |
| Post-trial Treatment | Post trial treatment will be available | Post trial treatment will be available | Post trial treatment will be available |
| Site Services | Transportation to and from the trial site can be made available | Transportation to and from the trial site can be made available | Transportation to and from the trial site can be made available |
| Reimbursement | Coverage for Services: Yes Out of Pocket Expenses: Yes | Coverage for Services: Yes Out of Pocket Expenses: Yes | Coverage for Services: Yes Out of Pocket Expenses: Yes |
| Pay to Participate | No | No | No |
| My Notes | <input checked="" type="checkbox"/> Enter your notes here Ask my physician if I meet the inclusion criteria. Research information about intravenous therapies. Print this off and share with my kids to see what they think. | <input checked="" type="checkbox"/> Enter your notes here | <input checked="" type="checkbox"/> Enter your notes here |

View Trial **View Trial** **View Trial**

Bookmark **Bookmark** **Bookmark**

COMMUNITY
Social Facet Name: 01.01.2017
Lorum ipsum dolor sit amet, consectetur adipiscing elit. Aenean euismod bibendum laoreet.

NAVIGATION
Home About Clinical Trials Advanced Search For Researchers Help

CONTACT
123 River St
Anywhere, PA
555.555.5555
Frame.Lname@email.com

Legal Notices Privacy Policy 

TRIAL DETAILS

Overview

After users have clicked on an individual trial, they are presented with the trial information page. The page organizes trial details in a structure and order most meaningful to a patient audience, minimizing the scrolling required to find information.

The screenshot shows the ROTF Trial Details page for a study titled "A study of Drug ABC in patients with advanced Solid Tumors". The page is organized into several sections:

- Top Bar:** Includes links for Home, About Clinical Trials, Advanced Search, For Researchers, Help, and various icons.
- Header:** Displays trial details: Status (Recruiting), Trial Type (Interventional), Phase (Phase 3), Sex (Female & Male), Age (18+), Participation Duration (+/- 6 mos.), and Number of Visits (+/- 15).
- Buttons:** "I'm Interested" (highlighted with orange marker 2) and "Hide Trial".
- Search Bar:** "Search within this trial" with a magnifying glass icon.
- Section Headers:** OVERVIEW, PARTICIPATION, LOCATIONS, RESOURCES, TRIAL RESULTS, NOTES.
- TRIAL PURPOSE:** Summary of the study's purpose and inclusion criteria (KRAS mutant colorectal cancer). Includes a "Read More" link.
- Immunotherapy:** No. Mechanism of Action: ABC 1 Inhibition. Molecular Composition of Tumor: KRAS Mutant.
- How do I know if this trial is right for me?** (highlighted with orange marker 10).
- Outcome Measures:** Expandable section.
- Basic Trial Details:** Estimated patients to participate in trial: 600. Trial first received: March 1, 2017. Trial start date: April 1, 2017. Trial end date: April 1, 2022. Last updated: April 22, 2017.
- Nearest Location:** Map showing the location of the nearest site (126 S 11th St, Philadelphia, PA) with a "Get Directions" button.
- Sponsor Information & Resources:** Shows Pharma XYZ as the sponsor. Funder Type: Industry. Contact: 1-800-555-5555. Other Sponsor Resources: Brochure 1, Leaflet 1, Pharma XYZ Information.
- NOTES:** A text input field for personal notes.
- People also viewed:** A list of related trials: "A study of Drug 1RX in patients with advanced Solid Tumors", "A study of Drug 231 in patients with advanced Solid Tumors", and "A study of Drug WWW in patients with advanced Solid Tumors".

11. Outcome Measures: expandable sub-section listing the clinical outcomes identified for the trial.

12. Basic Trial Details: basic statistics and time stamps for the registry entry and for the overall trial.

- Trial At-a-Glance:** the trial title and a set of standard iconography describing basic trial attributes is visible at the top of every trial information page.
- "I'm Interested" button:** reveals a pop-up window indicating the preferred contact method for the nearest site location conducting the trial.
- Search box:** allows users to search for key words found on the trial information page across all tabs and sections.
- Bookmark, alerts, download, print and sharing features:** operate in a similar manner to the search results page, but for individual trial information.
- Notes:** allows users to type personal notes and, at their discretion, save the notes on the trial for future reference. Patient feedback revealed a desire to track questions or discussion points for conversations with a physician or family member.
- Nearest Location on Map:** visual representation of the nearest site location for the clinical trial along with a link to retrieve directions.
- People Also Viewed:** alternate method of trial search enabling users to view trials to which other users viewing this same trial have also navigated.
- Sponsor Information & Resources:** transparent trial sponsor details, including trial sponsor category and contact information.
- Trial Purpose:** summary of trial followed by an option to click "Read More" to reveal the full description.
- How Do I Know if This Trial is Right for Me:** expandable sub-section clarifying the presence or type of placebo arm(s) on a trial and inclusion/exclusion (eligibility) criteria organized into several categories for easier comprehension.

The Participation Tab ➤

Provides details which illustrate what it might be like to participate in the trial.



TRIAL DETAILS

Participation and Location

Users may navigate to additional tabs for more information about the trial.

1. Potential Participation:

icons emphasize attributes relevant to participation and a brief series of short fields provides practical details for prospective trial participants.

2. Visit by Visit:

displays an interactive timeline showing both the full scope of participation as well as individual visit details. Users may navigate to the details of each visit in the trial by clicking on each visit icon.

3. Using information obtained with permission from each site location, a pop-up via the "Contact" button will display the preferred method of contact for each site.

The Location Tab ➤

Provides both visual and list-based representations of the various site locations involved in a particular trial, regardless of individual site status.

The Resources Tab ➤

Created to address patients' requests for additional connections to resources and communities relevant to their condition or diagnosis.

This screenshot shows the ROTF (Research On Trial Framework) platform interface. At the top, there's a navigation bar with links to Home, About Clinical Trials, Advanced Search, For Researchers, Help, and various icons. Below the navigation is a banner for a trial titled "A study of Drug ABC in patients with advanced Solid Tumors". The banner includes filters for Status (Recruiting), Trial Type (Interventional), Phase (Phase 3), Sex (Female & Male), Age (18+), Participation Duration (+/- 6 mos.), and Number of Visits (+/- 15). Below the banner are several buttons: "I'm Interested" (blue), "Hide Trial" (orange), and a search bar. The main content area has tabs for OVERVIEW, PARTICIPATION, LOCATIONS, RESOURCES, TRIAL RESULTS, and NOTES. The RESOURCES tab is currently selected, displaying a table of external resources:

| NAME | TYPE | LINK |
|---------------|-----------------|--|
| Group XYZ | Advocacy Group | www.GroupXYZ.com |
| Group ABC | Advocacy Group | www.GroupABC.com |
| Group 123 | Advocacy Group | www.Group123.com |
| WebSource ABC | Informational | www.WebSourceABC.org |
| LMNOP Group | Patient Support | www.LMNOP-Group.com |

To the right of the table is a notes section with a placeholder "Enter your personal notes here". Below this are three collapsed sections: "A study of Drug IXX in patients with advanced Solid Tumors", "A study of Drug 231 in patients with advanced Solid Tumors", and "A study of Drug WWW in patients with advanced Solid Tumors". Each section has a "View" button. At the bottom is a "View All" button.

TRIAL DETAILS Resources and Trial Results

Users may navigate to additional tabs for more information about the trial.

The Trial Results Tab ➤

Created to house trial results fields currently specified by most major clinical trial registries along with links to additional documentation (such as lay summary results) where available. Users may also elect to be notified when trial results become available.

This screenshot shows the same ROTF platform interface as the previous one, but the TRIAL RESULTS tab is now selected. The main content area displays a message: "There are no results for this trial at this time. The sponsor of this clinical trial has chosen to provide lay summary results to all participants upon completion of the trial. General trial results will also be posted on this page after trial completion." Below this message is a "NOTIFY ME" button. To the right of the message, there are three collapsed sections: "A study of Drug 231 in patients with advanced Solid Tumors", "A study of Drug WWW in patients with advanced Solid Tumors", and another "A study of Drug WWW in patients with advanced Solid Tumors". Each section has a "View" button. At the bottom is a "View All" button.

USER ACCOUNT

A user account enables additional features which help to personalize the experience and make the registry platform “go to work” for the user, such as the ability to:

- Save display or search preferences on the platform (preventing duplicate entry of criteria during successive trial searches or visits)
- Record and save personal notes about specific trials
- Bookmark individual trials or search types (sets of criteria) for future reference or use
- Set up automated alerts for trials matching previously entered criteria

Creating a user account should be optional and should not make mandatory the provision of any information beyond an email and a password.

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

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Account Settings (UserJohnDoe) Search within settings

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|--|------|------------|-------|-------------------|-------|------------|----------|----------------|----------|---------|-----------|-----------------------------|-------------|------------|-------------|-------------------------|------------|---|------|--|-----------|--|---------------|---|-----------------|---|
| About Me <ul style="list-style-type: none"> @ General 🔍 Search Criteria 📋 Medical Condition Bookmarks & Alerts <ul style="list-style-type: none"> 🔗 Bookmarks 🔔 Alerts | General Info <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>Name</td><td>(Optional)</td></tr> <tr><td>Email</td><td>JohnDoe@email.com</td></tr> <tr><td>Phone</td><td>(Optional)</td></tr> <tr><td>Password</td><td>***** (Change)</td></tr> <tr><td>Language</td><td>English</td></tr> <tr><td>Time Zone</td><td>Eastern Standard Time (EST)</td></tr> <tr><td>Date / Time</td><td>DD/MM/YYYY</td></tr> <tr><td>Measurement</td><td>Imperial (Mi / ft / lb)</td></tr> </table> Accessibility <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>Voice Over</td><td><input type="radio"/> Yes <input checked="" type="radio"/> No</td></tr> <tr><td>Zoom</td><td>50% <input checked="" type="radio"/> 100% <input type="radio"/> 150%</td></tr> <tr><td>Text Size</td><td>s <input checked="" type="radio"/> M <input type="radio"/> L</td></tr> <tr><td>High Contrast</td><td><input type="radio"/> Yes <input checked="" type="radio"/> No</td></tr> <tr><td>Auto Speak Text</td><td><input type="radio"/> Yes <input checked="" type="radio"/> No</td></tr> </table> | Name | (Optional) | Email | JohnDoe@email.com | Phone | (Optional) | Password | ***** (Change) | Language | English | Time Zone | Eastern Standard Time (EST) | Date / Time | DD/MM/YYYY | Measurement | Imperial (Mi / ft / lb) | Voice Over | <input type="radio"/> Yes <input checked="" type="radio"/> No | Zoom | 50% <input checked="" type="radio"/> 100% <input type="radio"/> 150% | Text Size | s <input checked="" type="radio"/> M <input type="radio"/> L | High Contrast | <input type="radio"/> Yes <input checked="" type="radio"/> No | Auto Speak Text | <input type="radio"/> Yes <input checked="" type="radio"/> No |
| Name | (Optional) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Email | JohnDoe@email.com | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Phone | (Optional) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Password | ***** (Change) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Language | English | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Time Zone | Eastern Standard Time (EST) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Date / Time | DD/MM/YYYY | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Measurement | Imperial (Mi / ft / lb) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Voice Over | <input type="radio"/> Yes <input checked="" type="radio"/> No | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zoom | 50% <input checked="" type="radio"/> 100% <input type="radio"/> 150% | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Text Size | s <input checked="" type="radio"/> M <input type="radio"/> L | | | | | | | | | | | | | | | | | | | | | | | | | | |
| High Contrast | <input type="radio"/> Yes <input checked="" type="radio"/> No | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Auto Speak Text | <input type="radio"/> Yes <input checked="" type="radio"/> No | | | | | | | | | | | | | | | | | | | | | | | | | | |

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help

Account Settings (UserJohnDoe) Search within settings

| About Me <ul style="list-style-type: none"> @ General 🔍 Search Criteria 📋 Medical Condition Bookmarks & Alerts <ul style="list-style-type: none"> 🔗 Bookmarks 🔔 Alerts | Alerts <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr><th>SEARCH NAME</th><th>DESCRIPTION</th><th>TEXT</th><th>EMAIL</th><th>FREQUENCY</th><th>ACTIONS</th></tr> </thead> <tbody> <tr> <td>My Serach 1</td><td>Showing 14 results - All trials have been locked at - waiting for new</td><td><input checked="" type="checkbox"/></td><td><input checked="" type="checkbox"/></td><td>New Results</td><td>(i) (x)</td></tr> <tr> <td>08/01/2017</td><td>Using multi-location (Phila & FL)</td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td>Frequency</td><td>(i) (x)</td></tr> <tr> <td>FL VHome</td><td>Search radius near vacation home in Florida</td><td><input type="checkbox"/></td><td><input checked="" type="checkbox"/></td><td>New Results</td><td>(i) (x)</td></tr> </tbody> </table> TRIAL NAME <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr><th>TRIAL NAME</th><th>TEXT</th><th>EMAIL</th><th>FREQUENCY</th><th>ACTIONS</th></tr> </thead> <tbody> <tr> <td>A study of Drug ABC in patients with advanced solid tumors</td><td><input type="checkbox"/></td><td><input checked="" type="checkbox"/></td><td>Results Posted</td><td>(i) (x)</td></tr> </tbody> </table> | SEARCH NAME | DESCRIPTION | TEXT | EMAIL | FREQUENCY | ACTIONS | My Serach 1 | Showing 14 results - All trials have been locked at - waiting for new | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | New Results | (i) (x) | 08/01/2017 | Using multi-location (Phila & FL) | <input type="checkbox"/> | <input type="checkbox"/> | Frequency | (i) (x) | FL VHome | Search radius near vacation home in Florida | <input type="checkbox"/> | <input checked="" type="checkbox"/> | New Results | (i) (x) | TRIAL NAME | TEXT | EMAIL | FREQUENCY | ACTIONS | A study of Drug ABC in patients with advanced solid tumors | <input type="checkbox"/> | <input checked="" type="checkbox"/> | Results Posted | (i) (x) |
|--|---|-------------------------------------|-------------------------------------|---|---|-----------|---------|-------------|---|-------------------------------------|-------------------------------------|-------------|---|------------|-----------------------------------|--------------------------|--------------------------|-----------|---|----------|---|--------------------------|-------------------------------------|-------------|---|------------|------|-------|-----------|---------|--|--------------------------|-------------------------------------|----------------|---|
| SEARCH NAME | DESCRIPTION | TEXT | EMAIL | FREQUENCY | ACTIONS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| My Serach 1 | Showing 14 results - All trials have been locked at - waiting for new | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | New Results | (i) (x) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 08/01/2017 | Using multi-location (Phila & FL) | <input type="checkbox"/> | <input type="checkbox"/> | Frequency | (i) (x) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| FL VHome | Search radius near vacation home in Florida | <input type="checkbox"/> | <input checked="" type="checkbox"/> | New Results | (i) (x) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRIAL NAME | TEXT | EMAIL | FREQUENCY | ACTIONS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| A study of Drug ABC in patients with advanced solid tumors | <input type="checkbox"/> | <input checked="" type="checkbox"/> | Results Posted | (i) (x) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

► LEARN MORE

Read the full TransCelerate proposal for Clinical Trial Registry of the Future:

[**"Improving the Value of Public Clinical Trial Registries to Patients: A Perspective and Call to Action"**](#)

► SPEAK OUT

Discuss the Clinical Trial Registry of the Future on social media using the hashtags #ClinicalTrial #RegistryOfTheFuture

► SHARE THIS EBOOK

Use this eBook in conferences, summits or in discussion with peers as a point of reference for continued dialogue on facilitating patient-focused improvements to public clinical trial registries.

The Clinical Trial Registry of the Future wireframe proof of concept illustrated in this eBook was designed by TransCelerate BioPharma for use in demonstrations to government authorities. The wireframe provides examples of how government-sponsored clinical trial registries could be organized and operated more effectively to enable patients to obtain much greater value from the registries. The wireframe is offered "as is," and nothing in the wireframe is meant to provide a legal opinion or imply compliance with relevant laws and regulations.

404

| Electronic Health Record | |
|--|-------------------------------|
| Data Field | Mock Data |
| Patient Name | John Deere |
| Patient Address | 1 New Road, Philadelphia |
| Gender | Male |
| Condition | B-Cell Lymphoblastic Leukemia |
| Date of Birth | 15-Jun-98 |
| Has patient consented to learn about available clinical research trials? | Yes |

Flowchart showing the process from Electronic Health Record to Clinical Trial Registry:

```

graph LR
    EHR[Electronic Health Record] --> CTR[Clinical Trial Registry]
    CTR --> EHS[Electronic Health Record System]
    
```

Clinical Trial Registry (CTR) Data:

| Clinical Trial Registry | |
|-------------------------|---|
| Trial Brief Title | CD19 CAR-T Cells for Patients With Relapse and Refractory CD19+ B-ALL |
| Inclusion Criteria | Diagnosed with CD19 positive B-cell acute lymphoblastic leukemia Age between 3-25 years old |
| Inclusion logic | Eligible IF 'Condition' EQUALS Mesh Term 'B-cell acute lymphoblastic leukemia' Eligible IF 'Date of Birth' BETWEEN 1-MAR-1995 AND 1-MAR-2017 |
| Exclusion Criteria | Pregnant or lactating female |
| Exclusion logic | Ineligible IF 'Gender' EQUALS 'Female' AND IF 'Reproductive status' EQUALS 'Pregnant' OR 'Lactating' |
| Locations | United States, Pennsylvania The Childrens Hospital of Philadelphia |
| Contact | Jeff Stanley |
| Phone | 111-111-1111 |
| Email | Jeffstanley@example.com |
| Principal Investigator | Dr.Shefford |

Eligibility Status:

- Diagnosed with CD19 positive B-cell acute lymphoblastic leukemia: PASS
- Age between 3-25 years old: PASS
- Pregnant or lactating female: FAIL
- United States, Pennsylvania: PASS
- The Childrens Hospital of Philadelphia: PASS
- Jeff Stanley: PASS
- 111-111-1111: PASS
- Jeffstanley@example.com: PASS
- Dr.Shefford: PASS

Flowchart showing the process from Clinical Trial Registry back to Electronic Health Record System:

```

graph LR
    CTR --> EHS
    EHS --> CTR
    
```

Electronic Health Record System (EHS) Data:

| Electronic Health Record System | |
|---|---|
| Trial Results | Mock Data |
| Eligible trials recruiting within 100Km of patients location? | Yes |
| Study Title | CD19 CAR-T Cells for Patients With Relapse and Refractory CD19+ B-ALL |
| Location | United States, Pennsylvania |
| Institution | The Childrens Hospital of Philadelphia |
| Contact | Jeff Stanley |
| Phone | 111-111-1111 |
| Email | Jeffstanley@example.com |
| Principal Investigator | Dr.Shefford |
| Do you want to refer this patient? | |
| Include medical notes in referral? | |

CLINICAL TRIAL REGISTRY OF THE FUTURE

Improving The Value
of Public Clinical Trial
Registries to Patients:
A Perspective and
Call to Action

Patients, their family members, and the health care professionals who care for them may consult a myriad of clinical research information resources, yet it is a commonly accepted struggle to navigate information about clinical research and clinical trial opportunities and make sense of it on a personal level. Why might this be, and what can be done about it? In this paper, TransCelerate offers a perspective, an illustrative proof of concept, and a call to action to advance discourse and collaboration on potential solutions which leverage existing, publicly funded clinical trial registries. The role of clinical trial sponsors and other stakeholders is also examined in the context of next steps which may be taken to improve patients' access to useful information about clinical trials.



HOW DID WE GET HERE?

The importance of publicly accessible information on clinical research has become widely accepted in recent years [1]. Knowledge of currently active clinical trials enables greater access to enrollment options for patients and further supports ongoing medical advancements to treat or help prevent the course of disease. Public access to the growing base of evidence generated by clinical trials improves health care decision making.

A common source of clinical trial information is through online registry interfaces publicly funded and managed by governments, which use information supplied directly by trial sponsors or responsible parties. They are often driven forward by legislation with an objective to make clinical trials more transparent to the public [2]. For example, the U.S. Food & Drug Administration Modernization Act of 1997 and the European Medicines Agency (EMA) 2001 Clinical Trial Directive (Article 11) resulted in the release of the ClinicalTrials.gov website and EudraCT database in the US and EU, respectively. The EU Clinical Trials Register website was later launched to provide the public with a searchable interface to the information held in the EudraCT database. Many trial sponsors or responsible parties have established Standard Operating Procedures (SOPs) which outline how and what clinical trial information is posted on these registries consistent with government mandates on required information as well as, occasionally, additional optional information. Such SOPs often cover company requirements on the timing and frequency of providing updates to the registries, fields which need to be posted, and the types of trials required to be posted.

Beyond providing basic transparency, a recognized use case for clinical trial registries has been to enable patients to search for clinical trials in which they might participate. At the time of the release of ClinicalTrials.gov in 2000, Donald A.B. Lindberg, M.D., Director of the U.S. National Library of Medicine (NLM), the government entity in charge of the platform, stated: "If we are to continue making the giant strides in diagnosis, treatment, and cure of illness that marked the last century, we must have active participation in clinical trials by well-informed volunteers." [3]

Public registries have gradually grown in size and purpose over the past two decades, and further legislation has expanded the scope of information required to be provided. ClinicalTrials.gov currently hosts over 250,000 studies with locations in 200 countries [4]. Trial sponsors or responsible parties submitting data to ClinicalTrials.gov are subject to the recently clarified and expanded regulatory requirements for registration and summary results under the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). National Institute of Health (NIH) Director Francis S. Collins, M.D., Ph.D. summarized the importance of the policy: "Access to more information about clinical trials is good for patients, the public and science." [5] In Europe, submission of a clinical trial summary has been mandatory since 2014, and a lay person summary by the sponsor after the end of a trial will become mandatory in 2019 per the Clinical Trial Regulation EU No 536/2014. [6]

Various non-government "hosts" of clinical trial data have also pioneered greater accessibility of online clinical trial information. The World Health Organization (WHO) established its International Clinical Trials Registry Platform (ICTRP) to provide a central access point to trials registered in various registries across the globe. Several additional country-specific registries offer access to clinical trial information and several newer platforms have begun focusing on facilitating easier comprehension of information and dynamic matching of patients to clinical trials.

Within the mission statements of various clinical trial information platforms, a common theme emerges: to provide accurate, searchable clinical research information for patients, caregivers, health care professionals, researchers, and the general public. WHO further expands upon its stakeholder base to include "all those involved in health care decision making." [7] For those who may now or may in the future benefit from a strong base of evidence on treatments for disease, clinical trials and accessible information on their design, their enrollment, and their results should naturally be viewed as a priority topic in health care.

WHAT DOES THE CURRENT INFORMATION LANDSCAPE LOOK LIKE?

With growing calls for transparency of clinical trial information and increasing recognition of its value, an unfortunate side effect has become a difficult-to-navigate landscape of data and information. Several complications exist:

- » **Information is not written for the general public.** Registries and other sources of clinical trial information often contain a high volume of scientific, jargon-rich data that is difficult to digest and interpret. Data and information requiring a relatively high learning curve to understand renders it inaccessible for a variety of practical purposes, minimizing its value. According to a recent survey of clinical trial sponsors (see “Methods”), less than one third of companies surveyed reviewed the information posted to ClinicalTrials.gov to ensure relevance and understanding to a lay audience.
- » **Search functions often result in a difficult and time consuming user experience.** Registry data search is not structured in the way users tend to search in other domains (as online consumers). For example, searching for available trials within a specified location radius, being alerted of new trials as they come online, or comparing trials side-by-side, are functions which are either not very straightforward today or do not yet fully exist. Additionally, pieces of information that would be valuable to a patient in a trial search and evaluation process are often missing.
- » **Display and mobility are “behind the curve” with respect to technology adoption.** We are in a highly digital, multi-device era; patients expect information at their fingertips to drive their own healthcare agenda at home, at a doctor’s office, or from wherever is convenient. However, many clinical trial registries are not yet mobile or tablet-enabled and do not offer capabilities which support use or sharing of the information in more practical, real-world settings (such as a fifteen minute patient-doctor visit). Greater portability, interoperability, and integration are needed to maximize use of information.

While a growing number of online information sources have attempted to address these gaps, an increased number of sources may actually cause added complexity. Platforms which

provide supplementary information about clinical trials beyond what is offered in public registries, but only do so for one trial sponsor or for a small portion of total available clinical trials, fall short on the objective to offer a comprehensive view of information for patients. Platforms which query or present data sourced from public clinical trial registries may enhance the user interface, but will continue to be hemmed in by the limitations of the source data.

In addition to the gaps noted above, various opportunities to use clinical trial registry data in new and novel ways are progressing at a slow pace relative to their potential value. Despite advances in health information technology implementation within healthcare systems around the world [8], there are still relatively few efforts to connect point of care electronic health record systems to potential clinical trial options. Closing this gap would help to embed clinical research into healthcare practices. For patients who wish to be connected to clinical trials, opting in to the use of their EHR data for this purpose would facilitate easier research referral pathways without placing unnecessary time burden on health care professionals. The value of facilitating referral pathways could be tremendous – it is estimated that nearly 59 million study participants are needed to fill the demand of enrolling studies just on ClinicalTrials.gov, equating to approximately 1 in 6 United States citizens [9]. Faster and more effective enrollment would enable faster medical advancements and access to more treatment options for patients.

Guided by a clear understanding of the opportunities for improvement to clinical trial information posted online and to public registry platforms housing the data, changes may be made which have the potential to encourage greater public understanding and engagement with clinical research, more informed patient populations, faster and more effective clinical trial enrollment, and faster access to therapies approved as a result of clinical trials.

WHAT DO PATIENTS THINK?

As the ultimate recipients of new therapies resulting from clinical research, and the primary advocates involved in clinical trial consideration and search, patients' perspectives regarding clinical trial information found online should naturally be of prime importance. Further supporting this position are statistics on the use of one of the world's most consulted registries: according to the U.S. National Library of Medicine, the single largest user group of the ClinicalTrials.gov registry consists of patients and family members/friends of patients (37%), substantially larger than the next largest user group of scientists/researchers (19%) [10]. Understanding patients' needs and preferences for clinical trial information, and the ways in which interested patients may be best connected to trial enrollment opportunities, is vital to making meaningful progress in this space.

Beginning in 2016, TransCelerate sought the input of a diverse group of patients on this topic [see "[Methods](#)" and "[Designing with patients, for patients](#)".]

Key Takeaway: Situational Context is Important

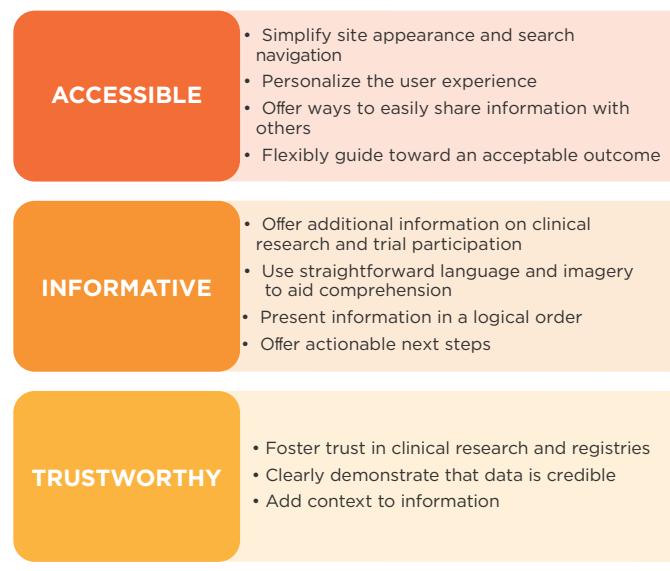
Understanding the situation patients (or caregivers) might find themselves in when visiting a clinical trial registry lends valuable context to their expectations of user experience. Many patients may feel they have landed at the registry as a last resort; others may be searching for hope that one day a promising treatment for an unmet medical need might be available for a loved one struggling with a rare disease. Whether a person is searching for a trial to participate in, results of past studies in a condition of interest, general clinical research education, or simply looking for hope, a common expectation is to be greeted with a welcoming, positive, and straightforward user experience. Minimally, an experience which does not contribute to the existing stress of disease or a recent diagnosis is desired. Unfortunately for patients who find themselves navigating existing registries, they may perceive the current experience to be cold, clinical, and confusing. The implications this has on the public's perception of clinical research or on individual patients' perception of clinical

trial participation may be more substantial than is currently acknowledged in the research community.

Key Takeaway: Opportunities Go Beyond Usability, to More and Better Information

Though general user experience is a key improvement opportunity, it is evident that further exploration into providing additional types of information valued by patients is needed. Three major improvement priorities were identified during discussions with patients, summarized in Figure 1 as guiding principles for clinical trial registry design.

Figure 1:
Guiding Principles for Clinical Trial Registry Design



Guiding Principle 1: Accessible

Clinical trial search and clinical research education or resources should be prominent upon entry to signal to patients that they are in the right place for their needs and can navigate the site with minimal guesswork. Peripheral information less relevant to patients (such as links to instructions for clinical trial sponsors) can be made available in less prominent parts of the website.

The platform should create an empathetic and personalized user experience, recognizing the unique priorities, interests, and circumstances

of each individual, including geography and language. This can be accomplished by using language which demonstrates empathy for the patient community (such as using “trial participant” in favor of “subject”), by offering opportunities for the user to personalize their experience based on information they choose to provide, and by proposing proper language or geographic display based on the user’s location. This is in contrast to an approach of pre-determining a user experience based on generic archetypes (such as “patient” or “professional”).

Whether searching for a trial to participate in or searching for other information, each user should be gracefully and flexibly guided closer to an acceptable outcome, even if it is not the one originally intended. This might include being presented with additional options for the search journey if no available clinical trials exist for a particular condition. Reducing manual effort required to arrive at a manageable set of search results (clicking and drilling down) and eliminating the need to “start over” previous search queries may help greatly reduce user frustration and time commitment. Where users are unable to find exactly what they are looking for, providing next-best-alternatives or complementary search results will provide useful encouragement to proceed in a positive direction. Offering features to help automate key functions (such as email alerts when a trial is found which matches user-entered criteria) would additionally lessen user burden, particularly for rare disease or rural populations which may find it more difficult to come across available opportunities. A global survey of patients and caregivers (see “Methods”) suggests automated email alerts are a top preference for keeping individuals aware of clinical trials conducted in their community.

Features which enable the use of the platform and associated information in multiple locations and formats – whether via desktop, tablet, mobile device, or hard-copy printout – facilitate more practical, real-world use of the information and sharing of information with others. Options such as print-ready summaries made available for a doctor’s visit, or links to quickly post a clinical trial on social media, broaden the reach of the information by enabling patients to discuss it with their trusted health care professionals, friends, or family members. For patients who

may feel isolated and overwhelmed with a recent diagnosis, for example, the ability to involve others in their community could help to alleviate the burden associated with evaluating next steps. In this same way, offering connections to the broader community of patient, disease, or research organizations by hosting a curated library of resources and links would enable users to seek complementary information and peer groups which are best facilitated by external organizations. As online communities become a bigger part of daily life for many people, the ability to more seamlessly move between information resources and community-based resources will become more important.

Guiding Principle 2: Informative

Guidance should be provided to help users understand what to look for and how to look for it. Educational resources on clinical research can support users who wish to become more familiar with the approach for developing new treatments, and key definitions relevant to clinical trials provided in a glossary-style format offer an additional point of reference.

Rather than simply presenting data, clinical trial registries should convey meaning through the use of straightforward language, consistent terms, and visuals where appropriate. Graphics and imagery should be used to represent more complex information, or should be used alongside text to add further visual interest and make the user experience more approachable. Text-heavy pages and long paragraphs should be avoided, where possible, in favor of concise sections of information presented in a logical order. Information should be sequenced in order of priority based on patient preferences. To aid the evaluation of multiple sets of information (such as a handful of trial search results), functions which allow side-by-side comparisons can further enhance the utility of the information to the user according to his or her own priorities.

Perhaps most importantly, potential trial participants should not be expected to wait until they are presented with a consent form or are in contact with a clinical trial site professional in order to feel well-informed about a particular clinical trial. Concise summaries of the purpose

of each trial, with context provided based upon trial phase, would help users narrow their options without requiring the support of a third party to help “translate” the trial aims. Users should also be able to expect access to information which helps them evaluate the potential impact trial participation might have on their personal lives (such as monthly time commitment, availability of clinical site transportation services, etc.). Each clinical trial opportunity should have actionable information pointing the user to possible next steps – including the specific location and contact details of individual research sites supporting the trial.

Guiding Principle 3: Trustworthy

Small improvements to both the content and the presentation of information in clinical trial registries could help to foster trust with patients, with health care professionals, and with the general public. Providing links within individual study records to related information and records relevant to the broader research landscape (such as for a particular therapy area or for a particular molecule) would place study record information in a useful context for the user that improves familiarity with clinical research overall. Using standard categories or “tags” to objectively classify clinical trials and trial characteristics could greatly improve perceptions around the credibility of registry information. For example, the use of basic ‘yes’ or ‘no’ classifications for questions such as “does this trial require me to pay to participate?” would enable users to better assess certain trials based on criteria they deem legitimate.

Additionally, metadata indicating when fields were last updated or clarifying information on missing data fields (such as why a data field has yet to be reported) would build confidence in the timeliness, completeness, and relevance of such information. Real-time or near-real-time data updates are also an important contributor to improving overall trustworthiness of information and could be made possible with common technologies which help trial sponsors or responsible parties automate the submission of registry data updates by pulling from their own information systems when an update is made in those systems or is required for submission. This

may be particularly helpful with trial site-level information; patients or caregivers who invest significant time researching available clinical trials in a registry platform should not have to find out afterward that several of the clinical trial sites listed are no longer accepting patients for enrollment.

WHAT COULD THE FUTURE LOOK LIKE?

In close collaboration with a diverse group of patients and caregivers (“[Designing with patients, for patients](#)”), TransCelerate developed a wireframe proof of concept for a “Clinical Trial Registry of the Future” which demonstrates the scenario of a user searching for information and opportunities for colorectal cancer trials. Several new features, capabilities, and data fields which do not exist today, in addition to features which may already exist in certain platforms, are illustrated in the proof of concept. Although the proof of concept does not include all elements currently found in existing clinical trial registries, its limited scope is intended to illustrate priority enhancements proposed for public registries based on patients’ stated priorities during the design process, and not to propose any constraints to information currently found in registries today. **The goal of the proof of concept is to serve as a point of reference for influencing change to existing, government-owned registries across multiple geographies, which serve as a trusted source of truth for clinical trial information for millions of people.**

Designing with patients, for patients

- » In August 2016, a team of TransCelerate representatives met with a group of ten patients, caregivers, and patient advocates (“Patient Advisory Board” or “PAB”) to begin a year-long process to design solutions for improving patient awareness of clinical research and access to information about clinical trial opportunities. Beginning with the first meeting and in successive meetings over twelve months, the team’s assumptions were consistently challenged by the insights and personal stories offered by the Patient Advisory Board.
- » A patient journey map co-developed with the PAB revealed several challenges, frustrations, and opportunities involved with the journey into a clinical trial from the moment of diagnosis (or lack of diagnosis, as the case may often be), to assessing eligibility for enrollment, all the way through the end of trial participation. Information overload, fear and uncertainty of suitable treatment paths, and discoordination among various stakeholders in the health care system were cited as significant barriers to discovering and considering clinical trial options. After confirming clinical trial registries as a common source of information used in online sources or used directly by patients, an objective was formed to leverage these existing platforms to better deliver meaningful information about clinical trials to patients and those who care for them.
- » Beginning in 2017, the team held several collaborative design workshops with the PAB on a Clinical Trial Registry of the Future concept in furtherance of the objective to improve the value of registries operated by government agencies to patients. First, an evaluation of the step-by-step user experience on existing clinical trial registries helped to identify a list of 30+ patient user needs statements and solution ideas. Second, a preliminary sketch of various registry screens and functions, based on developed user needs statements, was presented to the PAB for further discussion and debate on user experience design choices, priority functions, and priority information types. Finally, several versions of a registry proof of concept were developed over a series of iterative design sessions with the PAB (beginning with a static, low-fidelity mock-up and moving to an interactive, semi-functional wireframe).

The resulting Clinical Trial Registry of the Future proof of concept would not have been made possible without the consistent involvement of the following Patient Advisory Board team members:

Helmut Bayer
Kelsey Brown
Ndeye Mariama Gueye
Marcia Horn

G. Korevaar
Bill McCue
Gillian Nembhard
Jack Whelan

Home Page

The aim of the home page is to allow users to feel welcome and comfortable while making it easy for them to get started with the site's primary function – searching for information on specific clinical trials.

ROTf

Home About Clinical Trials Advanced Search For Researchers Help

Over 30,000 Clinical Trials Seeking Participants

Browse publicly and privately supported clinical trials conducted around the world.

Begin Search Below

Seeking Participants ▾ Enter medical condition or keyword Location Miles

LATEST STORIES [\(View All\)](#)

 HEAR HER STORY
Caitlin Anderson tells her father Reed Anderson about her experience living with multiple sclerosis and her decision to be a part of clinical trial for MS at the National Institutes of Health.
[Read More](#)

 COLON CANCER SPOTLIGHT
Colon cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death in men and women combined in the United States.
[Read More](#)

 ADVOCACY GROUPS
What are they? What is their role? How can they help? Learn about how advocacy groups are connecting patients together.
[Read More](#)

RECENTLY VIEWED

| | | |
|--|---|--|
| Clinical Trial A with Drug ABC Brief purpose of clinical trial A with Drug ABC. | Clinical Trial 2 with Drug 1RC Brief purpose of clinical trial 2 with Drug 1RC. | Clinical Trial 123 with Drug B Brief purpose of clinical trial 123 with Drug B. |
| Clinical Trial 6 with Drug BNS Brief purpose of clinical trial 6 with Drug ABC. | Clinical Trial IE with Drug XY Brief purpose of clinical trial IE with Drug 1RC. | Clinical Trial 00 with Drug 01 Brief purpose of clinical trial 00 with Drug B. |
| Clinical Trial AB with Drug J9 Brief purpose of clinical trial AB with Drug X7. | Clinical Trial P7 with Drug XZ Brief purpose of clinical trial P7 with Drug X7. | Clinical Trial J9 with Drug 01 Brief purpose of clinical trial J9 with Drug X7. |

COMMUNITY
Social Feed Name 01.01.2017
Lorem ipsum dolor sit amet, consectetur adipiscing elit. Aenean euismod bibendum laoreet.

NAVIGATION
Home About Clinical Trials Advanced Search For Researchers Help

CONTACT
123 River St
Anywhere, PA
555.555.5555
Fname.Lname@email.com

Legal Notices Privacy Policy

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A banner of links and icons at the top of the page are visible on every screen in the platform, allowing navigation to:

- » **About Clinical Trials:** educational information about clinical trials
- » **Advanced Search:** study search capabilities for more advanced users
- » **For Researchers:** library of pages relevant mainly to the research community (allowing the focus of the home page to remain on patients and caregivers)
- » **Help:** additional resources supporting clinical trial education and search
- » **Bookmarks:** content previously bookmarked by the user
- » **Language Preferences (Globe):** drop-down to select appropriate language/region preference to personalize display (e.g. kilometers versus miles)
- » **User Account:** create or display previously created account with personalized features and preferences

The Latest Stories section displays content from three general categories – personal stories, condition spotlights, and advocacy group spotlights – included to address patient feedback that the platform should foster hope and a sense of community.

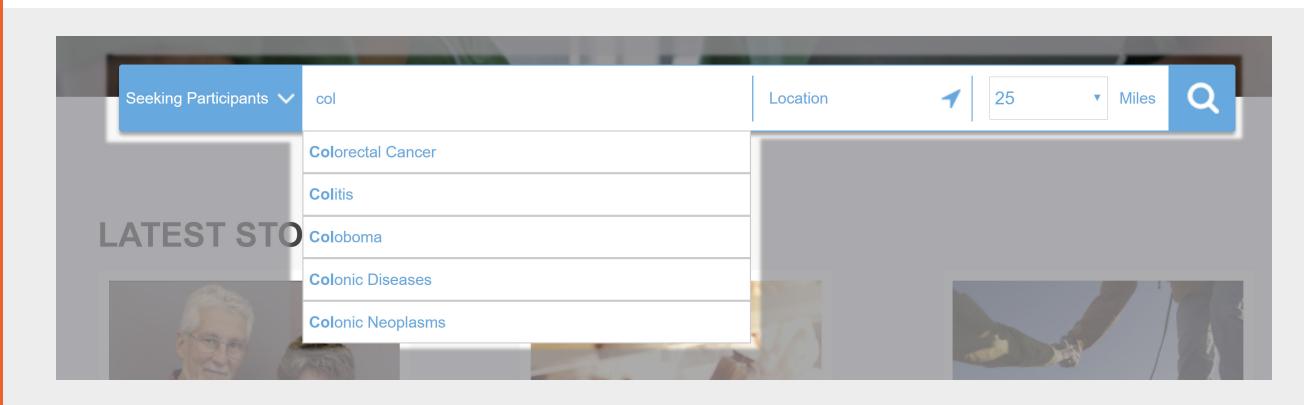
The Recently Viewed section provides easy access to a user's previously viewed clinical trials.

Searching for a Trial

Patient feedback highlighted the need to simplify the process of searching for specific clinical trials near a desired location that are seeking participants.

A basic search function is available directly from the home page. After selecting one of three common search scenarios (“seeking participants,” “completed with results,” or “all trials”), the user may enter desired medical condition, location of any type (address, postal code, city, etc.) including the ability to detect location, and a desired search radius from location.

The condition search field features type-ahead functionality using available controlled vocabulary terms (e.g. NLM’s Medical Subject Headings or MeSH) to help users find a condition faster and/or select a condition from a pre-defined list.



Viewing Search Results

After selecting the search icon from the home page, the user is brought to a search results page. The option to revert back to a simple search is left at the top of the screen, alongside several icons enabling additional features designed to make it easier for users to share or re-visit search results:

- » **Bookmark:** searches may be bookmarked by users. A visual indicator (filled in icon) demonstrates a search has already been bookmarked.
- » **Alerts:** users may also request alerts for specific searches to be notified when there are changes to the results associated with that search.
- » **Download, Print, or Share:** users may click on several icons to use the search results in different formats (including offline) or in communication with others via email, social media, etc.

A grid of results listing available clinical trials matching entered criteria is shown alongside a filter pane to further refine search results.

The criteria selected for search on the home page may be cleared (removed from search criteria) directly from the search results page without needing to revert back to the original search box.

Default columns shown in the grid include basic trial attributes as well as details generally found to be most important to patients when starting the process of refining search results for trials seeking participants. A dynamic grid presenting different columns based on initial search type (such as for completed trials with results) can also be envisioned.

The Commitment column indicates the number of visits and total participation duration according to each trial's protocol; for some trials, these figures may be variable, as shown in this example. Though this data field does not exist in registries today, patient feedback revealed a clear desire for time commitment information in future listings.

FILTER BY

Showing: 1 - 10 of 22 trials

Trials per page: 10

| NAME | CONDITION | INTERVENTION | DISTANCE | COMMITMENT | STATUS | ACTIONS |
|---|---------------------------------|---------------|----------|-----------------------------|----------------------|---------|
| A study of Drug ABC in patients with advanced solid tumors | Colorectal Cancer, Colon Cancer | Drug ABC | 12 Mi | Months 6 +/- Visits 15 +/- | Seeking Participants | |
| A study of Drug 1RX in patients with advanced solid tumors | Colon Cancer | Drug 1RX | 13 Mi | Months 4 +/- Visits 18 +/- | Seeking Participants | |
| A study of Treatment 123 in patients with advanced solid tumors | Colorectal Cancer | Procedure 123 | 15 Mi | Months 5 +/- Visits 14 +/- | Seeking Participants | |
| A study of Drug AJB in patients with advanced solid tumors | Colon Cancer | Drug AJB | 16 Mi | Months 8 +/- Visits 23 +/- | Seeking Participants | |
| A study of Treatment P&R in patients with advanced solid tumors | Colorectal Cancer, Colon Cancer | Procedure P&R | 17 Mi | Months 6 +/- Visits 17 +/- | Seeking Participants | |
| A study of Drug 2WO in patients with advanced solid tumors | Colon Cancer | Drug 2WO | 18 Mi | Months 18 +/- Visits 38 +/- | Seeking Participants | |
| A study of Drug WWW in patients with advanced solid tumors | Colorectal Cancer | Drug WWW | 18 Mi | Months 5 +/- Visits 10 +/- | Seeking Participants | |

Icons in the right-most Actions column of the grid, clockwise from top left, include:

- » **Bookmark trial:** enables logged-in users to bookmark the individual trial.
- » **Hide Trial:** enables users to hide the trial from the grid view. Hidden trials may be recalled using the filter pane.
- » **Mark as Interested:** saves the trial as a high priority bookmark, allowing differentiation between trials of personal interest versus trials for reference.
- » **Notes:** indicates to users the trials for which they have previously written personal notes within the platform (see "View Trial Details" for a description of the notes feature).

A gold bar next to select trials indicates to logged-in users the trials which have been newly posted since the time of their last search.

The use of simple icons, such as those shown in the Intervention column, help to communicate information in an engaging and easy to understand way.

Map View

In addition to a grid view, search results may also be plotted on a map view leveraging a Google Maps API, allowing for zoom-in and zoom-out capability and at-a-glance understanding of the geographical spread of available trials and trial sites.

Within the map view, location pins may be clicked on to reveal site location-specific details, including address and preferred method of contact, in addition to overall trial details and a link to the trial details page.

Showing: 14 of 14 trials

A study of Drug ABC in patients...

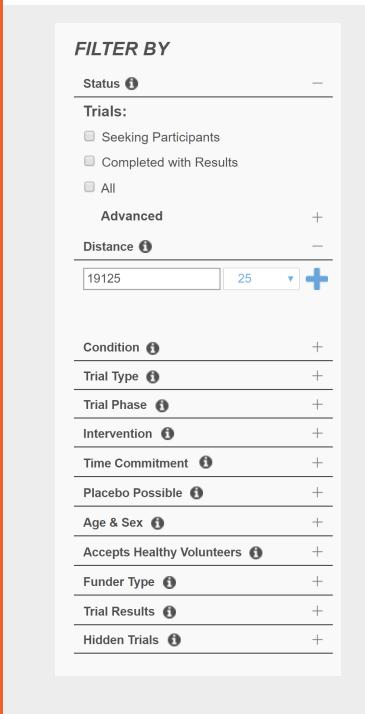
name:
A study of Drug ABC in patients with advanced Solid Tumors

Purpose:
This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. Read More >

Address:
Location XYZ
126 S 11th St
Philadelphia, PA 19125

Site Contact:
1800-555-5555

http://liz9r0.axshare.com/#g=1&p=trial_detail



Filtering Search Results

The filter pane to the left of the search results grid allows users to continue to refine their search based on additional trial attributes and other key criteria important to patients during trial search. Real-time updates to the search grid occur when modifying the filters.

Status and Distance categories are open by default; all other categories may be expanded or collapsed using the + sign.

Information icons provide hover-over information describing or defining the filter category. Additionally, most filter options should also have hover-over definitions, supported by a complete glossary, for ease of understanding to the user.

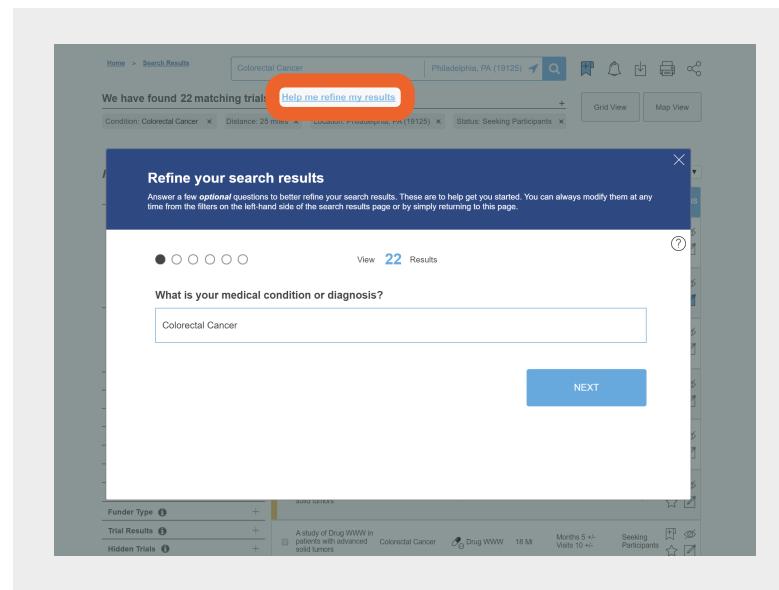
Some filters include advanced subcategories available via expansion (such as Status) in an effort to simplify the filter pane view and display common criteria most prominently.

The Distance category allows the user to change search location, search radius, and also to add a second search location and radius.

Help Me Refine My Results

For users looking for a more guided search experience, the “Help me refine my results” link at the top center of the page allows access to optional guided filters customized by medical condition. In the proof of concept example for colorectal cancer, the user might select condition-specific criteria such as stage of cancer, microsatellite status, and molecular profile of tumor, in addition to common filters such as age and sex.

All guided search steps are optional and the user can exit out at any time by clicking the “x” in the upper right corner or the “View ## Results” heading at the top center of the window. With each selection at each step, the number of results shown at the top of the window changes dynamically to reflect the selection’s impact to the search result. The guided search questionnaire was intentionally created as a second and optional step in the search process after the user sees initial results. Patient feedback revealed a preference to provide minimal personal information prior to seeing initial results.



Comparison Page

To further enable simpler and faster refinement of search results from the search grid, users may also create their own trial comparison page. By checking boxes to the left of desired trial listings and clicking a Compare Selected button beneath the grid, the user is presented with a trial comparison page to quickly identify differences between options.

The comparison page is designed to allow for side-by-side comparison of trial attributes most important to patients during the search and evaluation process, including free text fields that cannot be made filterable on the filter pane. Several of the trial attributes considered for this proof of concept in the comparison page are not commonly available today in existing registries.

Similar to other pages, the user has the option to Download, Print, or Share the comparison page. This was found to be a particularly useful feature in discussion with patients, who may wish to bring this level of detail with them to a doctor visit. The user may also record personal notes underneath each trial, navigate to the full trial details page for each trial, or bookmark each trial for future reference.

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

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[About Clinical Trials](#)
[Advanced Search](#)
[For Researchers](#)
[Help](#)

[< Back to Search Results](#)

COMPARE SELECTED TRIALS

| Name | A study of Drug ABC in patients with advanced Solid Tumors | A study of Drug 1RX in patients with advanced Solid Tumors | A study of Treatment 123 in patients with advanced Solid Tumors |
|----------------------------|---|--|--|
| Purpose | This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. | This is a multicenter, randomized, phase 3 study to evaluate Drug 1RX in patients with KRAS mutant colorectal cancer. | This is a multicenter, randomized, phase 3 study to evaluate Treatment 123 in patients with KRAS mutant colorectal cancer. |
| Status | Seeking Participants | Seeking Participants | Seeking Participants |
| Distance | 12 Miles | 13 Miles | 15 Miles |
| Nearest Location | Address: 126 S 11th St Philadelphia, PA 19125 Get Directions | Address: 857 Main Street Philadelphia, PA 19125 Get Directions | Address: 333 Lake Street Philadelphia, PA 19125 Get Directions |
| Condition | Colorectal Cancer, Colon Cancer | Colon Cancer | Colorectal Cancer |
| Type | Interventional | Interventional | Interventional |
| Phase | Phase 3 | Phase 3 | Phase 3 |
| Intervention | Drug ABC | Drug 1RX | Procedure 123 |
| Time Commitment | Months 6 +/- Visits 15 +/- | Months 4 +/- Visits 18 +/- | Months 5 +/- Visits 14 +/- |
| Placebo | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. | Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone. |
| Age & Sex | Age: 18 + Sex: Female & Male | Age: 18 + Sex: Female & Male | Age: 18 + Sex: Female & Male |
| Accepts Healthy Volunteers | No | No | No |
| Funder Type | Industry | Academic | Government |
| Post-trial Treatment | Post trial treatment will be available | Post trial treatment will be available | Post trial treatment will be available |
| Site Services | Transportation to and from the trial site can be made available | Transportation to and from the trial site can be made available | Transportation to and from the trial site can be made available |
| Reimbursement | Coverage for Services: Yes Out of Pocket Expenses: Yes | Coverage for Services: Yes Out of Pocket Expenses: Yes | Coverage for Services: Yes Out of Pocket Expenses: Yes |
| Pay to Participate | No | No | No |
| My Notes | <input type="checkbox"/> Enter your notes here Ask my physician if I meet the inclusion criteria. Research information about intravenous therapies. Print this off and share with my kids to see what they think. | | |
| | View Trial | View Trial | View Trial |
| | Bookmark | Bookmark | Bookmark |

View Trial Details

After users have clicked on an individual trial/trial listing, they are presented with the trial information page. The page was designed to balance the goal of visual simplicity with the goal of organizing trial details in a structure and order most meaningful to a patient audience, minimizing the clicking and scrolling required to find information.

Friendly icons at the top of the page provide an at-a-glance view of basic trial attributes just beneath the trial name.

Disclaimer: This interactive wireframe was designed by TransCelerate BioPharma for use in demonstrations to regulatory authorities. [Read More >](#)

ROTF

Home About Clinical Trials Advanced Search For Researchers Help

A study of Drug ABC in patients with advanced Solid Tumors

Status: Recruiting | Trial Type: Interventional | Phase: Phase 3 | Sex: Female & Male | Age: 18+ | Participation Duration: +/- 6 mos. | Number of Visits: +/- 15

I'm Interested Hide Trial Search within this trial

OVERVIEW PARTICIPATION LOCATIONS RESOURCES TRIAL RESULTS NOTES

TRIAL PURPOSE

This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. [Read More >](#)

| | |
|--------------------------------|------------------|
| Immunotherapy | No |
| Mechanism of Action | ABC 1 Inhibition |
| Molecular Composition of Tumor | KRAS Mutant |

How do I know if this trial is right for me? +

Outcome Measures +

Basic Trial Details -

Estimated patients to participate in trial: 600
Trial first received: March 1, 2017
Trial start date: April 1, 2017
Trial end date: April 1, 2022
Last updated: April 22, 2017

Sponsor Information & Resources

Pharma XYZ
Funder Type: Industry
Contact: 1-800-555-5555
Other Sponsor Resources:
[Brochure 1](#) [Leaflet 1](#) [Pharma XYZ Information](#)

Nearest Location: [Get Directions](#)

Enter your personal notes here

People also viewed:

- A study of Drug 1RX in patients with advanced Solid Tumors [View](#)
- A study of Drug 231 in patients with advanced Solid Tumors [View](#)
- A study of Drug WWW in patients with advanced Solid Tumors [View](#)

[View All](#)

Features which enable quick actions related to the trial are also located near the top of the page, and could be visible at all times on the page:

- » The blue I'm Interested button reveals a pop-up window indicating the preferred contact method for the nearest site location conducting the trial (also indicated in a small map view on the same page)
- » A search box allows users to search for key words found on the trial information page across all tabs and sections
- » Bookmark, alerts, download, print and sharing features operate in a similar manner to the search results page, but for individual trial information
- » A Notes field allows users to type personal notes and, at their discretion, save the notes on the trial for future reference. Patient feedback revealed a desire to track questions or discussion points for conversation with a physician or family member.
- » "People also viewed," located on the right side of the page, is an alternate method of trial search enabling users to view trials to which other users viewing this same trial have also navigated.

View Trial Details — Overview Tab

The trial information page is further organized into tabs near the top of the page for simpler navigation and retrieval of information in key categories.

The Overview tab is the default tab when viewing trial details. Envisioned sections include:

- » **Trial Purpose:** brief, lay language summary statements(s) followed by an option to click “Read More” to reveal the full description.
- » **Key Trial Attributes:** in the proof of concept, three trial attributes were chosen to be useful in the context of colorectal cancer to describe the particular trial illustrated (immunotherapy, mechanism of action, molecular composition). Specifying a library of structured fields tagged to trials in certain conditions, or to all trials, would support users searching for particular trial attributes. Mechanism of action, for example, may be a good candidate as a structured field for every trial listing to enable keyword searches for desired therapy types.
- » **Nearest Location on Map:** visual representation of the nearest site location for the clinical trial along with a link to retrieve directions to the site from the user’s location.
- » **How Do I Know if This Trial is Right for Me:** expandable sub-section clarifying the presence or type of placebo arm(s) on a trial and inclusion/exclusion (eligibility) criteria organized into several categories for easier comprehension. It is envisioned that future eligibility criteria may be organized using a structured library of searchable (and machine readable) terms to enhance consistency of presentation across trials and trial sponsors, as well as to facilitate integrations with platforms matching eligible patients to available trials. Additionally, where appropriate, it may also be worth considering presenting the *probability* of receiving a placebo during each clinical trial, using either percentages or ratios.
- » **Outcome Measures:** expandable sub-section listing the clinical outcomes identified for the trial.
- » **Basic Trial Details:** basic statistics and time stamps for the registry entry and for the overall trial.
- » **Sponsor Information & Resources:** transparent trial sponsor details, including trial sponsor category and contact information.

[OVERVIEW](#) [PARTICIPATION](#) [LOCATIONS](#) [RESOURCES](#) [TRIAL RESULTS](#)

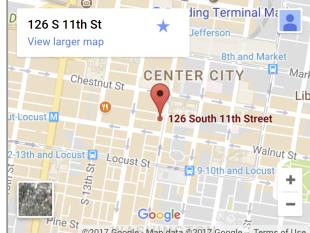
TRIAL PURPOSE

This is a multicenter, randomized, phase 3 study to evaluate Drug ABC in patients with KRAS mutant colorectal cancer. [Read More >](#)

Immunotherapy No

Mechanism of Action ABC 1 Inhibition

Molecular Composition of Tumor KRAS Mutant



Nearest Location: [Get Directions](#)

126 S 11th St

View larger map

How do I know if this trial is right for me?

Might I receive placebo on this trial?

Participants will not receive placebo. Participants will receive either usual care (standard of care) in addition to the study intervention or usual care (standard of care) alone.

Inclusion Criteria

| | |
|--|--|
| Condition | Histologically- or cytologically-confirmed CRC that is metastatic and is KRAS mutant |
| Progression of disease after both oxaliplatin and irinotecan-based therapies | |
| Laboratory Values | Adequate bone marrow, cardiac, kidney and liver function |
| ECOG status 0-2 | Haematology and biochemistry laboratory results within the limits normally expected |
| Lifestyle | |
| Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy from screening through follow-up if of childbearing potential | |
| Males must agree to take appropriate precautions to avoid fathering a child from screening through follow-up | |

Exclusion Criteria

| | |
|--|--|
| Medical History | Major surgery within 4 weeks prior to the first dose of Drug ABC |
| Concurrent participation in another interventional clinical trial | |
| Known allergy to Drug ABC or compounds of similar biologic composition | |
| Any medical, mental, psychological, or psychiatric condition that would not permit the patient to complete the trial | |

Required Drug Administration Method

Inability to take oral medication

Inclusion Criteria

| |
|---|
| • ECOG status 0-2 |
| • Haematology and biochemistry laboratory results within the limits normally expected |

Exclusion Criteria

| |
|--|
| • Known allergy to Drug ABC or compounds of similar biologic composition |
| • Any medical, mental, psychological, or psychiatric condition that would not permit the patient to complete the trial |

Outcome Measures

Basic Trial Details

Estimated patients to participate in trial: 600
Trial first received: March 1, 2017
Trial start date: April 1, 2017
Trial end date: April 1, 2022
Last updated: April 22, 2017

Sponsor Information & Resources

Pharma XYZ
Funder Type: Industry
Contact: 1-800-555-5555
Other Sponsor Resources:
[Brochure 1](#) [Leaflet 1](#) [Pharma XYZ Information](#)

View Trial Details — Participation Tab

The Participation tab was designed to address patient feedback that details on what it might be like to participate in a trial are desired, but often missing, from publicly available clinical trial information resources.

OVERVIEW **PARTICIPATION** LOCATIONS RESOURCES TRIAL RESULTS

Potential Participation

Participating in a clinical trial contributes to medical knowledge. The results can make a difference in the care of future patients by providing information about the benefits and risks of therapeutic, preventative, or diagnostic products or interventions. During a clinical trial, doctors, nurses, social workers, and other health care providers might be part of your treatment team.

Below is an approximation of what a trial participant (volunteer) might expect while participating in the trial.

| | | | |
|--|--|---|---|
| Participation Duration  +/- 6 mos. | Number of Visits  +/- 15 | Off-site Requirements  None | Intervention  Oral Drug |
| Post Trial Treatment Post trial treatment will be available | Reimbursement Coverage for Services Yes Out of Pocket Expenses Yes | | |
| Site Services Transportation to and from the trial site can be made available | | | |
| Pay to Participate No | | | |
| Lay Summary Results Lay summary trial results will be provided to every trial participant (volunteer) upon completion of the trial | | | |

Visit by Visit



VISIT 1

VISIT
1/15

WEEK 1

VISIT DURATION


 6-8 Hours

DURING YOUR VISIT

| | |
|---|--|
|  Informed Consent to Participate |  Pregnancy Test |
|  Questionnaire |  CT-Scan |
|  Blood Sample | |

Similar to the Overview tab, at-a-glance information about trial participation is included at the top of the page. Descriptive icons for basic attributes are placed above a brief series of short fields (envisioned to include both structured and semi-structured fields) providing practical details about trial participation.

A Visit by Visit section displays an interactive timeline showing both the full scope of participation as well as individual visit details. Users may navigate to the details of each visit in the trial by clicking on each visit icon. In the proof of concept, the first visit is described in terms of approximate duration, lab tests to be expected, and additional activities expected of the participant including informed consent and a questionnaire.

The screenshot shows the 'LOCATIONS' tab of a trial details interface. At the top, there's a navigation bar with tabs: OVERVIEW, PARTICIPATION, LOCATIONS (which is selected), RESOURCES, and TRIAL RESULTS. Below the navigation bar is a map of the Mid-Atlantic region (Pennsylvania, New Jersey, Delaware, Maryland, Virginia, West Virginia, Ohio) with seven numbered blue circles indicating site locations. A legend identifies the numbers: 1 (Philadelphia), 2 (New Jersey), 3 (New York), 4 (Baltimore), 5 (Pittsburgh), 6 (Washington D.C.), and 7 (Newark). Below the map is a table with columns: LOCATION, DISTANCE, STATUS, and ACTIONS.

| LOCATION | DISTANCE | STATUS | ACTIONS |
|---|----------|----------------------|---------|
| 126 S 11th St Philadelphia, PA 19125 | 12 Mi | Seeking Participants | Contact |
| 1184 Riverside Dr Monroeville, NJ 08343 | 50 Mi | Seeking Participants | Contact |
| 8273 No Road St Polk Township, PA | 81 Mi | Not Yet Recruiting | Contact |
| S 1st St Bethel, PA 19507 | 81 Mi | Seeking Participants | Contact |
| 73 Main St Eldersburg, MD 21784 | 127 Mi | Seeking Participants | Contact |
| 953 Old Town Ln Washington, DC 20418 | 270 Mi | Not Yet Recruiting | Contact |
| 7417 John F. Kennedy Blvd North Bergen, NJ 07047 | 290 Mi | Not Yet Recruiting | Contact |

View Trial Details – Locations Tab

The Locations tab provides both visual and list-based representations of the various site locations involved in a particular trial, regardless of individual site status (seeking participants, not yet recruiting, etc.).

Using information obtained with permission from each site location, a pop-up via the “Contact” button will display the preferred method of contact for each site.

View Trial Details – Resources Tab

The Resources tab was created to address patients’ requests for additional connections to resources and communities relevant to their condition or diagnosis.

The tab could contain condition-specific resources with hyperlinks to external websites; a possible method of acquiring and maintaining suggested resources over time could be to partner with public or non-profit organizations who can support the curation of appropriate resources.

Allowing individual users to “rank” resources based on perceived value could be an additional feature of benefit to patients and would further encourage the “community-based” approach preferred by patients involved in proof of concept design.

The screenshot shows the 'RESOURCES' tab of a trial details interface. At the top, there's a navigation bar with tabs: OVERVIEW, PARTICIPATION, LOCATIONS, RESOURCES (which is selected), and TRIAL RESULTS. Below the navigation bar is a table with columns: NAME, TYPE, and LINK.

| NAME | TYPE | LINK |
|---------------|-----------------|--|
| Group XYZ | Advocacy Group | www.GroupXYZ.com |
| Group ABC | Advocacy Group | www.Group-ABC.com |
| Group 123 | Advocacy Group | www.Group_123.com |
| WebSource ABC | Informational | www.WebSourceABC.org |
| LMNOP Group | Patient Support | www.LMNOGroup.com |

View Trial Details — Trial Results Tab

The Trial Results tab was created to house trial results fields currently specified by most major clinical trial registries along with additional documentation (such as lay summary results) where available.

This screenshot shows the 'TRIAL RESULTS' tab selected in a navigation bar. Below the tabs, a message states: 'There are no results for this trial at this time.' It also notes that the sponsor has chosen to provide lay summary results to all participants upon completion of the trial, and that general trial results will be posted after trial completion. A button labeled 'NOTIFY ME' is present for receiving notifications when results become available.

As this proof of concept demonstrated a recruiting trial, no trial results would be available; however, statements indicating the expected availability of both general and lay summary trial results in the future would be appropriate. The ability for a user to be notified when trial results become available may be valuable for a variety of users, including patients, health care professionals, and researchers.

User Account

A personal user account is a key enabler of several features in the proof of concept (including bookmarks and alerts) and can more easily facilitate a patient's trial search.

Creating a user account would be optional and would not require anything more than an email and a password.

The option of supplying additional personal information could further customize the user's experience and prevent duplicate entry of information for each visit to the registry or each trial search. Categories of information envisioned in this proof of concept include general user preferences, standard search criteria, and details on medical condition.

The top screenshot displays the 'General Info' section of the account settings. It includes fields for Name (Optional), Email (JohnDoe@email.com), Phone (Optional), Password (..... (Change)), Language (English), Time Zone (Eastern Standard Time (EST)), Date / Time (DD/MM/YYYY), and Measurement (Imperial (Mi / ft / lb)). The bottom screenshot shows the 'Search Criteria' section, which includes fields for Age (Optional), Sex (Female, Male, Other), Location (Address Optional, City Optional, State Optional, Zip Optional), Radius (Select Miles, SET CRITERIA AS DEFAULT), and a link to '+ Add another location'.

Bookmarks and Alerts

Bookmarks and Alerts can be found in the User Account page. Both individual trials and individual searches (encompassing all desired criteria for a particular search) saved by the user for future reference would be managed from a single location.

Account Settings (UserJohnDoe)
Search within settings

About Me

- General
- Search Criteria
- Medical Condition

Bookmarks & Alerts

- Bookmarks
- Alerts

Bookmarks

| SEARCH NAME | DESCRIPTION | FILTERS | ACTIONS |
|----------------|---|--|---------|
| Colon Cancer1 | Search for Colon Cancer w/in 25 mi of my Philadelphia residence | Colon Cancer, Seeking Participants, 25mi, 19125, Male, 47..... | |
| My Search 6 | Search created for only completed trials with results | Trials Completed with Results, Colon Cancer | |
| 01/11/2018 | Trials Seeking Participants near 19103 location | Colorectal Cancer, Seeking Participants, 25mi, 19103, Male, 47..... | |
| Multi-Location | 19125 & 19103 (Colorectal Cancer) | Colorectal Cancer, Seeking Participants, 25mi, 19125, 19103, Male, 47..... | |

Trials

| TRIAL NAME | CONDITION | INTERVENTION | DISTANCE | COMMITMENT | STATUS | ACTIONS |
|---|---------------------------------|---------------|----------|-----------------------------|----------------------|---------|
| A study of Drug ABC in patients with advanced solid tumors | Colorectal Cancer, Colon Cancer | Drug ABC | 12 Mi | Months 6 +/- Visits 17 +/- | Seeking Participants | |
| A study of Drug 1RX in patients with advanced solid tumors | Colon Cancer | Drug 1RX | 13 Mi | Months 18 +/- Visits 38 +/- | Seeking Participants | |
| A study of Treatment 123 in patients with advanced solid tumors | Colorectal Cancer | Treatment 123 | 15 Mi | Months 5 +/- Visits 10 +/- | Seeking Participants | |

The user can fine tune their desired alerts on this page to choose the frequency and method (e-mail or SMS text), eliminating the need to frequently check back in the registry for new trials or changes to existing trials (such as recruiting status).

Account Settings (UserJohnDoe)
Search within settings

About Me

- General
- Search Criteria
- Medical Condition

Bookmarks & Alerts

- Bookmarks
- Alerts

Alerts

| SEARCH NAME | DESCRIPTION | TEXT | EMAIL | FREQUENCY | ACTIONS |
|-------------|---|-------------------------------------|-------------------------------------|--|---------|
| My Serach 1 | Showing 14 results - All trials have been looked at - waiting for new | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="button" value="New Results"/> | |
| 08/01/2017 | Using multi-location (Phila & FL) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="button" value="Frequency"/> | |
| FL V.Home | Search radius near vacation home in Florida | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="button" value="New Results"/> | |

Trials

| TRIAL NAME | TEXT | EMAIL | FREQUENCY | ACTIONS |
|--|--------------------------|-------------------------------------|---|---------|
| A study of Drug ABC in patients with advanced solid tumors | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="button" value="Results Posted"/> | |

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About Clinical Trials and Help Pages

The About Clinical Trials and Help pages may be accessed from any screen in the proof of concept.

About Clinical Trials is designed to quickly answer important questions commonly asked about clinical trials. Use of videos and imagery, in addition to text, helps the user more easily digest and engage with the information.

This wireframe illustrates the layout of the 'About Clinical Trials' page. At the top, there's a navigation bar with links for Home, About Clinical Trials, Advanced Search, For Researchers, Help, and various icons. Below the navigation is a large banner featuring a doctor in scrubs holding a stethoscope over a patient's arm. A video player interface is overlaid on the banner. To the left of the banner, the text 'ABOUT Clinical Trials' is displayed. Below the banner, there are several sections with links: 'What is a clinical trial?', 'Why clinical trials?', 'Who can participate?', 'How are you protected?', 'Who conducts the study?', 'What should I know before participation?', 'What should I expect during participation?', and 'Want to learn more?'. A detailed description of what a clinical trial is follows, along with a bulleted list of questions it aims to answer. At the bottom of this section, a note states: 'The development of a new medicine can take more than 10 years. Although know...'

Help is designed to assist the user with a variety of additional questions and resources related to clinical trials and clinical trial search through registries, including FAQs, a Glossary of Terms, an Education Library (interactive content), and Guides & Tutorials. Users also have the option of utilizing a search bar to ask specific questions which may be answered with content found on the platform.

This wireframe shows the 'Help' page. At the top, a search bar contains the placeholder 'Enter your question' with a magnifying glass icon. Below the search bar, the heading 'How can we help you?' is centered. Four cards are displayed below this heading, each representing a different resource: 'FAQs' (represented by a question mark icon), 'Glossary of Terms' (represented by a document icon), 'Education Library' (represented by a book icon), and 'Guides & Tutorials' (represented by a location pin icon). Each card has a brief description underneath it.

Beyond the Proof of Concept

In addition to the features and functions demonstrated in the proof of concept, other longer-term capabilities also deserve further exploration. Integration between clinical trial registries and electronic health records would provide an opportunity to link clinical research opportunities to points of care. Efforts to bridge this gap have already shown promising signs of success.

For example, using inclusion and exclusion criteria sourced from clinical trial protocols, IBM's Watson technology supported a 78% reduction in the time taken to screen 90 patients against three breast cancer protocols in a research center with Electronic Medical Records (EMRs)[11]. Continued progress in the space of automating evaluation of eligibility could break down a key barrier to research participation. The potential for registries to be connected to EHRs has shown early signs of being feasible [12], assuming the quality and structure of inclusion/exclusion data is improved. As the prevalence and sophistication of EHRs continues to grow, even patients in remote and rural locations may gain greater awareness and access to potential clinical trial opportunities.

WHO MUST PLAY A ROLE IN FUTURE IMPROVEMENTS?

Research has shown that as a source of information, online clinical trial registries maintained by governments are most trusted, more so than online patient communities or pharmaceutical company websites [13]. Prioritizing investments in government registries and/or the information housed in government registries, in contrast to private platforms, could encourage greater harmonization of clinical trial information transparency across the research community while also impacting downstream platforms which currently rely on public clinical trial registries as a data source.

Ultimately, the changes discussed in this proposal rely heavily on those who supply clinical trial information (trial sponsors or responsible parties) and those who host clinical trial information (public registries) to work together to improve the information landscape for the benefit of patients, caregivers, researchers, health care professionals, and others.

Encouragingly, changes are already underway in key areas – for example, the NLM has already released the first two phases of usability enhancements to ClinicalTrials.gov in June and September of 2017, including an updated home page, re-sizing display to fit multiple devices, and better navigation of search results, among other improvements [14, 15]. Forthcoming delivery of the new EU clinical trial portal and database is expected in 2019, and will provide clinical trial statistics, advanced search, and reporting [6]. Collaboration efforts between industry and government on related topics has also seen promising success; in May 2017 TransCelerate announced that it had collaborated with the U.S. Food & Drug Administration (FDA) and National Institutes of Health (NIH) to create a new, technology-enabled Common Protocol Template geared toward industry studies which aligns with the common protocol template developed by FDA and NIH for investigator-led studies [16].

Proposed Role of Trial Sponsors/Researchers

Trial sponsors and/or responsible parties have a fundamental role in providing high quality data to clinical trial registries. Recent legislation aimed at increasing transparency and guidance clarifying the expectations for compliance should naturally encourage sponsors to place greater emphasis on building processes which can flexibly deliver against changing clinical trial disclosure requirements.

However, taking action in response to regulation alone will not be sufficient. Evolving acceptance of the need to provide clinical trial information in formats accessible to a lay audience is a significant contributor to the goal of providing better information to patients and their caregivers. Additionally, guided by the evolving frameworks for data submission offered by public registries, trial sponsors should be prepared to respond to growing calls for transparency by non-government actors and increasing demand for information not traditionally found in clinical trial registries, such as the possibility of receiving a placebo during the trial, estimated time commitment, site visit details, and trial participation overviews.

Trial sponsors can consider several aims:

- » Identifying gaps in data submission practices within current registry infrastructures by undertaking a formal review of compliance practices for required fields and quality of data submitted for required fields
- » Exploring greater and more consistent utilization of optional fields which may benefit patients' understanding of clinical trials
- » Embracing a culture shift within transparency functions to focus on conveying meaningful information to patients in addition to compliant disclosure of data
- » Considering how clinical trial information may ultimately be consumed by the patient, caregiver, and HCP communities and documenting guidance accordingly on registry information authoring/ submission best practices
- » Proactively gathering patient and patient advocacy organization input on information format preferences, including leveraging existing frameworks developed in collaboration with patients
- » Collaborating across companies to deliver a consistent set of guidance on the above aims for voluntary adoption across industry

More extensive self-assessments on the part of clinical trial sponsors with respect to current registry data submission practices and quality may be the most appropriate first step. TransCelerate's own research (see "Methods") suggests that opportunities exist for sponsors to employ greater use of optional registry data fields for the benefit of patient audiences and to provide information in a format useful to lay audiences. Interestingly, even for sponsors who may not use existing public registries to their full potential, several have developed their own clinical trial portals accessible to the public with the intent of improving the usefulness of information to patients and the user experience.

Proposed Role of Public Registry Platforms/Government Entities (All Geographies)

Public registries also have a fundamental role, in hosting and structuring clinical trial data. Registries additionally play a role in accommodating evolving expectations of the types and formats of information offered to patients, ensuring the platforms are developed to support trial sponsors and other responsible parties in supplying this information. Registries across multiple geographies can consider several aims:

- » Enhancing user-friendliness of platforms to ensure their accessibility to the public, while approaching enhancements in an iterative fashion in partnership with patient groups
- » Enabling the provision of additional types of information useful to patient communities
- » Providing clear guidance to support consistent submission of data for key fields, including offering standardized text options to supplement free text
- » Offering structured data submission frameworks, particularly for fields which could have high-value downstream uses (e.g. machine-readable eligibility criteria)
- » Facilitating data submission processes and policies which encourage compliance and consistency across platforms in different geographies, accounting for common challenges and circumstances faced by trial sponsors
- » Publishing analytics on the usage of registry platforms, making available to researchers useful information that may help in designing

better trials, such as the types of trial searches conducted and in which locations, trial attributes (filter criteria) most important to patients, etc.

- » Enabling greater openness of registry platforms to other entities who may offer complementary services based on source data, allowing for solutions which may be integrated with additional aspects of the patient experience

Proposed Role of Standards-Setting Bodies & Health Information Technology Providers

These groups will be relied upon to provide a foundational infrastructure upon which new data submission and search capabilities may be made possible.

- » Method(s) to enable automated submissions from source data systems directly to registries and other appropriate destinations (author once and distribute)
- » Common standards for clinical trial data formats to ensure adaptability and compatibility between systems
- » Unified set of data requirements for submission of clinical trial information on public registries to eliminate varying requirements from different public registry owners, which may result in decreased data quality or inconsistent posting of trials
- » New solutions which encourage greater interoperability and portability of information

Great strides have already been made in this space. The WHO Trial Registration Data Set specifies the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered [17]. CDISC has developed the Clinical Trial Registry XML - Version 1.0 of the CTR-XML standard, a provisionally approved standard based on the CDISC Operational Data Model (ODM) for clinical trial registry submissions primarily to the World Health Organization (WHO), European Medicines Agency (EMA) EudraCT Registry, and United States ClinicalTrials.gov [18]. Working with organizations such as these on the development of standards can effectively drive efficiencies and trial sponsor compliance, while also laying the foundation for innovation as technologies can leverage common data structures.

As indicated in Figure 2, several stakeholder groups can come together to influence improvements in access and quality of clinical trial information, including patient groups whose input on the types, formats, and practical applications of information will be critical. The Clinical Trial Registry of the Future proof of concept may serve as a point of reference to provoke further conversation and collaboration between stakeholders on a roadmap for change.

Figure 2:
Proposed Collaboration among Clinical Trial Information Stakeholders



WHAT COULD A CHANGE ROADMAP LOOK LIKE?

Gaining alignment on the sequence of key improvement goals would allow for a methodical and aligned approach and ensure stakeholders who are key to implementation, including trial sponsors, are prepared to address the changes required to enable the future vision. TransCelerate has identified a potential roadmap consisting of three phases of objectives (Figure 3).

Short Term: Enhance Use of Existing Data Sets

Short term objectives can be achieved with existing clinical trial data sets disclosed in most

Figure 3:
Proposed Improvement Roadmap



public registries. Trial sponsors can first consider a self-evaluation of the quality of data currently submitted to registries, using various dimensions including data completeness, accuracy, timeliness, and applicability to a lay audience. In parallel, overall platform usability enhancements including changes based on user experience testing, a simplified or streamlined appearance,

and guided trial search navigation would improve overall accessibility of registry platforms to patients and other stakeholders.

Expanded search features such as allowing a variety of input types for location (similar in fashion to a Google location search), search results by a specified location radius, and global geographic mapping for clinical trial sites, would improve the search experience to a level on par with what is commonly available on websites in other consumer-oriented fields. Additional features such as a “trial comparison view” (allowing side-by-side comparison of trials similar to features found in consumer-focused websites) and more logically organized presentation of study records would improve comprehension of information. Finally, features which “meet patients where they are” might include multi-device display capability and the ability for end users to personalize their experience or to be sent alerts (of new trial opportunities or the availability of trial results) based on a user-created profile.

Medium Term: Explore More & Better Data/Information

Medium term objectives would require more significant changes to the types of data hosted on registries and thus, additional or transformed data provided by trial sponsors. These changes would also build upon and further enhance capabilities developed in the short term. New data fields valuable to trial consideration, such as details ordinarily found in sponsors’ schedule of assessments which provide transparency on the total number of visits, participation duration, and details of each site visit, should supplement existing fields. Where possible, additional data fields should be indexed and made more easily searchable by the user or machine readable by other platforms, such as eligibility criteria. Additional standard “tags” for study records could improve understanding of trial parameters, such as presence of a placebo versus usual care (standard of care) and availability of support services for the trial, as well as indicate sponsors’ commitment to transparency, such as a commitment to provide lay summary results at the closing of the trial.

Lay language considerations should continue to be prioritized and may require registries to provide specific, common guidance or template submission forms for key fields; this would help to ensure trial sponsors take a harmonized approach to authoring fields critical to study record comprehension (e.g. trial purpose).

Finally, registries should capitalize on opportunities to better educate the user base on clinical research. Broadly, this may include providing more interactive or visual educational resources about clinical trials (e.g. brief videos, infographics). More specifically, the use of “hover-over” capabilities to present brief definitions of terms throughout the platform and a central glossary of important clinical research terms, would keep the user informed throughout navigation without needing to consult external references to aid comprehension.

Long Term: Integrations with Health Care, Tech Platforms

Long term objectives may require significant alignment on standards across industry and investment in additional technologies. Greater linkages to point-of-care and EHR systems could enable greater discussion and consideration of options between patients and their health care professionals while also allowing for the patient to opt-in to automated clinical trial recommendations/referrals based on available patient data matched to trial eligibility criteria. The development of more automated mechanisms for data submission to public registries, including the ability to pull new data directly from specified sponsor information systems, could help to achieve real-time or near-real-time updates to multiple public registries at once.

WHAT IS THE CALL TO ACTION?

As summarized in this paper, many patient-focused improvement opportunities for clinical trial registries and associated information exist today. In addition to several key gaps identified by patients, the digitization of health information and the pervasiveness of computer technology in our lives put an increased importance on the quality and use of clinical trial registries. Though proposed improvements may involve significant effort and cross-stakeholder coordination, many short-term, “quick win” improvements are possible, some of which are already underway.

TransCelerate invites clinical trial sponsors and researchers, clinical trial registries, patient communities, advocacy organizations, health care organizations, technology vendors, standards bodies, government health authorities and regulators, and other stakeholders of the public to:

1 SUBMIT YOUR COMMENTS

Comment on the perspective and proposed roadmap offered in this paper:
<http://bit.ly/2yYMEym>

2 ENGAGE IN PUBLIC DIALOGUE

Discuss this topic during organized summits, conferences, webinars, etc. Advance thought leadership on next steps within collaborative settings that involve multiple stakeholders.

3 ADVOCATE FOR CHANGE

Ask your government representatives and national policy makers for patient-focused improvements to public clinical trial registries. Engage with health authorities to explore ways to enable change.

Together, we can make meaningful improvements to public clinical trial registries for the benefit of patients and for those who care for them.

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METHODS

TransCelerate sought patient input prior to the development of this perspective paper using two primary methods:

(1) Patient Advisory Board (PAB).

TransCelerate commissioned a PAB through the Center for Information & Study on Clinical Research Participation (CISCRP). Input from the PAB was sought during several in-person meetings and offline feedback collection spanning August 2016 – August 2017. Ten patients, patient advocates, or caregivers, aged 21 to 70 years, from the US (6), Canada (1), Europe (2), and Africa (1) participated in the PAB. Half of the participants had previous trial experience. Participants represented gastrointestinal, metabolic, neurologic, oncologic, and hematologic conditions. Several user experience feedback sessions and co-creation sessions were used to identify issues, unmet expectations, opportunities, and preferences with respect to clinical trial registry design and clinical trial information. See “Designing with patients, for patients” sidebar for more information.

(2) Global Patient Survey.

Discussions with the PAB were supported by a base understanding of information needs and preferences uncovered by a global survey commissioned by TransCelerate and conducted by CISCRP across a global sample of patients and caregivers. The 52-question survey was conducted in August-September of 2016 and distributed online globally to patients and caregivers with the support of CISCRP, Clarity, CenterWatch, and TransCelerate through outreach efforts within their patient/caregiver communities. There were 3,045 respondents who self-identified as patients (73.8%), caregivers (7.6%), or “other” (18.6%). Fifty-eight percent (1762/3045) of the respondents were 55 years of age or older. Participants represented 36 countries across North America, Latin/South America, Europe, Asia Pacific, and Africa. Four countries (US, Canada, Germany, and Australia) contributed more than 250 respondents each.

TransCelerate additionally conducted a survey to gather insight into current registry data reporting practices by trial sponsors:

(3) Trial Sponsor Survey.

TransCelerate distributed an online survey in August-September of 2016 to 18 multi-national biopharmaceutical companies within its membership organization. Thirteen companies (72%) responded. Companies submitted responses to a third-party consultant who blinded and aggregated the survey results. (shown on next page)

DISCLAIMER

The Clinical Trial Registry of the Future wireframe proof of concept illustrated in this proposal was designed by TransCelerate BioPharma for use in demonstrations to government authorities. The wireframe provides examples of how government-sponsored clinical trial registries could be organized and operated more effectively to enable patients to obtain much greater value from the registries. The wireframe is offered “as is,” and nothing in the wireframe is meant to provide a legal opinion or imply compliance with relevant laws and regulations.

ICONS

Several of the icons used in the Clinical Trial Registry of the Future wireframe proof of concept were obtained courtesy of the Universal Patient Language Graphic Assets Library found at www.upl.org.

Reference Table: Trial Sponsor Survey Results

| | | |
|--|-----------|---------------|
| Does your company have a specific SOP which outlines how and what clinical trial information is posted on registries? | | N = 13 |
| Yes | 13 (100%) | |
| No | 0 (0%) | |
| Which scope is covered by the SOP? (select all that apply) | | N = 13 |
| Which studies to post | 12 (92%) | |
| Specific fields to submit/post | 2 (15%) | |
| Formatting of information posted in fields | 0 (0%) | |
| Timing and/or frequency of updates | 10 (77%) | |
| Other | 4 (31%) | |
| Does the guidance in the SOP differ depending on registry? | | N = 13 |
| Yes – there are differences/different SOPs | 8 (62%) | |
| No – there are no differences | 5 (38%) | |
| For each interventional trial posted on ClinicalTrials.gov, does your company post: | | N = 13 |
| Only information elements required by FDAAA801* | 3 (23%) | |
| Information elements required by FDAAA801* and additional voluntary/optional information elements | 4 (31%) | |
| Both of the above, depending on the specific trial | 6 (46%) | |
| Is the information posted on ClinicalTrials.gov reviewed to ensure relevance/understanding to the lay person? | | N = 13 |
| Yes | 4 (31%) | |
| No | 9 (69%) | |
| Does your company have its own website for the general public to find details regarding clinical trials it is sponsoring? | | N = 13 |
| Yes | 8 (62%) | |
| No | 5 (38%) | |
| Please check all statements which apply to the purpose or general objectives of your company-specific website containing details of your sponsored clinical trials: | | N = 8 |
| Improved comprehension of trial information to a lay audience | 5 (63%) | |
| Improved trial search/navigation experience | 4 (50%) | |
| Resource to facilitate conversation between patients/caregivers and health care professional(s) | 3 (38%) | |
| Enrollment/ease of referrals | 3 (38%) | |
| Other | 1 (13%) | |

* Survey was administered prior to the release of the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), which clarifies and expands the requirements in FDAAA 801.

Submission No.: 194

Date: 3/13/2020

Name: Ravi Thadhani

Name of Organization: Partners HealthCare

Attachment: CT.gov Modernization RFI Response-RTsigned.pdf



FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL
AND MASSACHUSETTS GENERAL HOSPITAL

March 10, 2020

ClinicalTrials.gov Information Team
National Library of Medicine

RE: Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003)

To Whom It May Concern:

I am writing on behalf of Partners HealthCare, a not-for-profit healthcare system committed to patient care, research, teaching, and service to the local community. Our hospitals, most notably Brigham and Women's Hospital, Massachusetts General Hospital, McLean Hospital, Spaulding Rehabilitation Network and Massachusetts Eye and Ear Infirmary receive substantial federal funding and have over 2,900 records on ClinicalTrials.gov. We appreciate the National Library of Medicine initiating a Request for Information for the ClinicalTrials.gov modernization initiative and planning for infrastructure enhancements.

We wholeheartedly agree that the public should have easy access to useful information regarding available clinical trials and results from closed trials. We also agree it is important that the research community is held accountable to conduct and report research in a transparent manner. However, the detailed, technical data required for registration and results reporting to meet regulatory obligations seems somewhat at odds with the needs of the public. This is especially the case as the regulatory requirements have evolved over time.

In addition, the way institutions facilitate registration and results reporting and oversee compliance within their own institution is variable. Similar to how large pharmaceutical companies manage the registration and results reporting process, some institutions have chosen to implement a centralized process providing significant support to researchers and providing dedicated staff to register studies and enter results on behalf of the Principal Investigator/Responsible Party. Other institutions have elected to take a decentralized approach offering some support to investigators but require the Principal Investigator/Responsible Party to register and post results themselves. Although these two approaches are both acceptable, it seems that the Clinical Trials.gov PRS website and functionality favors those institutions that have created the infrastructure to manage this centrally. The website functionality should facilitate both centralized and decentralized approaches equally.

Below please find our suggestions related to the public website, information submission and data standards.

Ravi I. Thadhani, M.D., MPH
Chief Academic Officer, Partners HealthCare | Professor of Medicine, Harvard Medical School
Dean for Academic Programs at Partners HealthCare, Harvard Medical School

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Tel: 617 278-1140, Email: rthadhani@partners.org

Public Website

- To improve transparency for the public, there should be information on the public ClinicalTrials.gov website regarding the various types of research studies posted on ClinicalTrials.gov and reasons/requirements for posting.
- When reading a public registration, having a list of other suggested studies that may be of interest to the users based off discreet values often chosen by the end user - e.g. Frequent tags, enrollment status, specific diseases and conditions, location etc., would be extremely helpful.
- Some information investigators and sponsors are required to submit is very technical and complex for the general public to understand especially in reporting results. If the goal of ClinicalTrials.gov is to provide the public with information regarding available clinical trials and results of those studies, we recommend that ClinicalTrials.gov consider requiring a plain language summary of results on the public site instead of the current format for results reporting.
 - This would be consistent with requirements for protocol documents such as informed consents, advertisements, and other study participant facing documents that must be written using plain language and at an eighth-grade reading level.
 - Consider having the plain language summary for the study results available as a default and if users wanted more technical, scientific information then provide the link to a publication or results already provided to the FDA, NIH, or other funding agency. This would reduce the number of times investigators are required to report the same information.
 - A potential benefit of providing a plain language summary of results and a link to a publication/report to funding agency may be increased compliance with results reporting.
 - Investigators have expressed concern about being required to report such detailed results on ClinicalTrials.gov related to possibly violating embargo policies of scientific journals. The plain language summary on the public site would allow investigators to meet the requirements of the law to report results but would not likely violate embargo policies of journals.

Information Submission

- Enhance template to accommodate different types of research studies and include additional relevant information.
 - Especially important since ICMJE journals are more frequently refusing to publish if a study is not registered even if registration is not required per regulations.
 - Current template is designed for traditional clinical trials but many of the studies posted do not meet the typical format of an industry-sponsored randomized, controlled clinical trial.
 - With the new requirement to post basic science protocols soon to go into effect, it will be necessary for the template to be more flexible.
 - Include additional options for Study Type field that more accurately identify the type of study: pilot, feasibility, registry, repository, etc.
 - Add field to identify study as Principal Investigator Initiated.
 - Add field to indicate study involves a non-significant risk device.
- When adding new users to the Access List on a record, allow the user to type in a name or user name instead of having to look through a long list of users to find the person to add.
 - This should also be an option when changing record owners.

- Since many Principal Investigators of PI-initiated studies that involve an IND or IDE do not plan to submit to the FDA for a new indication, mode of administration, or licensing, we recommend the addition of a data field to indicate this. There is a significant difference between FDA regulated research that will involve submitting to the FDA for licensing or new indication and/or mode of administration and those PI-initiated studies that simply require an IND or IDE for the research study to take place.
 - This misleads the public into thinking that all clinical research studies posted on ClinicalTrials.gov involving an IND or IDE are created equally which is simply not the case.
- Increase permissions for individuals on the Access List for a record to include some functions currently restricted to the Responsible Party. Just as in a clinical research study where the PI can delegate certain responsibilities, the Responsible Party should be able to delegate some responsibilities related to a ClinicalTrials.gov record. Example: releasing a record.
- Include a Comments section within a record (not to be made public) that allows the Responsible Party to communicate with PRS reviewers within the record to provide relevant information for the reviewers to consider for which there is no appropriate data field available.
- Create a process for questions to be submitted to the ClinicalTrials.gov PRS reviewers directly from within the record and for the ClinicalTrials.gov PRS reviewers to respond directly to questions within a record. This would facilitate and streamline communication between researchers and the ClinicalTrials.gov reviewers (not to be made public).
 - This could also be used to submit Extension Requests.
- Embed PRS Comments and flags within record so users can see comments next to the field that requires updating so users do not need to navigate between multiple windows while responding to comments or addressing errors.
- Enhance functionality to allow the use of End Note or other citation organizer so users can easily add citations to a record.
- Instead of leaving a record flagged as “late per FDAAA” until results have been accepted by ClinicalTrials.gov reviewers, create a new flag for records that have had results submitted but the record is under review and/or there are comments/issues to be resolved such as “Results submitted – review and approval pending”.
- Allow organization PRS Administrators to identify two main contacts for the organization rather than ClinicalTrials.gov providing researchers a list of all individuals with administrator access for the organization. Consequently, researchers often end up sending an email to the entire group or to individuals who are not responsible for creating accounts. This can result in a delay in addressing the researcher’s question or lead to two people working on the issue simultaneously.
- Include data field clarification/definitions within the template that allow users to hover over a data field or click on a question mark next to the data field rather than requiring users to go to the Definitions hyperlink.
- Create a flag or record type for cases where an investigator voluntarily registers a study on ClinicalTrials.gov that does not meet the regulatory requirements for registration and results reporting. Investigators are doing this more frequently to avoid problems with publishing.
- Although the Planning Report includes information regarding the records that meet the FDAAA ACT or NIH clinical trial criteria, this is not flagged on the record in the PRS system for researchers and researchers who do not have administrative access.
 - It would be ideal to include a flag for a study that will meet the requirement to upload an informed consent.

- It may improve compliance if researchers could readily see a FDAAA or NIH flag on records that have reporting requirements for these regulatory groups. We have research teams with over 20 records and when they download a spreadsheet with all their records listed these additional flags would be helpful to them.
 - Make Planning Reports available to users other than those with Admin access. For example, we have an investigator who is listed as the Responsible Party on more than 20 records so having access to a Planning Report available for records associated with a specific Responsible Party or user would be helpful and facilitate compliance.
 - Another option would be to merge the Planning Report with the usual view in the RRS system since each view includes helpful information but, in some cases, not the same information.
 - Planning Report does not list “Problems” as identified on the and the normal view does not include the FDAAA column
 - Alternatively, allow the user to navigate within the record to their planning report.
- Terms and conditions in certain K awards from the NIH prohibit use of the funds for “clinical trials”. Recipients of these awards are concerned that if they register their study on ClinicalTrials.gov in order to publish that the NIH will assume the study was a clinical trial even though the study did not meet the criteria for a clinical trial as outlined by the NIH. There should be an option for identifying a record as not meeting the definition of a clinical trial but it was posted for informational and publishing purposes only.
- Streamline the process as much as possible for ease of navigation, such as minimizing the number of clicks necessary to move within a record.
- Our experience is that researchers are more than willing to comply with the requirement to register and report results but the inflexibility of the ClinicalTrials.gov template, confusion related to the various requirements, differences in requirements between FDA, NIH, ICMJE, WHO, etc., and rigid timelines create problems for investigators. Efforts on the part of ClinicalTrials.gov to incentivize or recognize researchers for compliance may not be fully appreciated by organizations and researchers if these impediments to achieving compliance are not addressed.
 - To reduce confusion and increase compliance the National Library of Medicine should encourage harmonization of the requirements of FDA, NIH, CMS, ICMJE, and WHO.

Data Standards

- A potential collaboration between Societies/Associations and ClinicalTrials.gov would allow for real time integration of discreet values defined by associations to better quantify data on a meta scale. There currently exists a mutual agreement between ICMJE and Public registries, using this as a platform for further development, allow for Medical Associations and Societies to tailor input parameters so that values can be more specific, accommodate the specific diseases being studied better, and allow for ClinicalTrials.gov to have a larger database of quantifiable data per field.

Sincerely,



Ravi I. Thadhani, M.D., M.P.H.

Submission No.: 195

Date: 3/13/2020

Name: Sarah White

Name of Organization: Brigham and Women's Hospital

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Investigators and PRS administrators identify difficulty with accurately reflecting specific protocol designs in registration and results reporting modules. Specific study designs include:
 - a. Master protocols: The study design of master protocols involves multiple interventions that may be initiated and completed at different time intervals. Over the course of the trial, interventions may be added. The master protocol recruitment status of the study remains open to accommodate active interventions, while other interventions arms are completed/closed, leading to difficulty in determining when results reporting is due. Additional guidance, in the form of example studies and/or short explanatory videos are needed regarding how to accurately reflect both registration and results reporting of the master protocol and interventions under the master protocol.
 - b. Social behavioral research: The study design of social behavior research routinely involves qualitative outcome measures including those that extract information from narratives and/or qualitative evaluation of behavioral interventions used to develop programs affecting health outcomes. Additionally, social behavioral studies can utilize multiple assessment tools to identify a single clinical diagnosis. There are instances where allowing for multiple tools to be grouped together for a single clinical outcome are helpful as behavioral diagnoses (or the severity of the disease) are often a compilation of a battery of examinations. Similar to master protocols, guidance is needed regarding how to accurately register and report results.

The CTRRR Taskforce recognizes that there may be additional study designs that Investigators struggle to submit in the PRS database. Further, innovative techniques within complex study designs (e.g. pooling placebos, step-wedge design) are currently difficult to reflect in the current PRS system, as are registering and reporting outcome measures with multiple time points. This is not only a burden to the individual submitting the study to the PRS database but leads to a lack of transparency in the public ClinicalTrials.gov website. ClinicalTrials.gov has previously published a number of Example Studies for Results Data Entry and we note that Investigators and PRS Administrators find these to be helpful tools. Short, just-in-time videos are also useful to those submitting registration and reporting results. We encourage NLM to work with experts in study design and those Investigators in the field using innovative study designs to identify and develop guidance/best practices on both registration and reporting results of innovative study design.

2. We request that ClinicalTrials.gov extend the Glossary function currently available on the public ClinicalTrials.gov site to the PRS database. The public site's Glossary is accessed by clicking an

information “i” link next to each data element. Clicking this link opens a pane on the right which contains only the definition for that data element. Links are provided so the user can easily access a complete set of definitions, if desired.

In the PRS database, there is a Definitions link at the top of each page, but it becomes invisible when the user scrolls down the page and is not near the data elements on the page. The Data Element Definitions documents are a great resource, but they are long and dense, and have a regulatory document look to them. It is helpful that clicking the Definitions link takes the user to the beginning of the part of the definitions page that corresponds to the section and module currently being edited, but the definition being sought is often quite a bit further down the document, often not visible until the user scrolls down the page.

Having a function similar to the public site Glossary, or a “What’s this?” link by each data element would improve the ease, speed, and quality of information entry because it is more likely that the user can quickly get to the needed information.

3. Change the font color for on-page short definitions to a color easier to see. These short definitions are one of the best features currently in place to enhance the ease, speed and quality of entry. As PRS administrators who routinely work with researchers, we point to these definitions and the users report not having seen them. The blue font color, being similar to the background color, is easily missed by the user’s eye.

4. Allow upload of graphs (e.g., JPEGs) to accompany data tables. While the CTRRR Taskforce appreciates that the structured database of ClinicalTrials.gov requires outcome measures to specify unique timepoints, there are some outcome measures (e.g. survival curves) in which presenting information in a visual way, would enhance the understandability of the results. These could be uploaded (in the PRS) and accessed (on the public website) by clicking a link next to the data table. We note that a similar function is available in the EU Clinical Trial Register.

5. Add a feature to copy statistical analyses, similar to the way outcome measures can currently be copied. More specifically, if there are multiple analyses done with the same type of statistical analysis, the ability to ‘copy’ in the same manner as the outcome measures would retain the statistical analysis information and text about power calculation, etc. Currently, the submitter has to add/enter each statistical analysis separately, which can be burdensome.

6. The CTRRR Taskforce appreciates the utility of the Planning Report. Taskforce members utilize their organization’s planning report on a regular basis to conduct both proactive communication and compliance outreach with Investigators and study teams. We suggest the following improvements to the functionality of the Planning Report:

a. Add the following elements under the ‘Show/Hide Columns’ in order to allow this information to be included in the Planning Report:

1. A ‘Select All’ element (rather than having to select all 38 options);
2. ‘Other funders’ and ‘Collaborators’ (in order to identify if the record is likely to require results reporting per non-statutory requirements);

3. ‘Access list’ (to easily identify all individuals with responsibility to enter information to the record);
4. The corresponding answer to ‘anticipated/actual’ option associated with the study start date;
5. Record owner email address (PRS administrators report it is currently a multi-step process to obtain the individual’s emails address from only the record owner name, especially if the full name of the individual is not used as the record owner name);
6. ‘Problems’ associated with the record (to easily identify and categorize the communication/intervention needed with the Investigator and study team).
 - b. Under the Custom Filter, allow the user to define date ranges upon which to generate the Planning Report.
 - c. Standardize the date format. The dates for “Results Expected”, “All Results Expected”, “Study Start Date”, “Primary Completion Date” and, “Study Completion Date” are a mix of MMM-YY (e.g., Jan 21) and MM/D/YYYY (e.g., 1/1/2021). This causes problems trying to analyze data.
 - d. Maintain consistent placement of the button for “All records” on the Planning Report with other screens. On the Planning Report screen “Action Expected” is the tab on the left and “All records” to the right. On the Home screen “All Records” is the tab on the left and “Problem Records” to the right. This results in PRS Administrators often downloading a report for only “Action Expected” at first and then having to go back and download the complete planning report for “All records.” See screen shot below.
7. We find the Spelling feature very helpful, but this has to be accessed separately from the Record Summary page. Overlay a spell check tool within the Registration and Results Reporting modules in order to detect potential spelling mistakes and unexpanded acronyms in real-time.
8. The CTRRR Taskforce requests that NLM consider adding a revision tracking feature within the PRS that enables Investigators and PRS Administrators to see what revisions were made as a result of ClinicalTrials.gov QC comments. Currently, anyone reviewing the revised document prior to release to ClinicalTrials.gov has to compare word for word to verify adequate changes have been made. It is only in the ‘Approve Stage’ that the submitter can see the revisions. For example, if a study team makes a modification to the inclusion criteria for a study, it would be helpful to see where the changes were made. This is especially important when verifying against a research protocol that has been updated. In addition, we request that NLM enable hyperlinking within the QC comments to link directly to data element that received the comment.
9. We suggest developing a function to flag studies that are late to report results and add “Results expected date” for NIH funded studies to the PRS database. This may be possible via interfacing with NIH Reporter as is already done in the secondary ID field.
10. Map data elements in the Protocol Section of the ClinicalTrials.gov record to the NIH/FDA e-protocol writing tool and protocol templates. While ClinicalTrials.gov Data Element Definitions clearly describe what information is expected for a given element, Investigators and study teams report that interpreting that definition and locating the corresponding information in a protocol document is a challenge. Inclusion of a feature in the PRS database registration module to display the sections in the NIH/FDA protocol template where the information is most likely to be found would reduce entry burden

by assisting in interpretation of the data element meaning, and indicating where the information to populate the data element may be found in the protocol source document. Ideally, such a feature could be displayed as links near the data elements, with pop-up window or pane that display that element, with the likely sources within the NIH/FDA protocol templates. Helping users correctly interpret and identify the correct information for a data element would improve the quality of the submitted information.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

The CTRRR Taskforce suggests creating additional automatic prompts to ensure accurate data entry into the PRS database during submission. We note that the NIH Manuscript Submission (NIHMS) system (<https://www.nihms.nih.gov/login/?next=/submission/>) was recently modernized and offers contextual and just-in-time help throughout the submission process. Similar functionality could be introduced to the PRS database. Another specific example includes a prompt to review data after entering results information and during the saving process of an outcome measure. A checklist that prompts the submitter regarding necessary elements of the outcome measure title, description, time frame, unit of measure listed, etc. could be displayed as a prompt to double-check entered information.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

1. ClinicalTrials.gov QC Reviewers encounter many errors during their review of the Registration and Results Reporting modules. We suggest that the most common QC comment scenarios be addressed by ClinicalTrials.gov staff by compiling a set of best practices and solutions to the common problems. These materials can be posted to the website.
2. The Brief Summary located in the Study Description section of the Registration module should be, as stated in the ClinicalTrials.gov Data Element Definitions, “written in a language intended for the lay public.” Despite this intention, brief summaries are often longer and more technical than the average person can understand. We suggest NLM work with experts in the field to develop guidance and tools to assist submitters in developing a brief summary that clearly communicates the purpose of the research.

Attachment: 2020-03-13 CTRRR Taskforce CTgov Moderization RFI_draft comments.pdf

Letter submitted electronically to NLM

March 12, 2020

ClinicalTrials.gov Information Team

National Library of Medicine

Submitted electronically at: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Re: Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003)

Dear ClinicalTrials.gov Information Team,

The Clinical Trials Registration and Results Reporting (CTR) Taskforce appreciates the opportunity to comment on the National Library of Medicine ClinicalTrials.gov Modernization Request for Information (RFI), released December 30, 2019.

The Clinical Trials Registration and Results Reporting (CTR) Taskforce is a national consortium of members of academic medical centers, universities, hospitals, and non-profit organizations focused on the implementation of domestic clinical trials registration and results reporting requirements in the ClinicalTrials.gov public repository. The objectives of the group are to identify best practices, develop solutions and tools for regulatory support and investigators, and serve as a communication forum. Members from over 200 academic organizations join monthly CTRR Taskforce teleconferences. Our members have extensive experience in the ClinicalTrials.gov Protocol Registration System (PRS) and are generally serving their organization in positions to manage the local organizational account and assist Investigators and study teams in submitting registration and results data.

Outlined below are comments responsive to the NLM's request for input focused on **Information Submission** and reflect suggestions to improve the quality, accuracy, and timeliness of information submitted through the ClinicalTrials.gov PRS database.

NLM Requested topic area: Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Investigators and PRS administrators identify difficulty with accurately reflecting **specific protocol designs** in registration and results reporting modules. Specific study designs include:
 - a. **Master protocols:** The study design of master protocols involves multiple interventions that may be initiated and completed at different time intervals. Over the course of the trial, interventions may be added. The master protocol recruitment status of the study remains open to accommodate active interventions, while other interventions arms are completed/closed, leading to difficulty in determining when results reporting is due. Additional guidance, in the form of example studies and/or short explanatory videos are needed regarding how to accurately reflect both registration and results reporting of the master protocol and interventions under the master protocol.
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 6. ‘Problems’ associated with the record (to easily identify and categorize the communication/intervention needed with the Investigator and study team).
 - b. Under the Custom Filter, allow the user to define date ranges upon which to generate the Planning Report.
 - c. Standardize the date format. The dates for “Results Expected”, “All Results Expected”, “Study Start Date”, “Primary Completion Date” and, “Study Completion Date” are a mix of MMM-YY (e.g., Jan 21) and MM/D/YYYY (e.g., 1/1/2021). This causes problems trying to analyze data.
 - d. Maintain consistent placement of the button for “All records” on the Planning Report with other screens. On the Planning Report screen “Action Expected” is the tab on the left and “All records” to the right. On the Home screen “All Records” is the tab on the left and “Problem Records” to the right. This results in PRS Administrators often downloading a report for only “Action Expected” at first and then having to go back and download the complete planning report for “All records.” See screen shot below.

The screenshot shows the ClinicalTrials.gov PRS interface. At the top, there's a navigation bar with links for 'Contact ClinicalTrials.gov PRS', 'Org: SKCCC', 'Admin: AKeyes', and 'Logout'. Below this is a 'Quick Links' section with 'New Record', 'Admin Quick Reference', and 'Problem Resolution Guide'. To the right are 'Records ▾', 'Accounts ▾', and 'Help ▾'. An email address 'akeyes1@jhmi.edu' with an 'Update' link is also present. A 'Help us improve: PRS Survey' link is at the bottom right. The main area shows a 'Record List' with buttons for 'All Records (486)', 'Problem Records (18)', and 'Custom Filter'. Below this, it says 'Showing: 1-10 of 486 records'. A 'Planning Report' section follows, with a 'Tip' about planning record updates and a 'Home' link. At the bottom, there's another set of buttons for 'Action Expected (183)', 'All Records (486)', and 'Custom Filter'.

7. We find the **Spelling** feature very helpful, but this has to be accessed separately from the Record Summary page. Overlay a spell check tool within the Registration and Results Reporting modules in order to detect potential spelling mistakes and unexpanded acronyms in real-time.
8. The CTRRR Taskforce requests that NLM consider adding a **revision tracking feature** within the PRS that enables Investigators and PRS Administrators to see what revisions were made as a result of ClinicalTrials.gov QC comments. Currently, anyone reviewing the revised document prior to release to ClinicalTrials.gov has to compare word for word to verify adequate changes have been made. It is only in the 'Approve Stage' that the submitter can see the revisions. For example, if a study team makes a modification to the inclusion criteria for a study, it would be helpful to see where the changes were made. This is especially important when verifying against a research protocol that has been updated. In addition, we request that NLM enable hyperlinking within the QC comments to link directly to data element that received the comment.
9. We suggest developing a function to **flag studies that are late to report results** and add "Results expected date" for NIH funded studies to the PRS database. This may be possible via interfacing with NIH Reporter as is already done in the secondary ID field.
10. **Map data elements** in the Protocol Section of the ClinicalTrials.gov record to the NIH/FDA e-protocol writing tool and protocol templates. While ClinicalTrials.gov Data Element Definitions clearly describe what information is expected for a given element, Investigators and study teams report that interpreting that definition and locating the corresponding information in a protocol document is a challenge. Inclusion of a feature in the PRS database registration module to display the sections in the NIH/FDA protocol template where the information is most likely to be found would reduce entry burden by assisting in interpretation of the data element meaning, and indicating where the information to populate the data element may be found in the protocol source document. Ideally, such a feature could be displayed as links near the data elements, with pop-up window or pane that display that element, with the likely sources within the NIH/FDA protocol templates. Helping users correctly interpret and identify the correct information for a data element would improve the quality of the submitted information.

NLM Requested topic area: Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

The CTRRR Taskforce suggests creating **additional automatic prompts to ensure accurate data entry** into the PRS database during submission. We note that the NIH Manuscript Submission (NIHMS) system (<https://www.nihms.nih.gov/login/?next=/submission/>) was recently modernized and offers contextual and just-in-time help throughout the submission process. Similar functionality could be introduced to the PRS database. Another specific example includes a prompt to review data after entering results information and during the saving process of an outcome measure. A checklist that prompts the submitter regarding necessary elements of the outcome measure title, description, time frame, unit of measure listed, etc. could be displayed as a prompt to double-check entered information.

NLM Requested topic area: Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

1. ClinicalTrials.gov QC Reviewers encounter many errors during their review of the Registration and Results Reporting modules. We suggest that the most **common QC comment scenarios** be addressed by ClinicalTrials.gov staff by compiling a set of best practices and solutions to the common problems. These materials can be posted to the website.
2. The **Brief Summary** located in the Study Description section of the Registration module should be, as stated in the ClinicalTrials.gov Data Element Definitions, “written in a language intended for the lay public.” Despite this intention, brief summaries are often longer and more technical than the average person can understand. We suggest NLM work with experts in the field to develop guidance and tools to assist submitters in developing a brief summary that clearly communicates the purpose of the research.

Thank you again for the opportunity to comment on this important issue. The CTRRR Taskforce believes that the NLM is in a unique position to update and enhance the user-experience for those submitting information via the PRS database and using/viewing information on the public ClinicalTrials.gov database. We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact Sarah White (sawhite@bwh.harvard.edu) or Anthony Keyes (akeyes1@jhmi.edu)

Respectfully submitted,

The RFI Subcommittee of the CTRRR Taskforce

Sarah A White, Brigham and Women’s Hospital
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Scott Patton, Stanford University
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Research Compliance and Integrity, UC San Diego
Tyrone Quarterman, Perelman School of Medicine
Jessica Shore, Loyola University Chicago

Submission No.: 196

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

1. It would be beneficial to have a more effective way to inform investigators of non compliant records, reminders of problem records immediately when they log into the PRS.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. Users have a hard time knowing where to put explanations about enrollment numbers, possible discrepancies. While there is space to offer explanations in population analysis description, it is not clear that one can utilize that space for that reason.

2. To ensure that scale information is indicated in outcome measure description, perhaps a section where user can indicate what specifically is being assessed and if a scale is being used, they can choose that specific assessment which would then prompt them to define the scale. Or pre-populated scales that are often times used could be built into the PRS.

3. Results are due 12 months after completion dates, however, if they are submitted on the day they are due, the following day, the study is flagged for having late results. If the results are expected to have all comments addressed and accepted by the deadline that should be reiterated in the PRS. Our workflow involves communication to inform users that results should be accepted by the deadline and to submit prior, but the "Results Expected By" date can lead users to think they are in the clear with FDAAA as long as they submit by that date.

4. It would be beneficial for studies that are federally funded to have results deadlines indicated. And notifications when they are late.

Submission No.: 197

Date: 3/13/2020

Name: Maathuri

Name of Organization: The Hospital for Sick Children

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

1) Patient and Family accessibility and user-friendly information and search functions for the public, patients and families. See the following examples <https://www.cff.org/Trials/Finder>

<https://clinicaltrials.bayer.com/>

<https://standuptocancer.org/for-patients-and-caregivers/clinical-trials/>

2) A separate decision pathway for registration of clinical trials that are not FDA regulated that meets the requirements for registration but does not require the more stringent FDA rules and information input. The users of this site are international, and the site should reflect this in the functionality.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Linking to and ability to upload publications and study specific data in lieu of the current requirements for posting results using the ct.gov tables

Posting of videos for patient and family knowledge and results

Having option to post the study website if available

Lay language results for knowledge translation to public, patients and families

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

1. Our Research Institute uses clinicaltrials.gov to register their clinical trials as required for publication. Very few of our trials fall within the purview of FDA regulations so the current set up and site requirements (e.g. the time-consuming requirements for posting results) are above and beyond the needs for registration. Once published, researchers consider their trial complete and finished; and as there isn't an option to just upload the publication in the results section, adding in the additional and labour-intensive step of completing separate clinicaltrial.gov results tables is not a priority. Thus, many of our researchers do not upload results and do not close their ct.gov record.

2. More and more, researchers are encouraged to provide study results to participants and the general public, if there was one place that provided easy results posting that would cover their requirements to

the participants/public and satisfy the requirements of clinicaltrials.gov with minimal struggle on their part, they may be more inclined to post results.

3. Error messages are hard to find or the instructions to fix the error are unclear.
 4. The requirements for updating a study every 6 months is too frequent and onerous once the study is recruiting. Please consider changing this requirement to an annual update (once per year)
- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Our use of clinicaltrials.gov is a wide range of studies, primarily paediatric.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Posting of results!! This process needs to be more user friendly and allow for the upload of publications and study data in the format relevant to the trial rather than in the current tables required. The majority of our institution's 'Problem Records' are due to the time-consuming requirements for posting results and these studies will likely never get closed in the system.

- 2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**

Although our institution may not be ready yet to align our current systems and processes, this is a fantastic idea for implementation to align with other electronic systems.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

Public, Patient and Family Centered Content- if the information required for input is in a more user-friendly format it will transition to content that will be useful on the public facing site.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

- For the initial submission the current information is sufficient.
- Previously the help/question function was very quick and helpful, more recently however, it has been our experience that this response time has increased to weeks.
- The new results PDF guide is helpful to navigate the current process, however the process for posting results needs to be streamlined and improved to facilitate closing a study (as described above).

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

If registering the trial also produced a more patient centric outward facing tool that would be educational and serve as a recruitment tool, teams would be more likely to make more effort in the content that is posted.

Make posting resulting easier and in a public, patient and family centered format that allows researchers to share their results with all stakeholders.

Having automated reminder emails sent to record owners to remind them to update/release their study record with clear instructions to ensure the required information is entered in a timely manner.

Institutional recognition on the public site for those who have posted results and/or maintained complete records – a twitter like feed of results and advertising publications?

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Rather than focus on strict standards for this terminology, could this be more ‘plain’ (lay) language or focus on the public facing site recognizing that the public, patient and families are also looking at this information? We support less complicated standards vs more complicated.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

For the scientific community, allow for upload of publications in lieu of separate reporting tables. Allow for a lay (or plain language) summary of reports for the public, patient and families.

Submission No.: 198

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

No comment.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Providing linkage between the public ClinicalTrials.gov (CT.gov) records and bibliometrics, altmetrics (non-traditional bibliometrics such as social media shares, mainstream media mentions, public policy documents, patents), and/or citation databases would facilitate research, highlight research collaborations, demonstrate the public/online reach of the trial, and potentially incentivize investigators to register, link PMIDs, and report summary results to CT.gov.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

At present, our team accesses the public site primarily to find examples of outcome measures and results reporting strategies for particular study or intervention types. As such, we search specific keywords within records with results posted as of 2017.

Specifically, we look to other public records to see how:

- certain imaging studies are registered
- certain qualitative measures are described and reported
- certain surveys that include multiple assessment types or sub-measures are reported

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

No comment.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

We have identified a number of potential PRS process improvements. Many of these improvements are related to NIH, ICMJE, and Revised Common Rule requirements, expanding the notifications beyond FDAAA Law and transforming the PRS into an all-inclusive user interface.

We recommend expanding the current source data for FDAAA results reporting requirements to include those that are registered in compliance with NIH Policy. This would enable us to use the planning report to keep track of non-ACT results due per NIH Policy.

Further, we suggest that when an NIH grant number is populated in the ‘Secondary ID’ field that CT.gov system sources data from public NIH system to determine whether or not it is a ‘clinical trial’ and subject to the NIH Policy for results reporting.

Per ICMJE guidance, a warning message that indicates a missing “Yes” or “No” response in the IPD section would be useful, as well as and the removal of the “Undecided” option.

We recommend a notification for ‘Consent Form Due’ for those trials that meet the Revised Common Rule requirement. Those trials that meet this requirement can be identified via the funding source / collaborator as per the NIH funded studies, or it might be useful to collect data in the Oversight Section at registration that documents the reason the registration record was created.

Additional data collected in the Oversight Section could be checkboxes that say ‘meets NIH Policy requirements’, ‘per ICMJE’, ‘per CMS’, ‘per FDAAA’, ‘meets Revised Common Rule requirements’. It would be beneficial to understand this when assisting study teams to ensure that they remain compliant, but it could also be used as source data for triggering various notifications that may be unique to that particular record, i.e. upload Consent Form, IPD Sharing Statement.

We recommend the records with ‘Problems’ be sortable into subcategories, as not all ‘problem’ records are non-compliant. It would be advantageous to easily sort and identify Late Results Records from records with Maintenance issues from records that have not been assigned NCT numbers by filtering them from the ‘Problems’ column. For reference, we keep track (on a monthly basis) of the number of late results, number of records with maintenance non-compliance, number of records that haven’t been released yet for NCT number assignment, and the number of records for which the results module is open but not yet due.

For clarity sake, is it reasonable or applicable to indicate in the Record Status section that ‘Results Due to the Public No Later Than XX/XX/YYYY’ in the Results Expected field? If results are submitted by the results expected date, but not made public for 25 days, are they officially late per FDAAA?

Finally, a recommendation for Investigators and study teams that do not log into the PRS system regularly. It would be helpful to have a pop up that indicates ‘What’s New’ since they last logged in – or perhaps shows them where to locate the new features.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Our institution uses and supports OnCore, RedCAP, and a custom IRB application to manage, collect, source, and report its clinical trials data. We would be very supportive of efforts to facilitate interoperability between these systems and the ClinicalTrials.gov PRS system. In some departments, interoperability between OnCore and ClinicalTrials.gov could conceivably keep those trials at or near 100% compliance as strict OnCore data field definitions exist for reporting requirements.

Certain funding agencies, such as NCI, require ongoing evidence of intra-departmental, inter-departmental, and inter-institution research collaboration. The ability to highlight these sorts of collaborative efforts on a ClinicalTrials.gov record would be valuable. This would involve creating source data for co-investigators and their departments to enable departmental reports that show all of the co-investigators and their respective departments/affiliations for active (or otherwise) clinical trials.

Our team uses the Planning Report for records maintenance, results reporting communications, as well as to run internal efficiency metrics. As such, we recommend a few additions to the Planning Report.

The addition of a record's "Initial Public Release date" would facilitate our tracking of the amount of time it takes from initial release to public release.

It would be great to be able to identify 'anticipated' vs 'actual' study start dates on the planning report just as you can for study completion dates.

To be able to see if a CT.gov record has study results linked to it in the references section would be welcomed. Our team is working to locate subsequent manuscripts to link to CT.gov records and if a PMID for Study Results column was on the Planning Report, these records could easily be identified.

We recommend including a column to track Non-ACT results expected per NIH Policy.

We recommend including a method to retrieve historical Planning Reports. As this is a dynamic report, it is challenging to obtain a snapshot of metrics. We currently track (on the first business day of each month):

- # of total records
- # active records requiring results per FDAAA
- % of active records that require results per FDAAA
- # active records
- # 'problem' records [# not yet registered, # late results, # maintenance queries, # results modules opened]
- # of late results in PRS review
- % of active records that are currently non-compliant
- % of ACTs with late or incomplete results

Tracking the status of results due per NIH Policy that are non-ACTs would be ideal.

We envision inputting a past date to retrieve the Planning Report from that date to understand the status of our records at that time for comparison with our current tracking system.

We suggest a process for bulk changing or tagging CT.gov records. For example, our Cancer Center recently changed its Central Contact email address. Preferably, we could select all records impacted and change them all at the same time.

Finally, we envision a dashboard capability within the PRS system, with several different audiences in mind. For example, a dashboard for senior leadership that would show the current snapshot of CT.gov at our institution, including total records, active records, late results, pending records, records with maintenance expected. Ideally, we could view departmental metrics as well, to identify a focus for outreach and education efforts as well as for providing recognition. Individual departments could keep track of their compliance via this sort of dashboard.

Dashboarding capability could also allow us to drill down into registration and results reporting cycles and cycle times and identification of the most common major comments. Our team is keeping track of this information but it currently takes quite a bit of time to mine the data in retrospect.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

At present, a PRS email goes out ~annually to Record Owners that have non-compliant records. We recommend this functionality be leveraged to be proactive.

First, we suggest emails are sent to both the Record Owners and those identified on the Access List. In many cases, the Record Owner is not the person who is actively updating the record. If individuals on the access list were notified that the record is in non-compliance, it would increase the probabilities of a prompt response.

Second, automated notifications from PRS could be emailed out to study teams (Record Owners and Access List) one month in advance of anticipated actions required. This is effectively what our team does with our monthly Planning Report actions. We've created scripts to email to study teams when various maintenance actions are approaching: Anticipated Study Start Dates, Primary Completion Dates, Annual Verification Dates, Consent Form Due Dates, Results Due Dates, Results follow up scripts... etc. The customization and automation of these sorts of communications directly from the PRS system might enhance records maintenance. The ability to turn on and off notifications for individual user accounts could be optional.

Finally, we recommend consulting with a stakeholder group that includes administrators and investigators who lead Observational, Basic Science, and Behavioral trials to test and provide feedback on modernization efforts going forward. The quality of the information submitted will largely depend upon flexibilities built into the system that enable all types of studies to be registered appropriately and reported with study-relevant measures.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Our team routinely references the PRS review criteria pdf, the Results beta Tutorial, the many 'help' and 'definition' links throughout the PRS system, and has benefited from the NIH Train the Trainer workshop. We also find email communication with the CT.gov PRS reviewer to be very helpful.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

We really like the idea of recognizing efforts and incentivizing study teams around record accuracy and compliance. This effort has the added potential of increasing clinical trials awareness and participation that is trackable via altmetrics.

We suggest offering study teams the option of sharing their trial registration to social media via icons. Teams could track the reach of their efforts.

It could be motivational for study teams to see the number of times their CT.gov record was viewed. It might also instruct them to shift the focus of their recruiting efforts.

We think that previously mentioned dashboard capabilities has the potential to ‘gamify’ compliance between departments, enabling Leadership to recognize the departments that are ‘on top’. From a PRS perspective, a nationwide dashboard of Academic Medical Centers or Industry or NIH-funded trials would highlight those entities that are most improved, or most compliant, or have the highest percentage of results reported. We know that peer reviewed publications that call out non-compliant institutions spread like wildfire, perhaps a publication that focuses on the ‘wins’ is prime.

Having the ability to compare our Academic Medical Centers with others would be valuable information.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

No comment.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Our team consulted with a biostatistician to review the current statistical analysis section in the Results Module and outlined the following recommendations to improve the data quality.

In the ‘Statistical Analysis Overview’ section, it would be useful to include the following questions as these questions drive the nature of what is chosen in the ‘Statistical Test of Hypothesis’ section:

- 1) Sample size (Total N) and power (%) for the study before recruitment
- 2) Sample size (Total N) and power (%) for the study at conclusion of the study

For example, if a researcher answers 70% starting power and 50% as the ending power (this means recruitment was not met), both are low power (they are both below 80%), then it becomes unsuitable to choose a parametric test (such as t-test) and must choose a non-parametric test instead (such as Kruskal-Wallis).

In the 'Statistical Test of Hypothesis' section, the [*] Method (required if a P-Value is entered) field, the recommendation for two additional questions for clarity includes:

- 1) Used multiple comparisons: Y/N
- 2) If Y above, Method of p-value adjustment (If applicable)

(Select One) Bonferroni

Sidak

Benjamini and Hochberg

Other _____

P-values are important to note but they are not useful if they have not been adjusted properly after multiple comparisons.

In the 'Other Statistical Analysis' section, it would be useful to include fields for these questions to help inform where any problems were encountered:

- 1) Were the aims of the study met? Y/N
- 2) If N above, please explain what the pitfalls were

Submission No.: 199

Date: 3/13/2020

Name: Eric Anthony

Name of Organization: International Society for Stem Cell Research

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

On behalf of the International Society for Stem Cell Research (ISSCR), I write to share our comments regarding the modernization of the ClinicalTrials.gov database (NOT-LM-20-003). The ISSCR is the leading professional organization of stem cell researchers and represents more than 4,000 members in the US and around the world. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic. As you seek to modernize the ClinicalTrials.gov database, we urge you to prevent the database from being abused by clinics marketing unproven stem cell interventions.

Unscrupulous clinics use the ClinicalTrials.gov database to give the appearance that their approaches have undergone a formal and rigorous review and promote their treatments to patients searching for clinical trials. These clinics exploit the database with promotional and false and misleading information, including links to sensational news stories and spurious claims that their interventions have a therapeutic benefit. The pollution of the ClinicalTrials.gov database with dubious listings negatively impacts the identification of and recruitment for legitimate trials. For a system that is designed to help patients, in its current form it increases the financial and physical risk to patients, including at least one patient who was blinded by an unproven stem cell treatment found on ClinicalTrials.gov.

The NIH should create a mechanism for constant surveillance of the website to identify and warn the public about dubious listings that contain false and misleading information. This would make the database a safer place for patients and physicians to find information about legitimate clinical trials. Section 402(j)(5)(E)(iv) of the Public Health Service Act authorizes the NIH to include the following warning on any listing that contains false information, “information in the entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law.” This warning should be prominently displayed on any dubious listing that contains false or misleading information, or that offers a biologically implausible intervention for a heterologous indication (for example, adipose derived cells for Parkinson’s disease, macular degeneration, or autism). While we understand that it may be impossible to review every listing, the database could have a flagging mechanism for the public to flag dubious listings for review by NIH, like Facebook’s and Twitter’s mechanisms for flagging inappropriate content.

The NIH could also improve the accuracy of ClinicalTrials.gov listings by requiring more information from registrants before listings are published in the database. During the submission process, registrants

should be asked questions to validate whether their products are regulated by the US Food and Drug Administration (FDA). If the product requires an Investigational New Drug Application (IND), registrants should be required to submit proof of their IND and update their listing with the status of the IND (e.g., active, inactive, on clinical hold) within thirty days of any change. When registrations provide false or misleading responses to these questions, their trial listings should display the warning mentioned previously.

Thank you for considering our recommendations to improve the ClinicalTrials.gov database. If the ISSCR can clarify any of these views or be of assistance, please contact Eric Anthony, ISSCR's Director of Policy at eanthony@isscr.org.

Sincerely,

Deepak Srivastava, MD

President, ISSCR

President, Gladstone Institutes

Attachment: ISSCR Comments on ClinicalTrials.gov Modernization March 2020.pdf

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March 13, 2020

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Joanna Wysocka
Stanford, CA USA

Hans C. Clevers, Ex Officio
Utrecht, Netherlands

Leonard I. Zon, Ex Officio
Boston, MA USA

Nancy Witty
Chief Executive Officer

Patricia Flatley Brennan
National Library of Medicine
8600 Rockville Pike
Bldg. 38, Rm. 2E-17
Bethesda, MD 20894

**Comments regarding RFI: ClinicalTrials.gov Modernization,
Notice Number: NOT-LM-20-003**

Dear Dr. Brennan,

On behalf of the International Society for Stem Cell Research (ISSCR), I write to share our comments regarding the modernization of the ClinicalTrials.gov database (NOT-LM-20-003). The ISSCR is the leading professional organization of stem cell researchers and represents more than 4,000 members in the US and around the world. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic. As you seek to modernize the ClinicalTrials.gov database, we urge you to prevent the database from being abused by clinics marketing unproven stem cell interventions.

Unscrupulous clinics use the ClinicalTrials.gov database to give the appearance that their approaches have undergone a formal and rigorous review and promote their treatments to patients searching for clinical trials. These clinics exploit the database with promotional and [false and misleading information](#), including links to sensational news stories and spurious claims that their interventions have a therapeutic benefit. The pollution of the ClinicalTrials.gov database with dubious listings negatively impacts the identification of and recruitment for legitimate trials. For a system that is designed to help patients, in its current form it increases the financial and physical risk to patients, including at least [one patient who was blinded by an unproven stem cell treatment found on ClinicalTrials.gov](#).

The NIH should create a mechanism for constant surveillance of the website to identify and warn the public about dubious listings that contain false and misleading information. This would

Promoting excellence in stem cell science and applications to human health.

make the database a safer place for patients and physicians to find information about legitimate clinical trials. Section 402(j)(5)(E)(iv) of the Public Health Service Act authorizes the NIH to include the following warning on any listing that contains false information, "information in the entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law." This warning should be prominently displayed on any dubious listing that contains false or misleading information, or that offers a biologically implausible intervention for a heterologous indication (for example, adipose derived cells for Parkinson's disease, macular degeneration, or autism). While we understand that it may be impossible to review every listing, the database could have a flagging mechanism for the public to flag dubious listings for review by NIH, like Facebook's and Twitter's mechanisms for flagging inappropriate content.

The NIH could also improve the accuracy of ClinicalTrials.gov listings by requiring more information from registrants before listings are published in the database. During the submission process, registrants should be asked questions to validate whether their products are regulated by the US Food and Drug Administration (FDA). If the product requires an Investigational New Drug Application (IND), registrants should be required to submit proof of their IND and update their listing with the status of the IND (e.g., active, inactive, on clinical hold) within thirty days of any change. When registrations provide false or misleading responses to these questions, their trial listings should display the warning mentioned previously.

Thank you for considering our recommendations to improve the ClinicalTrials.gov database. If the ISSCR can clarify any of these views or be of assistance, please contact Eric Anthony, ISSCR's Director of Policy at eanthony@isscr.org.

Sincerely,



Deepak Srivastava, MD
President, ISSCR
President, Gladstone Institutes

Submission No.: 200

Date: 3/13/2020

Name: Christine Gleave

Name of Organization: Geisinger

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- At our institution, we post a lot of internally funded investigator-initiated studies. Some studies meet the criteria for FDAAA regulations. Most studies are registered for publishing in ICMJE journals.
- Things that work well for us are the help and definitions provided in the site.
- For some studies, issues of non-compliance occur because the study contacts were not notified by CT.gov of required updates. This could be that a date needs to be updated, the annual verification is due, or results are due. We, as Office of Research Compliance staff, attempt to avoid “problem records” by reaching out the study teams. It would be useful if CT.gov sent out a reminder prior to records becoming non-compliant. If emails are sent out, it would be useful to include us (PRS Administrators) on the email.
- At times, study teams struggle with the rigid format of CT.gov when submitting non-traditional clinical trials.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

- Our site has a lot of non-traditional clinical trials that are registered for meeting the definition of a clinical trial per ICMJE (for example, behavioral studies, studies where the intervention is a diet or program rather than a drug or device). The criteria for submissions seems that it is designed for traditional drug trials. Could different selections populate if it is not a drug study?

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- Automatically send an email to alert study team and PRS administrator of upcoming deadlines (results are due or annual update is due)

- Automatically send an email to alert study team and PRS administrator of errors that pop up in already approved studies that do not require the annual update – for example, dates that need updated (anticipated start date is in the past)
- With an increase in behavioral studies being posted, expand the CT.gov template to be better aligned to behavior aims and outcomes. The current template appears to be built for drug trials, perhaps before as many behavior studies were considered clinical trials.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- Help and definition tools are both useful

Submission No.: 201

Date: 3/13/2020

Name: Max Narovlyansky

Name of Organization: FlowCell

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Comparison of studies, especially adjacent fields

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Tracking corporate progress using ClinicalTrials.com

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Both broad and narrow searches are necessary.

The key is have to narrow down the broad search to specifics topics and options for comparison.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

The results of clinical trials are completely obscure.

Whether trials are completed or terminated, there's virtually no study results anywhere.

Is this information about success of the trial NOT available?!

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I'm building my own graphical tool USclinicaltrials.org

- 2e.** Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

MANDATE full reporting. Incentives are for private business.

Submission No.: 202

Date: 3/13/2020

Name: Mary M. Langman

Name of Organization: Medical Library Association & Association of Academic Health Sciences Libraries

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Health sciences librarians assist patients, researchers, research administrators, clinicians, and others in identifying clinical trials for personal or professional purposes. The ClinicalTrials.gov registry has become a vital tool in the librarians' kit for responding to these various needs and populations. Particularly with the rising importance of systematic reviews in promoting evidence-based practice, the breadth of trials reported to ClinicalTrials.gov support unbiased synthesis of research findings, providing access to unpublished clinical trials findings and data, including studies that produce negative or null findings. ClinicalTrials.gov also provides a pathway toward participation in trials for patients and their doctors. With the increasing importance of the registry to vastly different user populations, it is necessary to keep in mind the different needs and perspectives of those ClinicalTrials.gov users in planning for this announced modernization.

Some search interface modernization suggestions include:

- Allowing for both robust advanced searching and broad topic/keyword box for basic searching. (functionality for different types of users)
- Expanding search parameters, including the ability to search by specific outcome measure, study design, etc.
- In results, suggesting ranked relevant results; provide a “more like this” feature that allows identification of similar trials
- Having information for age ranges or additional specific populations such as adolescents would be useful
- Adding a “save all” feature for searches with numerous results instead of clicking each box to save to clipboard for eventual download.
- Adding an email alert feature (in addition to RSS feed subscription) for new studies on a condition or topic.
- Adding RIS format as a data export format for use in citation managers
- Adding the ability to export a custom number of results or selected results from a set of search results
- Adding an export tool in the study details page

- Supporting the ability to search for terms, or a company, or PI name, and then creating a basic chart that would show the number of trials in a year for the years in the results

- Showing visualizations of how many trials have concluded, not yet been recruited for, and active
- Additional website functionality improvements might include:

- Adding a standardized geographic locator for each trial location to in a format that can be easily imported in mapping and geographic analysis software
- Improving the capability to search in specific geographic areas for trials, particularly those which are actively enrolling patients
- Adding the ability to customize export fields, e.g., only export contacts or PI information from records
- Adding a tool that automatically works with or links to PubMed to generate an easily exportable list of all publications related to the trial (instead of having to search manually)
- Considering additional linked PubMed features, e.g., links to all publications by an investigator listed on a registered protocol
- Linking to de-identified patient data or other research outputs or documents relevant to the study when possible (e.g., if data are shared in PubMed Central or on other reasonably persistent and reliable platforms)
- Facilitating links to external sources that can assist in publicizing a trial in recruitment, e.g., social media outlets
- Implementing a trend visualizer with exportable output. This would be a basic tool that the user could add a few inputs to from the search and get a few basic data visualizations out of. One might then be able to download the chart in a .jpeg, .png, or similar format and the raw data in a .CSV or tab delimited format for use in analysis programs such as R and Tableau.
- Adding features that help patients or non-medical professionals efficiently and effectively use the website, e.g., embedded tutorials, scroll-over definitions of terms, FAQ designed with patients in mind

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

ClinicalTrials.gov is only as good as it is complete and trustworthy. Lack of compliance with FDAAA 801 and the Final Rule can be traced back to two main areas: 1) difficulty in using the site and 2) lack of sanctions for noncompliance. In general, academic researchers have learned that there is no penalty for not using the system and therefore do not. Industry submission rates have been much greater. This is a recipe for noncompliance, lack of credibility, and eventual obsolescence. A suggestion is to improve user interface and penalization for noncompliance in tandem. Other suggestions include:

- Modernizing and simplifying the submission process to support flexibility and ease of importing data
- Ensuring the stability of the system. The system is out of date and researchers report regularly receiving errors during the submission process
- Reviewing data elements and determining a core set of elements to allow for a minimal compliance
- Using drop down options where plausible for common data elements
- Implementing the financial penalties as already mandated by the Final Rule
- Publicly flagging studies that are non-compliant as “Failure to Submit”
- Creating incentives for compliance

Submission No.: 203

Date: 3/13/2020

Name: Saad

Name of Organization: Hoffmann-La Roche

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

- To select an outcome measure from a data dictionary of standard measures e.g. drop down options for outcome measure titles and accepted descriptions. This will enable more standardized data reporting across all registrants.
- Allow the system to generate an XML that could directly be uploaded onto other registries e.g. EudraCT. This would allow sponsors to have consistency of global reporting.
- The Outcome Measures section of the Results Reporting Form should be more flexible to improve its readability for a results reviewer and the edit ability for the editor. Presently, only a single descriptive statistic (e.g. Mean or Median) and Dispersion Type can be selected for a single outcome measure title. If more than 1 statistic needs to be reported, multiple different outcome measures have to be created, which breaks the flow of information and is generally not the best presentation of results.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We are currently able to download study data from Clinicaltrials.gov but may not be interested in all elements. New functionality that allows users to select particular data elements from specific study records can enable additional data analysis for multiple purposes e.g. analyzing consistency of messaging, improvements/worsening of data quality, areas of most quality associated comments and the type of comments, etc....

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

Have more customized email messages that advise a submitter of whether their submission passed in attempt 1, 2 or 3, when any Reviewer comments are received or if the record has been released.

Submission No.: 204

Date: 3/13/2020

Name: Sarah White

Name of Organization: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

Attachment: 2020-03-13 MRCT Center_ClinicalTrials.gov modernization RFI.pdf

March 13, 2020

ClinicalTrials.gov Information Team

National Library of Medicine

Submitted electronically at: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Re: Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003)

Dear ClinicalTrials.gov Information Team,

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the National Library of Medicine ClinicalTrials.gov Modernization Request for Information (RFI), released December 30, 2019.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as a neutral convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The MRCT Center believes in the sharing of both summary and individual data with participants and enabling increased access to sharing of individual participant-level clinical trial data. Further, in the past two years, the MRCT Center has convened experts in the field and led a Health Literacy in Clinical Research project to develop tools and resources that support adopting and implementing health literacy principles at all points of the clinical research life cycle.

We note the challenges ClinicalTrials.gov faces as it strives to meet the mission of providing information about ongoing and completed clinical trials, creating a registry that meets the rigid criteria of US law, FDA regulations, and NIH policies, and accommodating the ever expanding expectations to enhance transparency of the clinical trial enterprise. We recognize and applaud the continuous technical updates to improve the system and provide recent training materials, including Train-the-Trainer courses, Protocol Registration and Results System (PRS) Guided Tutorials, and others. Most importantly, the willingness and assistance of very knowledgeable ClinicalTrials.gov staff to help whenever we have questions or technical challenges is invaluable. Any suggestions we have, therefore, are made knowing that the clinical research enterprise has come to rely on, in many different ways, the unbiased and readily available information found in the ClinicalTrials.gov system.

The MRCT Center uses the ClinicalTrials.gov database on a regular basis to search for a wide range of study types. Our searches focus on a specific data elements or categories of baseline characteristics submitted such as: race, ethnicity, age, sex, gender, and region/country; study phase; submitted documents; or studies within a date range. The MRCT Center generally utilizes the Advanced Search feature and we are grateful for the assistance the ClinicalTrials.gov staff have provided in answering questions and running custom searches in order to obtain specific baseline characteristic data.

Outlined below are comments responsive to the NLM's request for information focused on the public Website Functionality and the PRS database Information Submission and reflect suggestions to improve the goal of enhancing the public-facing components of ClinicalTrials.gov with a focus on patients and potential participants. We also make a few suggestions to enhance usability by investigators and research staff.

Website Functionality: the public ClinicalTrials.gov registry

As noted in the background of the RFI, potential benefits of ClinicalTrials.gov registration and results reporting registry include 'greater public availability of information about ongoing and completed clinical studies' and helping 'individuals find and compare clinical studies for which they may be eligible to enroll.' We know, however, that in the United States, fully one third (33%) of *English*-speaking individuals have a basic or below basic health literacy levels (see <https://nces.ed.gov/pubs2006/2006483.pdf>). Therefore, members of health care and research delivery systems should strive to communicate in ways that are designed to promote understanding in the populations they serve. As such, the MRCT Center recommends assigning additional effort to the creation of a user interface that the public can use to easily find plain language information about clinical research studies. The benefits of clear communication in the context of clinical research include an increase in public access, knowledge, and awareness that may in turn contribute to higher recruitment rates, even in underserved populations, and increased trust in the research enterprise. Given this, we suggest the following:

1. The section of the public website titled 'For Patients and Families,' accessed from the ClinicalTrials.gov home page, could benefit from incorporating fundamental elements of health literacy including plain language, numeracy, and clear design principles. As currently written, the information is highly technical and lengthy for the general public. For example, the section 'How to Read a Study Record' includes a long list of technical language and could be presented in a more engaging way that a patient, unfamiliar with research, can understand. In order to make the information on ClinicalTrials.gov more understandable to the greater public, NLM should consider ways to improve the readability and usability of the website and reduce the lengthy lists of technical information. Efforts should be made to engage experts in the field of health literacy and usability testing to create an engaging user experience.
2. The MRCT Center also advises engaging health literacy and usability experts to ensure key elements of a specific study record posted on the ClinicalTrials.gov registry can be understood by the lay person. A specific example that could benefit from this is as follows: within a specific Study Record Detail webpage, a colored box in the top right corner contains information regarding the recruitment status and posted dates. For those studies that have results posted, the box is red. The use of the color red is generally associated with the communication of an issue or problem with the record. Health literacy and usability experts would be able to advise on how to use appropriate fonts, colors, images/diagrams, spacing and layouts to make the website more accessible and user-friendly to a wider audience. An idea would be to include a diagram or flow chart of the study design, including study arm and randomization information as applicable.
3. The MRCT Center suggests NLM consider creating a new patient/participant facing view in the ClinicalTrials.gov registry. The current 'Study Details' and 'Tabular View' present details about a clinical study that are unnecessarily technical and confusing to a patient or potential participant.

While we realize that the concept of a patient/participant facing view can be achieved in several different ways, we suggest creating a new tab within the study record located to the left of the current ‘Study Details’ tab that can contain basic information about the study that a patient/participant would want to see including:

- a. Brief title
- b. Brief Summary (please see below regarding comments to improve the quality of the brief summary)
- c. Study Intervention
- d. Recruitment Status
- e. Eligibility Criteria
- f. Contact information
- g. Verification Date
- h. For completed studies: an optional field for Return of Aggregate Results to Participants.

Ideally, the ClinicalTrials.gov study record could be configured to default to the patient/participant-friendly interface, while leaving the more technical information in additional tabs for those desiring an increased level of detail. As one example that might serve as a helpful guide, we note the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au) provides basic information and easy navigation to help patients/participants understand the study status, date of last update, key trial information and eligibility information. A link to the full trial details is provided for those who want more information.

4. In many cases, patients and potential participants, who search and find studies of interest may want (and are encouraged) to speak with health care providers regarding whether they are eligible for a recruiting study. We suggest ClinicalTrials.gov develop a function to obtain a ‘printable’ or ‘emailable’ version of a clinical trial registration or results record. The utility of this feature would allow patients and potential participants to share and review this information with providers during decision-making conversations.
5. As stated in the RFI, information in the ClinicalTrials.gov registry “may help individuals find and compare clinical studies for which they may be eligible to enroll” yet a compare feature which would allow patients and potential participants to consider different clinical studies is not a current function in ClinicalTrials.gov. Basic information (as listed above in #2 above) could be compared across a table. We note that compare functions are very common features of websites where consumers may want to compare specific elements of a product.

As stated above, the MRCT Center uses the Advanced Search feature to identify a wide range of study types. We have two specific comments as it pertains to searching the public ClinicalTrials.gov registry:

1. We would like NLM to consider including the ability to search on the investigational status of a product.
2. The increased search capabilities of the Expert Search function are impressive. We note however that it should be moved to a more intuitive place for increased visibility. Additionally, it may be helpful to have short videos that demonstrate a variety of specific expert search functions.

Information submission: Protocol Registration System (PRS) database

Following our comments above regarding a new patient/participant facing view in the ClinicalTrials.gov registry, the MRCT Center strongly urges NLM to determine a way to assist PRS database record owners to improve the readability and consistency of information submitted to the PRS database. We suggest the following:

1. Brief Summary. We note that there is great heterogeneity in how different sponsors complete the Brief Summary section and that it is often longer and more technical than is functionally useable. The current data element definitions note that the character limit for brief summaries is 5000 words, which is longer than necessary to describe the purpose of the study. We believe that integrating health literacy principles would improve the understanding of visitors to the public site. We suggest NLM work with experts in the field to not only develop and adopt guidance, tools, and examples to assist submitters in developing a brief summary that clearly communicates the purpose of the research, but also to explore a means to assess various elements of health literacy automatically and provide real-time feedback to those entering the brief summary into the PRS database. We note the Transcelerate Clinical Trial Registration Tool (<https://transceleratebiopharmainc.com/events/overview-transcelerates-clinical-trial-registration-tool/>) is one such option.
2. Similarly, if an optional data element for aggregate return of results to participants were developed, NLM could explore tools and templates to electronically guide data submitters through the basic information that communicates summary results (in narrative form) to the public. The MRCT Center notes that creating and sharing clinical trial summaries ensures the study participants, and others including health care providers, are informed about the trial results.
3. We encourage NLM to consider providing an option for the data submitter to indicate whether *key eligibility criteria* or *complete eligibility criteria* are being submitted in the protocol section of the registration module. We recognize that requiring all eligibility criteria will increase utility for—and decrease frustration of—patients and potential participants who spend time finding an apparently appropriate trial only to be told of a minor eligibility criterion that precludes participation.

We recognize the interest that ClinicalTrials.gov has shown in aligning the PRS submission process with internal organizational processes. We request NLM consider engaging the REDCap (<https://www.project-redcap.org/>) community to promote higher interoperability between the PRS database and academia. REDCap, developed by Vanderbilt University, is a browser-based, metadata-driven EDC software and workflow methodology for designing clinical and translational research databases. The software is used by almost 4000 academic institutions in over 130 countries. While the majority of REDCap projects involve building and managing online surveys and databases (individual research projects), we are aware of several academic institutions that have developed systems for tracking and managing the local ClinicalTrials.gov records within REDCap. In these cases, information is ‘pulled’ (albeit not automatically) from the ClinicalTrials.gov PRS databases (e.g. Planning Report) to inform compliance efforts. Additionally, over the past year, the MRCT Center in collaboration with our local REDCap developers have created a REDCap Adverse Event reporting module that collects individual study adverse events and then subsequently aggregates the information into a format that can be ‘pushed’ into the PRS database. Given the number of academic institutions (and individual study teams)

that have access to REDCap, further exploring the usability and interoperability of REDCap could catalyze development of important tools for not only submitting results data but also improve tools for academic institutions to perform ClinicalTrials.gov compliance activities at their institutions.

We are aware that Investigators and study teams struggle accurately reflecting **specific protocol designs** in registration and results reporting modules. The specific study designs include master protocols, social behavioral research, basic experimental science studies, as well as innovative techniques within complex study designs (e.g. pooling placebos, step-wedge design) This is not only a burden to the individual submitting the study to the PRS database but leads to a lack of transparency in the public ClinicalTrials.gov website. ClinicalTrials.gov has previously published a number of *Example Studies for Results Data Entry* and we note that Investigators and PRS Administrators find these to be helpful tools. Short, just-in-time videos are also useful to those submitting registration and reporting results. The MRCT Center encourages NLM to work with experts in study design and those Investigators in the field using innovative study designs to identify and develop guidance/best practices on both registration and reporting results of innovative study design.

The MRCT Center encourages that NLM ensure that links to PUBMED are as accurate and up to date as possible. In addition, links to relevant parts of high-quality systematic reviews are helpful to those viewing the information on the public website and conducting critical appraisal of a trial.

Thank you again for the opportunity to comment on this important issue. The MRCT Center believes that the NLM is in a unique position to update and enhance the user-experience for those submitting information via the PRS database and using/viewing information on the public ClinicalTrials.gov website. We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact Sarah White (sawhite@bwh.harvard.edu).

Respectfully submitted,

Sarah A White, MPH
Barbara E Bierer, MD
Mark Barnes, JD, LLM
Sylvia Baedorf Kassis, MPH

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

Submission No.: 205

Date: 3/13/2020

Name: Lindsay Clarke

Name of Organization: Alliance for Aging Research

Attachment: NLM_CTgov_Alliance for Aging Research Comments.pdf



1700 K Street, NW | Suite 740 | Washington, DC 20006

T 202.293.2856

www.agingresearch.org

[@Aging_Research](https://twitter.com/Aging_Research)

March 13, 2020

ClinicalTrials.gov Information Team

National Library of Medicine

8600 Rockville Pike

Bethesda, MD 20894

Dear ClinicalTrials.gov Information Team,

As the leading nonprofit organization dedicated to accelerating research to enhance aging and health through public policy and education, the [Alliance for Aging Research](#) also serves as a voice of older Americans. We are grateful for the opportunity to bring this important voice to the process with our comments on the National Library of Medicine's (NLM) effort to improve and modernize the ClinicalTrials.gov database.

The Alliance recognizes the invaluable role volunteer clinical trial participants play in advancing lifechanging and lifesaving saving innovations and breakthroughs. ClinicalTrials.gov continues to serve as the world's largest public clinical research results database and as such, is relied upon by patients, caregivers, researchers and members of the medical and advocacy communities. We applaud the NLM's work to improve the usability and functionality of this vital resource. Below are our recommendations we hope the NLM will take into consideration throughout the modernization effort.

Establishment of an Advisory Group

As members of the National Health Council, we echo their [comments](#), particularly with regards to patient engagement in the modernization of ClinicalTrials.gov. As the NHC recommends, the Alliance also supports the establishment of an advisory group of patients and caregivers. We strongly suggest that this advisory group include older adults who would be able to provide important insights on usability, including ways to address accessibility, such as:

- Design aspects like optimal font, font size, and use of color;
- Health literacy considerations like accessible reading level of language used in summaries, definitions, and descriptions; language that allows users to process the meaning and usefulness of the clinical trial information, to understand the choices/consequences of available clinical trials, and to decide which trials match their needs and preferences;
- Opportunities for instructional tools in various communication formats, such as “explainer” videos that illustrate how to best navigate and use the database; and
- Ways to improve search functionality with additional filters, enhanced navigation, etc.

Platform Optimization to Serve both Researchers/Clinicians and Patients

The Alliance encourages the NLM to consider the National Cancer Institute's Physician Data Query (PDQ) database as a strong example of a resource effectively structured for both medical and patient audiences. All content is provided in a healthcare professional version AND a patient version, as well as in Spanish versions of both, and we encourage the NLM to consider the benefits of creating two, bilingual portals for ClinicalTrials.gov.

Conclusion

We appreciate this opportunity to provide feedback on the importance of inclusion of patients in the modernization of ClinicalTrials.gov and are happy to answer any questions. We would also welcome the opportunity to continue the dialogue and serve as a resource. Please do not hesitate to contact us at lclarke@agingresearch.org and lsmith@agingresearch.org.

Sincerely,

Lindsay Clarke, J.D.
Vice President of Health Education and Advocacy
Alliance for Aging Research

Lauren Smith, MBA
Vice President of Communications
Alliance for Aging Research

Submission No.: 206

Date: 3/13/2020

Name: Emily Spitzer

Name of Organization: Cook MyoSite Inc.

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

- Pitt+Me <https://pittplusme.org/>
- SUI Clinical Study <https://www.suiclinicalstudy.com/Default.aspx>
- Center Watch <https://www.centerwatch.com/clinical-trials/listings/location/united-states/PA/Pittsburgh/>

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Linking publications (link to website) would be helpful as publications clearly explain the methodology of the study (in comparison to a complex statistical analysis plan or protocol). Also, linking to patient advocacy groups (websites) would be ideal for recruitment of subjects as patients are more likely to search within their indication first.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Cook MyoSite uses the website to list clinical trials as a Sponsor. We also direct potential subjects to CT.gov to read more about the trial and find a site close to them. I like the specific resources (i.e. definitions) linked to each part of the trial listing so I do not need to search for what something is and click through pages. Some improvements we identified were:

- Better organization of search results. We suggest the trials be grouped by Sponsor and indication type, with the most current and recruiting trial listed at the top.
- Overall, to make the searches and format easier for a potential subject to find and understand. Suggest using more lay-terms that the general public understands (versus medical terminology).

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Our primary use relies on #2 in which limiting the search results to a certain subset of indications would allow potential subjects to identify recruiting trials faster/more efficiently.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- Remove the need to link the protocol, statistical analysis plan, and other confidential documents, and build these fields into the system. Linking complex documents does not appeal to patients and consistency within disclosures is best built in the system (same questions and required fields across all studies and Sponsors).

- Overall remove the need to link any documentation, and instead building the fields into the system. This would help with consistency across trials.

- Create templates for registering trials and results of trials as resources for Sponsors to use to complete prior to entering into the system. This would streamline the data entry portion.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

The use of templates prior to data entry into the system would align best with our organization's processes.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The quick guides Ct.gov list per page are very useful at the time of submissions and when the organization has to refer to specific definitions. The use of templates prior to data entry into the system would make the quality control portion easier in which a review could occur prior to the data entry portion.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

A way to recognize organizations would be to give organizations a rating (think Better Business Bureau, Yelp, Angie's List) in which timely submissions would give a higher rating, whereas untimely submissions or neglect of CT.gov would deduct from the organization's ratings.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Build protocol, statistical analysis plans, etc. information into the system versus having the requirement to attach such documents. The standardization of required fields would then standards across studies. Begin with high-level required fields but allow the addition of specific fields for flexibility. Create a template of these required fields so that the needs are known when creating study-specific documents.

Submission No.: 207

Date: 3/13/2020

Name: Juliane Baron

Name of Organization: Federation of Associations in Behavioral & Brain Sciences

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

The expansion of the definition of ‘clinical trials’ to include BESH studies raises a series of problems for the functionality of ClinicalTrials.gov, a vehicle that was originally designed to accommodate traditionally defined clinical trials.

Specifically, BESH studies are often relatively small, short studies. Unlike a trial that lasts for a year or more, BESH experiments may be completed within weeks. Reporting BESH in a database like ClinicalTrials.gov could impose the paperwork burden of a drug safety trial, a considerable administrative burden out of line with the minimal associated risks or the scientific purpose.

Furthermore, BESH studies generally have relatively few participants, often healthy volunteers. This significantly reduces the usefulness of extensive discussion of the patient population as is currently required on ClinicalTrials.gov. Again, this is a potential burden without a significant benefit.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

BESH research is often iterative in nature, evolving with new information. Often times, as the work progresses, specific experiments originally outlined in a grant proposal are massively modified or are never conducted. In BESH research, this is typically not evidence of a failed clinical trial. More typically it is evidence of good BESH science where the next experiment is informed by results of the last experiment. A future ClinicalTrials.gov registration should allow for this flexibility. This is different from the goal of monitoring deviations from the protocol of a multi-year “real” clinical trial and extremely challenging to register in advance.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

Capturing results - FABBS supports the idea of having a brief record of experiment outcomes, even for experiments that seemed interesting at the time but produced no relevant, publishable results.

Typically, uninteresting BESH studies do not get published. Thus, it would be useful to have a record of

such work (if only to keep another researcher from heading down the same dead end path). However, it would not be wise to have unpublished BESH results contribute to statistics that seemed to show that BESH scientists were failing to be open about their research.

Continuing with the goal of recording the results of all experiments, even failures, the resulting database will be of most use if its search tools clearly distinguished between basic behavioral research and true clinical trials and if the search tools made it possible for other BESH researchers to efficiently and effectively access relevant studies.

Submission No.: 208

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

As reference, we can consider Citeline/Trialtrove service.

I would like to have more functionalities in the search parameters. Search to identify investigators or institutions by indication, location. See the number of enrolled pts (real number) and the number that the sponsor estimated. The same for number of sites. See the trial enrollment duration (months), by country would be an excellent idea if ct.gov has the info available. Create some filters based on diseases. Gastric cancer. Rheumatoid Arthritis. Add 2-3 extra single line bars to refine the search criteria as Brain cancer + second line of treatment + stage III or IV. Depressive disease + moderate + resistant to XXX. An option to combine more than 2 diseases in cases like oncology (solid tumors) or Lung+gastric+brain cancer.

An easy way to export the info in excel. Just one click to export directly instead to make 2-3 steps to do it. Include the search criteria in the exported file.

Some options to edit, color the map view. Export map view

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I use to export trial info for data analysis.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

(1) a wide range of studies, multicountry

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

Create a ranking or a visible webpage or table regarding the number of trials by sponsor or institutions posted with or without results in ct.gov. So people can see which ones has more data and more interest to share with the public.

Submission No.: 209

Date: 3/13/2020

Name: [Not provided]

Name of Organization: Allergan

Attachment: NLM Modernization Efforts RFI AGN Response 14 Mar 2020.pdf



On behalf of Allergan, thank you for the opportunity to provide comments on the ClinicalTrials.gov modernization efforts initiative currently being undertaken by the NLM.

1. **Website Functionality.** NLM seeks broad input on the [ClinicalTrials.gov](#) website, including its [application programming interface](#) (API).
 - a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.
 1. Support complex clinical trials with multiple parts or multiple protocols when entering protocol registration information. Studies with multiple parts (ex. Part A and Part B or Phase 1/2) may include separate, randomized patient populations with separate start and completion dates, as well as specific outcome measures for each part. For example, study NCT03726658 was initially registered as a Phase 1b study but an amendment to the protocol added in Phase 2a. Until the phase 2 portion was ready to enroll, the study status was changed to ‘active, not recruiting’ and then back to ‘recruiting’. Technically, the study was not an applicable clinical trial that required registration to ClinicalTrials.gov until the protocol amendment but for the trial information to be understandable, registration needed to occur at study start. Two separate records which could be linked together would help clarify the trial design for potential participants and the public. Also, there are instances where results data is pooled together between patient populations from two studies and reported in one CSR. In this case, linking results postings between two studies would be beneficial.
 2. Allow for the entry of pre-populated reporting groups in results reporting, similarly to EudraCT (i.e., per protocol population, safety set, efficacy set) where the population descriptions, arms, etc. are saved, and the user is then able to select that population for each outcome measure instead of having to enter/edit it for every outcome measure. Allow a user to associate an Outcome Measure Analysis Population Description across multiple outcome measures.
 - b. Describe resources for possible linking from [ClinicalTrials.gov](#) (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.
 1. Recommend adding the functionality to link and/or upload a plain language summary to a study in ClinicalTrials.gov by adding “plain language summary” as an option to the document type data element. This will provide participants and the public access to both the technical results and the results in plain language for ease of understanding.
 2. Recommend adding a link to sites/portals where patients can access individualized results data. Clicking on the link should navigate a user directly to the site and not to an “exit notice” landing page.
 3. Recommend adding links to other registries where study information may be registered as this will provide participants with access to additional information about a study in multiple languages. An alternative recommendation is when adding a secondary ID, enable functionality to add the link to the relevant registry home page where a user can search using the secondary ID provided. Include help text for guidance on how to search other registries using the secondary IDs provided.

- 4. Recommend adding links to patient advocacy organizations based on the conditions provided in the protocol registration.
- 5. Build support for linking to the upcoming EU CTIS.
- 6. Allow responsible parties to specify the language of uploaded documents (i.e. – translated ICF's).
- c. Provide specific examples of how you currently use the [ClinicalTrials.gov](#) website, including existing features that work well and potential improvements.
 - 1. Allergan uses ClinicalTrials.gov to register a broad range of clinical studies. Different templates for observational study (i.e. retrospective chart review studies, RWE studies) registration would be beneficial. The current system is somewhat restrictive on how registration information for these studies can be entered. For example, chart review studies do not have site locations in which a patient can enroll into the study; however, the system still requires at least one “recruiting” location. Recommend creating a template for chart review studies where locations are not a required field as the use of locations for these types of trials can be misleading to the public.
 - 2. Recommend creating a new template for results submission for terminated studies where the results information being provided may be collected results information only and not analyzed results information. There are concerns that reporting collected, but not analyzed, data in the outcome measure module will be misconstrued as meaningful efficacy data - despite having a statement in the Limitations and Caveats Field that the study is underpowered.

Additionally, the current Outcome Measure Data Table uses the word ‘Analyzed’ in several places, such as ‘Number Analyzed’.

| | |
|---|----------------------|
| * Arm/Group Title: | Placebo |
| * \$ Arm/Group Description: | Oral administration. |
| In Statistical Analyses: 1 , 2 | |
| * Overall Number of Participants Analyzed: | 145 |
| + Add Units Analyzed | |
| (Optional) Use only if analysis is based on units other than participants (e.g., eyes, lesions) | |
| Analysis Population Description: | |

This could give the impression that the responsible party is reporting analyzed efficacy data.

One possible remedy is giving PRS the ability to remove the word ‘analyzed’ where it appears in Data Element definitions, only for studies with an overall recruitment status of ‘Terminated’.

Below is the list of relevant Data Elements.

Baseline Characteristics Section

- Baseline Analysis Population Description -> Baseline Population Description
- Number Analyzed -> Number

Outcome Measures Section

- Analysis Population Description -> Population Description
- Overall Number of Participants Analyzed -> Overall Number of Participants

3. Expand Character limits for the following Data Elements:

Recruitment Details – Expand to 500 Characters

Pre-assignment Details – Expand to 100 Characters

Milestone Title – Expand to 62 Characters

Other Reason (For Reason Not Competed Data Type) – Expand to 100 Characters

Category or Row Title – expand to 100 characters

Arm/Group Title – expand to 100 characters

Baseline Analysis Population Description – expand to 500 characters

Measure Analysis Population Description – expand to 500 characters

Analysis Population Description – expand to 500 characters

4. Add in functionality/comment to indicate that no changes have been made since the last update as opposed to relying on the updated “Last Verified” date which is currently located on the bottom of the page.

5. Recommend updating the Study Official’s Role to a free text field as the current choices, Study Chair, Director, Principal Investigator do not always apply. As an alternative, remove the official’s role data element altogether or change to reference the Scientific Point of Contact like the contact information in the results submission.

6. Recommend adding a “date acquired” or “date transferred” field to allow the public to see when the legal responsibility for the study has transferred to another responsible party.

7. Add in Least Squares Mean Difference into Statistical Analysis, Method of Estimation/Estimation Parameter as a data element.

8. Allow for the customization of arms/groups based on treatment period/milestone in Participant Flow tab.

9. Recommend providing the same functionality as proposed above for participant flow to create different arms and analysis populations in the Other Adverse Event section.

10. Recommend permitting the inclusion of multiple Other Adverse Event tables, instead of only one as recent QA comments have asked that Other Adverse Events be reported by intervention received, instead of by the study arms pre-specified in the protocol. Depending on the study design, AEs are sometimes separated into different time periods, e.g. Washout/Lead-In, Treatment Period, Safety Follow-Up period.

Locations: **United States, Alabama**

Central Research Associates, Inc
[Recruiting]
Birmingham, Alabama, United States, 35205
Contact: 205-558-2266

United States, Arkansas

HealthStar Research
[Not yet Recruiting]
Hot Springs, Arkansas, United States, 71913
Contact: 501-760-2903

12. Allow public to filter within recruiting study sites and/or color code individual sites by how recently that individual site was updated - within 30 days, 31-90 days, more than 90 days to allow users or participants seeking a recruiting site to easily identify when a site has recently started recruiting. Currently, the age of an update to an individual study site can only be determined by comparing the History of Changes of a study for Locations/Contacts, which is cumbersome in practice. Allowing the public to filter for only the most recently updated Recruiting sites increases the likelihood of finding a study site that still has open spots for enrollment.
13. Add in pop-up functionality for patients/public that will provide additional information on common outcome measures/scale information in plain language. (ex. What is MADRS? What is CSSR-S?)
14. Add in functionality to the PRS where e-mail reminders are sent to the responsible party when study start dates, primary completion and study completion dates have passed and need to be updated.
15. Allow for easier data entry of inclusion/exclusion criteria by re-formatting the data entry field. Recommend separating into two fields – one for inclusion and one for exclusion. Allow for easier formatting of bulleted lists of sub-criteria.

2. **Information submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.
 1. Implementing a more objective QA review process as opposed to the current subjective QA review to avoid multiple rounds of QA comments.
 2. Assigning studies to the same QA reviewer upon resubmission of registration and/or results information.
 - b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
 - c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.
 - 1. Recommend providing examples of common QA review comments.
 - 2. Recommend adding a guidance document on how to draft outcome measures and how to report endpoints for safety studies.
 - 3. Recommend adding in the study start date and the sponsor to the public site report.
 - 4. When searching by study ID on the PRS, navigating back to the home page clears the filtered results causing a user to re-enter the search criteria.
 - 5. Implement functionality to be able to release a delay of results request without having to delete results information that has been previously entered but not submitted.
 - e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.
3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.
 - 1. Recommend updating the PRS to implement the WHO 24-field data set to achieve global harmonization across the multiple required registries.
 - 2. Standardize keywords/conditions field or allow responsible parties to suggest new standardized terms for conditions. This would allow for easier searching for relevant clinical trials. Recommend disabling functionality where the NLM enters in keywords based on the conditions provided by the responsible party.
 - b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.
 - 1. Recommend implementing functionality for all studies regardless of PRS status to allow someone entering data to be able to copy a record and then modify it for instances where two studies are similar in design.

Many thanks,

Clinical Trial Registries Team

Submission No.: 210

Date: 3/13/2020

Name: Stacey Berg

Name of Organization: Baylor College of Medicine

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Thank you for the opportunity to comment on ClinicalTrials.gov modernization. As an academic institution, Baylor College of Medicine is primarily concerned about the impact of current Protocol Registration and Results System (PRS) requirements for clinical scientists who serve as sponsor-investigators. In particular, the current PRS results reporting format is widely regarded among investigators as inflexible, difficult to use, and burdensome.

PRS currently requires investigators to prepare and submit results in a tabular format specific to PRS. This requirement frequently creates a mismatch in form between the stated primary aim of a study (for example, to define the maximum tolerated dose of Drug X) and the results reported (for example, a table of the dose-limiting toxicities observed in each cohort). If the initial description of the outcome

While the data entry process itself poses a substantial burden for study teams, an additional significant problem is that published data may not necessarily align with that required for clinicaltrials.gov submission. Thus PRS reporting often necessitates separate, additional data analysis, and often additional support from biostatisticians, which increasing both the burden and the cost of the study.

Finally, because the data is displayed without narrative text, the table(s) must be self-explanatory, relying solely on row/column labels. Especially for studies of higher complexity (multiple arms, endpoints, etc.), the summary results tables often become unwieldy. Thus the results reporting does not actually facilitate an understanding of the study results for end users like investigators, patients, and the general public.

We suggest that clinicaltrials.gov provide greater flexibility in the format and submission of results. In particular, removing the “summary” requirement and enabling use of published data tables, or permitting uploading of a full manuscript/publication in lieu of completing the “basic results” table(s) for non-industry sponsors, would be a significant enhancement of the PRS system.

Submission No.: 211

Date: 3/13/2020

Name: Jackie Foster and Anna DeSalvo

Name of Organization: National Marrow Donor Program / Be The Match

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The Jason Carter Clinical Trials Program (JCCTP) is a program offered by the National Marrow Donor Program (NMDP). Through the JCCTP, we help patients with blood cancers and blood disorders find and join clinical trials. We do this through one-on-one clinical trial navigation support, educational resources, a travel grant, and an online clinical trial search tool at JCCTP.org, which relies heavily on data from ClinicalTrials.gov.

The JCCTP.org search tool connects to ClinicalTrials.gov information through the Aggregate Analysis of ClinicalTrials.gov (AACT) database. We are able to keep the search tool current through daily alerts of new trials added to, removed from, or revised on ClinicalTrials.gov. The alerts are created by our website vendor using the AACT database and API. We take the trial information published on ClinicalTrials.gov and revise for plain language. The revised trial description is published on JCCTP.org and the search tool searches terms both in the revised and original trial descriptions. We have approximately 1,200 trials accessible through the search tool.

We include all clinical trials that are:

1. Treating either:
 - a. Disease for which hematopoietic cell transplantation (HCT) is a treatment option (e.g. hematologic malignant and non-malignant diseases or disorders, inherited metabolic disorders, immunodeficiency disorders)
 - b. Complication of HCT, such as graft-versus-host disease
2. Recruitment status is "Recruiting"
3. Recruitment is happening in the United States
4. Phase 1, 2 or 3

We are notified daily when there are changes to trial information on ClinicalTrials.gov. If there is a change in recruitment status, eligibility criteria, or intervention, we then update JCCTP.org accordingly. When a trial's recruitment status changes from "Recruiting" to anything else, the trial is automatically removed from the JCCTP.org search tool.

We have connected with nearly 700 patients or their loved ones since the program launched in July 2017. In that time, we have helped over 100 people find and join a clinical trial. On average, there are 3,000-4,000 clinical trial searches completed on JCCTP.org each month.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Provide or link to patient-friendly versions of the clinical trial summaries. For example, the Jason Carter Clinical Trials Program (JCCTP) provides patient-friendly versions of the clinical trial descriptions on ClinicalTrials.gov through the program website, JCCTP.org. This would be useful for physicians and researchers to be able to share a patient-friendly description with their patients to aid in recruitment.

Provide or link to patient-friendly summaries of relevant research. For example, the Center for International Blood and Marrow Transplant Research (CIBMTR) shares 1-page summaries of published research in patient-friendly language. The JCCTP will also be providing this information soon. For people who are reading about a clinical trial testing a new drug or therapy it would be helpful to have links to relevant published research on that drug or therapy.

For newer therapies, like gene therapy, the amount of patient-friendly education is often very limited. Provide links to relevant, approved patient education resources for these newer therapies.

It would be helpful if PIs could upload a publicly available, IRB-approved protocol document and/or consent form. Our goal at the JCCTP is to help people find and join clinical trials so as much information as we can have access to is helpful so we can navigate patients appropriately.

Since it would be difficult for ClinicalTrials.gov to manage and maintain all these resources for possible linking, there could be defined partnerships with organizations that could either apply or meet certain criteria and then those partner organizations would be able to add relevant links.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

In addition to using the API through the AACT as described above in part a, we use CT.gov quite a bit.

1. Search tool—Find a study and the resulting page with the results from your search
 - a. Works well:
 - i. The autofill function when typing into the “condition or disease” field. For example, when you start typing “acute” multiple diseases and conditions pop up for you to select from
 - ii. Having the option to add additional information in the “other terms” field. This helps to be able to further define your search to include a specific center, drug, disease status, etc.
 - iii. Having the option to use additional filters such as –“recruitment” (we primarily use “recruiting”, “Eligibility criteria” (we primarily use age), “study type” (we primarily use “interventional” but may use “observational” more in the future) and “location”
 - iv. The ability to change what columns are shown on the results page. We also appreciate that it saves your choices for the next time you open the site. For example, you can easily choose to show or

hide the columns for 'status', 'condition', 'interventions', 'study type', 'phase', 'sponsor/collaborators', 'funder type', etc.

v. The ability to download and export the results with the columns you select to an excel file

vi. RSS feed— we use this to export and add trials to the JCCTP.org website

b. Potential improvements:

i. Sorting the results by column— for example, it would be nice to be able to sort the trials that come up from a search in ascending or descending order based on location so that all of the trials being done at certain institutions are in a row

ii. Additional filtering options (beyond the ability to type it into the "other terms" field)

1. Some filters that would be helpful: specific mutations or markers, by center/institution, relapsed or refractory disease vs. newly diagnosed

iii. Additional options to select or input for the distance away from a certain location (right now you can select 50, 100, 200 or 300 miles). It would be nice to have the option to be even more focused (for example 5 miles). This is especially helpful for places like New York City.

1. In addition, most patients with Medicaid must stay within their home state, so an option to search close to a city but just within a state, would be helpful. For example, patients with Pennsylvania Medicaid need to stay within Pennsylvania, but with the existing system you must search within 50 miles of Philadelphia, and you get many results that are outside of the state of Pennsylvania.

iv. When downloading/exporting search results to an excel file, it would be great if each trial location/site could be an individual cell or at least an individual line within a cell. Currently, when you export the trials, all of the locations/sites are in one line separated by "|" and it is difficult to do any analysis without a lot of manual work

v. Include more transparency about the order the trials are listed in when results are populated from a search. When there are multiple pages of results what trials are prioritized to the first page? The trials that are on the first few pages are likely viewed more often than the ones on the last pages. What order are the trials in? Is it based on the ones that are most recently updated, most recently added, number of keywords present (i.e. 'most relevant'), etc.? This is important information for individuals to know as to not think that earlier trials are necessarily better or endorsed differently

2. Trial descriptions and information provided about specific trials (once you click on the title of the trial from the search results):

a. Works well:

i. We appreciated the "sponsor" and "responsible party" information being pulled out and clearly labeled near the top for easy access and transparency

ii. The color-coded box with information about the "recruitment status", "first posted" and "last updated" dates

- iii. We appreciate the boxes/tables at the top under “study description” so you can easily and quickly see what condition/disease, intervention/treatment and phase the study is
 - iv. We appreciate that there is a list with clear headings with the study design information so you can easily see the study type, estimated enrollment, allocation, intervention model, masking, study start date, estimated primary completion date and estimated study completion date. We use all of that information for each trial, so an easy way to see this snapshot is important
 - v. We appreciate that there is a table in the “arms and interventions” section where you can easily see the arms and interventions/treatment.
 - vi. We appreciate that within the “outcomes measures” section there are details at the end of each measure with the length of follow-up so an individual can get a rough idea of how long they would be followed-up/participating in any given portion of a trial
 - vii. We appreciate that at the top of the “eligibility criteria” section there is a label and information that clearly states the ages that are eligible for the study. We use this section as the source of truth for the age criteria.
 - 1. Sometimes information in the study description or in the detailed eligibility criteria is different than the information at the top of the eligibility criteria section with the heading “Ages eligible for study”. For example, it may say ages 18-45 are eligible in the study description section but then at the top of the eligibility criteria section it says ages 18-35 are eligible. For this example, we would use ages 18-35 as the ‘correct’ age range for this trial.
- b. Potential improvements:
- i. Require the name of at least one PI to be listed for every trial
 - ii. Incentivize or remind (or both) trials to be updated. We are especially concerned about the contact information. We frequently come across trials that patients are interested in joining or may qualify for (and for many it may be the only trial that). We then have to spend too much time tracking down the correct contact at the trial site because the contact information listed on the trial description is wrong or the person listed has left the institution. Many times, when you finally track down the right person, they tell you the trial isn’t even recruiting anymore. In addition, frequently the phone number listed is the front desk or main line to a department and the person answering has not been trained to understand what the trial is. They often don’t know what we are referring to when discussing the trial.
 - iii. Another area that updates are important is with drug names. The drug names change and there should be a way that tagging is performed so that all of the appropriate trials come up when searching for synonyms. For example, Hu5F9-G4 and magrolimab are the same drug. When you search for one name, you get different results than if you search for the other.
 - iv. A contact for each site should be required. For example, sometimes there is contact information provided for the trial as a whole near the top of the “contacts and locations” section, but then within each site there aren’t specific email addresses and/or phone numbers. This would need to stay updated. There could be a link to their clinic site or wherever they do keep their contact information up to date if they are not willing to update it on the CT.gov site.

v. There should be a way to mark which sites are full and which ones are still recruiting, if it is a multi-site trial. Sites that are full should not come up on a search for trials with location parameters that include trials that are full.

vi. Submitters include information differently in the arms and interventions table— some don't even add the information here and include it above in the trial description. Others put it in both places and there are often discrepancies in the data between the “study description” and the “arms and interventions” section. For example, the “study description” may say treatment is given on days 1, 7 and 14 and in the “arms and interventions” section it says treatment is given on days 1 and 7 only. It doesn't inspire much confidence in research when a trial is inconsistent and confusing for patients. Encourage submitters to proofread and only include information in one section so if there are changes, they don't miss changing it in multiple places

vii. Within the “arms and interventions” section, it should be clearer for cancer trials how long each cycle is. Many times, it says how many cycles each patient would get but doesn't define how long a cycle is. Encourage submitters to include this information with a prompt or a field to enter this information

viii. The option to have a different view (the tabular view) is confusing, the way it's laid out now makes it seem like this is different information than is listed in the “study details” tab

ix. The trial descriptions are not in patient-friendly language. There are many organizations who translate the trials into patient-friendly language. You could link to those. If there are multiple organizations working on the same trials, you could have applications to be the site that gets linked to. If that is too much work, you could have those organizations somehow tag their own link to the trial (with oversite by NLM for final approval)

x. The organization of the “eligibility criteria” section varies significantly among trials. We understand that much of this is based on how the submitter is entering the information, however:

1. There are often inclusion criteria listed in the exclusion section and vice versa

2. The hierarchy/organization of bullet points should be clearer. Trials often have inclusion criteria or exclusion criteria that is only pertinent for certain diseases or groups of patients. What criteria are contingent on other criteria and what criteria apply to everyone in a trial gets confusing especially when the indentation of the bullet points is off. For example, a trial may be for people with acute myeloid leukemia and acute lymphocytic leukemia but the criteria may differ for people with each disease. Under the inclusion criteria it will say: “Has acute myeloid leukemia with the following:”. Then on the next few lines there will be criteria for the acute myeloid leukemia (does not have FLT3 mutation, has been treated with 2 lines of treatment, etc.), but the lines won't be indented to show that they correspond only to the patients with acute myeloid leukemia. Then the next lines (in the same level of indentation as the lines above) will say “Has acute lymphocytic leukemia with the following:”. And the lines below will be the criteria for the acute lymphocytic leukemia (has been treated with 3 lines of treatment, does not have Ph+ leukemia, etc.). Then the next bullet points below will say some general criteria for everyone “must sign consent form, must agree to contraception, etc.”. All of these criteria are listed with bullet points in a row with no difference in indentation or spacing so it's unclear what applies to just people with one disease or another and what applies to everyone

xi. It would be helpful if it was clearer in the trial descriptions what part of the trial is experimental/investigational and what parts are standard of care. What exactly is being studied should be highlighted somewhere for every trial.

3. History of changes:

a. Works well:

i. We routinely use the history of changes section to determine if there are pertinent changes made to the trial descriptions that we then need to edit on our website's trial description.

ii. We appreciate that you can select the date the changes were made

iii. We appreciate that you can specifically see what was changed within the trial with words either crossed off and in red or added by highlighting them in green

iv. We appreciate that if a section had no changes made to it, it is blank and show no words. This helps so that you don't have to scroll through sections of text where nothing was changed

b. Potential improvements:

i. If a section or sentence was copied and pasted elsewhere into the trial description, it would be great if this didn't show up in revisions. For example, submitters will often move information around in the eligibility criteria section. This shows up as crossed off text in red and then the same text will be elsewhere highlighted in green. You have to read through line by line to make sure nothing was changed when it is the exact same information

4. Results:

a. Potential improvements:

i. Highlight trial results better

ii. Have patient friendly versions of the results available or link to versions of patient friendly results

iii. Make it clearer how to access the results

5. Protocols:

a. Potential improvements:

i. Make it clearer which trials have protocol documents attached/available

ii. Make it clearer how to access the protocols

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We need access to a wide range of studies in terms of study types, intervention types and geographical locations, but we are interested in a limited range of disease types (albeit still relatively broad). We

primarily work with disorders that are treatable with hematopoietic stem cell transplant or cellular therapy. As cellular therapies continue to expand, so is our scope, so it's important that we can search for many different diseases and interventions but then narrow that to be specific for any given patient given their age, location, prior treatment, interests, etc.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

We feel very strongly that in order for trials to meet accrual and for patients to continue to want to be involved in clinical research, we cannot create barriers to clinical trial access and participation. Not being able to contact the trial to join or ask questions turns patients and their advocates away. Contact information and whether or not a trial is recruiting needs to be updated and accurate. This should be incentivized by having disclaimers or awards/certificates listed on trials. Trials that do this should be prioritized or listed higher on search results.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Areas that standardization would be helpful are:

- Drug names - The drug names change or are updated as they move through various trials and there should be a way to tag these trials so that all of the appropriate trials come up when searching for one name versus another
- Encourage submitters to proofread and only include information in one section of the trial description so if there are changes, they don't miss updating them in multiple places - Information about the "arms and interventions" should only be entered in that section (not also in the study description section), the same would go for the eligibility requirements. The ages eligible should not be listed in more than one place as to avoid inconsistencies.
- Encourage data to be entered for how long a cycle is for treatment– an explicit field for this may help as a reminder
- Add an explicit field that describes what is being studied or what part of the trial treatment is experimental/investigational and what is standard of care

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Recommend links to other websites where trials are actually updating their contact and recruitment status information. For example, trials may update their own websites but do not update their listing on clinicaltrials.gov. If they could provide a link to where they are actually making updates, this would be helpful.

Attachment: ClinicalTrials.gov Modernization RFI.docx

Purpose

The purpose of this Request for Information is to solicit public input to guide the National Library of Medicine (NLM) in planning infrastructure enhancements aimed at users and submitters of ClinicalTrials.gov as part of a multi-year modernization initiative.

https://nlmenterprise.co1.qualtrics.com/ife/form/SV_e2rLEUAx99myump

Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

- a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

The Jason Carter Clinical Trials Program (JCCTP) is a program offered by the National Marrow Donor Program (NMDP). Through the JCCTP, we help patients with blood cancers and blood disorders find and join clinical trials. We do this through one-on-one clinical trial navigation support, educational resources, a travel grant, and an online clinical trial search tool at JCCTP.org, which relies heavily on data from ClinicalTrials.gov.

The JCCTP.org search tool connects to ClinicalTrials.gov information through the Aggregate Analysis of ClinicalTrials.gov (AACT) database. We are able to keep the search tool current through daily alerts of new trials added to, removed from, or revised on ClinicalTrials.gov. The alerts are created by our website vendor using the AACT database and API. We take the trial information published on ClinicalTrials.gov and revise for plain language. The revised trial description is published on JCCTP.org and the search tool searches terms both in the revised and original trial descriptions. We have approximately 1,200 trials accessible through the search tool.

We include all clinical trials that are:

1. Treating either:
 - a. Disease for which hematopoietic cell transplantation (HCT) is a treatment option (e.g. hematologic malignant and non-malignant diseases or disorders, inherited metabolic disorders, immunodeficiency disorders)
 - b. Complication of HCT, such as graft-versus-host disease
2. Recruitment status is "Recruiting"
3. Recruitment is happening in the United States
4. Phase 1, 2 or 3

We are notified daily when there are changes to trial information on ClinicalTrials.gov. If there is a change in recruitment status, eligibility criteria, or intervention, we then update JCCTP.org accordingly. When a trial's recruitment status changes from "Recruiting" to anything else, the trial is automatically removed from the JCCTP.org search tool.

We have connected with nearly 700 patients or their loved ones since the program launched in July 2017. In that time, we have helped over 100 people find and join a clinical trial. On average, there are 3,000-4,000 clinical trial searches completed on JCCTP.org each month.

- b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Provide or link to patient-friendly versions of the clinical trial summaries. For example, the Jason Carter Clinical Trials Program (JCCTP) provides patient-friendly versions of the clinical trial descriptions on ClinicalTrials.gov through the program website, JCCTP.org. This would be useful for physicians and researchers to be able to share a patient-friendly description with their patients to aid in recruitment.

Provide or link to patient-friendly summaries of relevant research. For example, the Center for International Blood and Marrow Transplant Research (CIBMTR) shares 1-page summaries of published research in patient-friendly language. The JCCTP will also be providing this information soon. For people who are reading about a clinical trial testing a new drug or therapy it would be helpful to have links to relevant published research on that drug or therapy.

For newer therapies, like gene therapy, the amount of patient-friendly education is often very limited. Provide links to relevant, approved patient education resources for these newer therapies.

It would be helpful if PIs could upload a publicly available, IRB-approved protocol document and/or consent form. Our goal at the JCCTP is to help people find and join clinical trials so as much information as we can have access to is helpful so we can navigate patients appropriately.

Since it would be difficult for ClinicalTrials.gov to manage and maintain all these resources for possible linking, there could be defined partnerships with organizations that could either apply or meet certain criteria and then those partner organizations would be able to add relevant links.

- c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

In addition to using the API through the AACT as described above in part a, we use CT.gov quite a bit.

1. Search tool – Find a study and the resulting page with the results from your search
 - a. Works well:
 - i. The autofill function when typing into the “condition or disease” field. For example, when you start typing “acute” multiple diseases and conditions pop up for you to select from
 - ii. Having the option to add additional information in the “other terms” field. This helps to be able to further define your search to include a specific center, drug, disease status, etc.
 - iii. Having the option to use additional filters such as - “recruitment” (we primarily use “recruiting”), “Eligibility criteria” (we primarily use age), “study type” (we primarily use “interventional” but may use “observational” more in the future) and “location”
 - iv. The ability to change what columns are shown on the results page. We also appreciate that it saves your choices for the next time you open the site. For example, you can easily choose to show or hide the columns for ‘status’, ‘condition’, ‘interventions’, ‘study type’, ‘phase’, ‘sponsor/collaborators’, ‘funder type’, etc.

- v. The ability to download and export the results with the columns you select to an excel file
 - vi. RSS feed – we use this to export and add trials to the JCCTP.org website
- b. Potential improvements:
- i. Sorting the results by column – for example, it would be nice to be able to sort the trials that come up from a search in ascending or descending order based on location so that all of the trials being done at certain institutions are in a row
 - ii. Additional filtering options (beyond the ability to type it into the “other terms” field)
 - 1. Some filters that would be helpful: specific mutations or markers, by center/institution, relapsed or refractory disease vs. newly diagnosed
 - iii. Additional options to select or input for the distance away from a certain location (right now you can select 50, 100, 200 or 300 miles). It would be nice to have the option to be even more focused (for example 5 miles). This is especially helpful for places like New York City.
 - 1. In addition, most patients with Medicaid must stay within their home state, so an option to search close to a city but just within a state, would be helpful. For example, patients with Pennsylvania Medicaid need to stay within Pennsylvania, but with the existing system you must search within 50 miles of Philadelphia, and you get many results that are outside of the state of Pennsylvania.
 - iv. When downloading/exporting search results to an excel file, it would be great if each trial location/site could be an individual cell or at least an individual line within a cell. Currently, when you export the trials, all of the locations/sites are in one line separated by “|” and it is difficult to do any analysis without a lot of manual work
 - v. Include more transparency about the order the trials are listed in when results are populated from a search. When there are multiple pages of results what trials are prioritized to the first page? The trials that are on the first few pages are likely viewed more often than the ones on the last pages. What order are the trials in? Is it based on the ones that are most recently updated, most recently added, number of keywords present (i.e. ‘most relevant’), etc.? This is important information for individuals to know as to not think that earlier trials are necessarily better or endorsed differently
2. Trial descriptions and information provided about specific trials (once you click on the title of the trial from the search results):
- a. Works well:
 - i. We appreciated the “sponsor” and “responsible party” information being pulled out and clearly labeled near the top for easy access and transparency
 - ii. The color-coded box with information about the “recruitment status”, “first posted” and “last updated” dates
 - iii. We appreciate the boxes/tables at the top under “study description” so you can easily and quickly see what condition/disease, intervention/treatment and phase the study is
 - iv. We appreciate that there is a list with clear headings with the study design information so you can easily see the study type, estimated enrollment, allocation, intervention model, masking, study start date,

estimated primary completion date and estimated study completion date. We use all of that information for each trial, so an easy way to see this snapshot is important

- v. We appreciate that there is a table in the “arms and interventions” section where you can easily see the arms and interventions/treatment.
- vi. We appreciate that within the “outcomes measures” section there are details at the end of each measure with the length of follow-up so an individual can get a rough idea of how long they would be followed-up/participating in any given portion of a trial
- vii. We appreciate that at the top of the “eligibility criteria” section there is a label and information that clearly states the ages that are eligible for the study. We use this section as the source of truth for the age criteria.
 - 1. Sometimes information in the study description or in the detailed eligibility criteria is different than the information at the top of the eligibility criteria section with the heading “Ages eligible for study”. For example, it may say ages 18-45 are eligible in the study description section but then at the top of the eligibility criteria section it says ages 18-35 are eligible. For this example, we would use ages 18-35 as the ‘correct’ age range for this trial.

b. Potential improvements:

- i. Require the name of at least one PI to be listed for every trial
- ii. Incentivize or remind (or both) trials to be updated. We are especially concerned about the contact information. We frequently come across trials that patients are interested in joining or may qualify for (and for many it may be the only trial that). We then have to spend too much time tracking down the correct contact at the trial site because the contact information listed on the trial description is wrong or the person listed has left the institution. Many times, when you finally track down the right person, they tell you the trial isn’t even recruiting anymore. In addition, frequently the phone number listed is the front desk or main line to a department and the person answering has not been trained to understand what the trial is. They often don’t know what we are referring to when discussing the trial.
- iii. Another area that updates are important is with drug names. The drug names change and there should be a way that tagging is performed so that all of the appropriate trials come up when searching for synonyms. For example, Hu5F9-G4 and magrolimab are the same drug. When you search for one name, you get different results than if you search for the other.
- iv. A contact for each site should be required. For example, sometimes there is contact information provided for the trial as a whole near the top of the “contacts and locations” section, but then within each site there aren’t specific email addresses and/or phone numbers. This would need to stay updated. There could be a link to their clinic site or wherever they do keep their contact information up to date if they are not willing to update it on the CT.gov site.
- v. There should be a way to mark which sites are full and which ones are still recruiting, if it is a multi-site trial. Sites that are full should not come up on a search for trials with location parameters that include trials that are full.

- vi. Submitters include information differently in the arms and interventions table – some don't even add the information here and include it above in the trial description. Others put it in both places and there are often discrepancies in the data between the “study description” and the “arms and interventions” section. For example, the “study description” may say treatment is given on days 1, 7 and 14 and in the “arms and interventions” section it says treatment is given on days 1 and 7 only. It doesn't inspire much confidence in research when a trial is inconsistent and confusing for patients. Encourage submitters to proofread and only include information in one section so if there are changes, they don't miss changing it in multiple places
- vii. Within the “arms and interventions” section, it should be clearer for cancer trials how long each cycle is. Many times, it says how many cycles each patient would get but doesn't define how long a cycle is. Encourage submitters to include this information with a prompt or a field to enter this information
- viii. The option to have a different view (the tabular view) is confusing, the way it's laid out now makes it seem like this is different information than is listed in the “study details” tab
- ix. The trial descriptions are not in patient-friendly language. There are many organizations who translate the trials into patient-friendly language. You could link to those. If there are multiple organizations working on the same trials, you could have applications to be the site that gets linked to. If that is too much work, you could have those organizations somehow tag their own link to the trial (with oversite by NLM for final approval)
- x. The organization of the “eligibility criteria” section varies significantly among trials. We understand that much of this is based on how the submitter is entering the information, however:
 - 1. There are often inclusion criteria listed in the exclusion section and vice versa
 - 2. The hierarchy/organization of bullet points should be clearer.

Trials often have inclusion criteria or exclusion criteria that is only pertinent for certain diseases or groups of patients. What criteria are contingent on other criteria and what criteria apply to everyone in a trial gets confusing especially when the indentation of the bullet points is off. For example, a trial may be for people with acute myeloid leukemia and acute lymphocytic leukemia but the criteria may differ for people with each disease. Under the inclusion criteria it will say: “Has acute myeloid leukemia with the following:”. Then on the next few lines there will be criteria for the acute myeloid leukemia (does not have FLT3 mutation, has been treated with 2 lines of treatment, etc.), but the lines won't be indented to show that they correspond only to the patients with acute myeloid leukemia. Then the next lines (in the same level of indentation as the lines above) will say “Has acute lymphocytic leukemia with the following:”. And the lines below will be the criteria for the acute lymphocytic leukemia (has been treated with 3 lines of treatment, does not have Ph+ leukemia, etc.). Then the next bullet points below will say some general criteria for everyone “must sign consent form, must agree to contraception, etc.”. All of these criteria are listed with bullet points in a row with no

difference in indentation or spacing so it's unclear what applies to just people with one disease or another and what applies to everyone

- xii. It would be helpful if it was clearer in the trial descriptions what part of the trial is experimental/investigational and what parts are standard of care. What exactly is being studied should be highlighted somewhere for every trial.

3. History of changes:

a. Works well:

- i. We routinely use the history of changes section to determine if there are pertinent changes made to the trial descriptions that we then need to edit on our website's trial description.
- ii. We appreciate that you can select the date the changes were made
- iii. We appreciate that you can specifically see what was changed within the trial with words either crossed off and in red or added by highlighting them in green
- iv. We appreciate that if a section had no changes made to it, it is blank and show no words. This helps so that you don't have to scroll through sections of text where nothing was changed

b. Potential improvements:

- i. If a section or sentence was copied and pasted elsewhere into the trial description, it would be great if this didn't show up in revisions. For example, submitters will often move information around in the eligibility criteria section. This shows up as crossed off text in red and then the same text will be elsewhere highlighted in green. You have to read through line by line to make sure nothing was changed when it is the exact same information

4. Results:

a. Potential improvements:

- i. Highlight trial results better
- ii. Have patient friendly versions of the results available or link to versions of patient friendly results
- iii. Make it clearer how to access the results

5. Protocols:

a. Potential improvements:

- i. Make it clearer which trials have protocol documents attached/available
- ii. Make it clearer how to access the protocols

- d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We need access to a wide range of studies in terms of study types, intervention types and geographical locations, but we are interested in a limited range of disease types (albeit still relatively broad). We primarily work with disorders that are treatable with hematopoietic stem cell transplant or cellular therapy. As cellular therapies continue to expand, so is our scope, so it's important that we can search for many different diseases and interventions but then narrow that to be specific for any given patient given their age, location, prior treatment, interests, etc.

Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.
- b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
- c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.
- d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you
- e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

We feel very strongly that in order for trials to meet accrual and for patients to continue to want to be involved in clinical research, we cannot create barriers to clinical trial access and participation. Not being able to contact the trial to join or ask questions turns patients and their advocates away. Contact information and whether or not a trial is recruiting needs to be updated and accurate. This should be incentivized by having disclaimers or awards/certificates listed on trials. Trials that do this should be prioritized or listed higher on search results.

Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan

Areas that standardization would be helpful are:

- Drug names - The drug names change or are updated as they move through various trials and there should be a way to tag these trials so that all of the appropriate trials come up when searching for one name versus another

- Encourage submitters to proofread and only include information in one section of the trial description so if there are changes, they don't miss updating them in multiple places - Information about the "arms and interventions" should only be entered in that section (not also in the study description section), the same would go for the eligibility requirements. The ages eligible should not be listed in more than one place as to avoid inconsistencies.
- Encourage data to be entered for how long a cycle is for treatment – an explicit field for this may help as a reminder
- Add an explicit field that describes what is being studied or what part of the trial treatment is experimental/investigational and what is standard of care
 - b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov

Recommend links to other websites where trials are actually updating their contact and recruitment status information. For example, trials may update their own websites but do not update their listing on clinicaltrials.gov. If they could provide a link to where they are actually making updates, this would be helpful.

Submission No.: 212

Date: 3/13/2020

Name: Elly Cohen

Name of Organization: BreastCancerTrials.org

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

We have been actively engaged in the activities led by the American Cancer Society Cancer Action Network (ACS-CAN) focused on addressing barriers to clinical trial participation. This includes our attendance at the January 2019 Trial Matching Summit and participation in follow-up committees that are exploring recommendations set forth from the summit. In an extension of our collaboration with ACS-CAN, we engaged with other stakeholders to discuss the CT.gov RFI and co-signed the joint response. We are also submitting this separate response to amplify the suggestions from ACS-CAN as well as provide further input based on our own experience using CT.gov data as the backbone of our BCT Trial Registry.

We appreciate NLM's request for unsupported, new uses of the CT.gov website as it develops a long-term strategic plan. However, we hope that in this phase of modernization, CT.gov focuses on improving the quality and accuracy of its data as it pertains to current uses and users.

NOTE: As with ACS-CAN, we are a cancer organization and our suggestions come from a cancer-centric perspective. Despite this limitation, we hope our comments can inform the full scope of CT.gov activities.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

- Directory of Resources: It would be a service to its users if CT.gov included a resource section that listed 3rd-party services to assist users seeking trials. This would include links to other clinical trial search or matching engines, such as disease specific applications such as BCT and Metastatic Breast Cancer Trial Search. It could also include educational materials produced by other organizations (such as BCT's Metastatic Trial Talk) and links to advocacy groups that provide supportive services such as trial navigation, insurance counseling, and transportation assistance. This would require internal governance for setting guidelines and vetting applicants.

- Links to 3rd Party Patient-friendly Trial Descriptions: CT.gov trial descriptions include medical and scientific terms that can be overwhelming to consumers searching for trials. The content and layout can even be difficult for providers searching CT.gov at the point-of-care. One solution is to require sponsors to upload patient-friendly trial summaries that adhere to health literacy guidelines.

Alternatively, CT.gov can leverage the work of advocacy organizations such as BCT by allowing them to upload their trial summary content into the relevant CT.gov records. BCT recasts trial descriptions in a

user-tested, patient-friendly format that incorporates literacy guidelines. It can be made easily available as a link embedded in the CT.gov record. The need for patient-centric trial information aligns with RFI responses from both ACS-CAN and PAIR.

- Study Calendar: BCT lists the number of required visits to a research site. Patients have confirmed that this is important to them when evaluating their capacity for travel. We commit a considerable amount of time to this effort. It would be helpful if sponsors were required to post their study calendars or a high-level summary of study visits.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Our main use of CT.gov is to download trial records through its API. Our process is twofold:

1. Query the CT.gov database broadly to identify records containing the search term “breast.”
2. Within those results, apply additional filters that refine the resultant records to those that are most relevant to our users.

For each trial in our database we:

- Curate the text-based eligibility criteria into standardized (SnoMed and Loinc), machine-readable statements that are available for matching.
- Translate the trial title and descriptions into patient friendly language that conforms to a user-tested template and incorporates literacy guidelines. Our descriptions include convenience factors such as number of required study visits and distance from the nearest research site.
- Tag each trial with terms that enable users to filter their trial matching results.
- Integrate trial site locations and contact information.

What works well:

- As the official repository of US clinical research, CT.gov provides access to a wide variety of studies including treatment trials, non-treatment trials, and observational studies, all of which are of interest to our users.
- Availability as a single source of eligibility criteria is essential to our trial curation services that form the heart of our applications.
- Inclusion of sponsor-entered trial content from which we derive our trial summary descriptions.

Suggestions for improving the quality and accuracy of data retrieved through the API:

Structured data input: ACS-CAN recommends that CT.gov enable the ability of sponsors to add structured data to a subset of eligibility criteria and the condition field. As our signature on the ACS-CAN submission states, we strongly support these recommendations and provide the following comments to amplify how these structured data inputs will impact the quality and efficiency of our work.

- Eligibility criteria: ACS-CAN suggests that CT.gov identify a subset of high-impact eligibility criteria that cut across cancer domains and develop a structured, controlled environment for sponsor input. A proposed slate of criteria includes:

- o Cancer Type
- o Cancer Subtype
- o Biomarker Status (may be subtype for some cancers)
- o Stage/Grade
- o # of Prior Therapies Allowed
- o Categories/Names of Excluded Treatments

Currently, we capture eligibility criteria as text through the API. This requires BCT staff to translate each criterion into a machine-readable format. Having even a subset of eligibility criteria available through the API will save time and effort. Even more important, in the process of curating criteria we have to interpret the protocol author's intent, which can be challenging. This can lead to errors, given the inconsistent language in which protocols are written. Having the protocol authors register their own criteria will relay more accurate data for trial matching since the intent will be explicitly captured.

The capture of cancer stage is particularly challenging. Many protocol authors use terms like "advanced cancer" or "locally advanced cancer" as a substitute for stage. While context for these terms may be intuitive to a provider, it is not to a machine, patient, or curator. With structured forms, sponsors will be forced to select all permissible stages for inclusion reducing coding errors based on misinterpretation.

To enhance compliance, we suggest that CT.gov work with sponsors to design and test the structured data forms before putting them into production on PRS registration.

In addition to the subset of structured criteria, we will need continued access to the complete list of eligibility criteria as our matching service acts on criteria beyond the proposed subset.

Therefore, we see the subset of criteria as an addition rather than a replacement for the full text version of eligibility that is currently available on CT.gov.

Lastly, we support ACS-CAN's work to encourage the adoption of a consistent syntax for composing eligibility criteria. This will make curation more accurate and efficient either with NLP or by manual coding, a direction we are actively exploring.

- Condition field: Applying a standardized set of structured data elements to the condition field as suggested by ACS-CAN benefits BCT in several ways:

- o Makes it easier for our automated query to capture relevant trials by simultaneously searching the parent/child hierarchy. This would minimize our need to apply multiple, secondary filters to refine our searches.
- o Make it easier for us to capture trials for which multiple cancers are included, but which do not specifically associate with breast cancer. These include solid tumor, basket, immunotherapy, and brain metastases trials. For example, if the condition field was configured for solid tumors and registrants

selected “solid tumor” from a picklist, they could be prompted to select all acceptable cancers or check a box that automatically associates the record with all cancer domains.

- o In the absence of a structured condition field, we currently work with a patient advocate who conducts manual searches on CT.gov to expose disease agnostic trials that are not identified by our automated systems.

Lastly, as an alternative to asking sponsors to adding structured elements to the condition field, we suggest that CT.gov explore a collaboration with the NCI CTRP program. With the caveat that this would apply only to cancer trials, this arrangement could leverage the indexing that is already being done by NCI’s trained curators resulting in reduced sponsor burden and more consistent indexing. It would also leverage the power of the NCI Thesaurus as an alternative to MeSH for cancer.

- Additional suggestions:

- o Make the fields for “additional MeSH terms” and “sponsor-added keywords” available through the API. Our inability to apply our filters to these fields has led to the omission of relevant trials in BCT, which have to be manually entered.
- o Add values to the Trial Type picklist for multi-arm studies such as basket trials, umbrella trials, and master protocol trials. This will make it easier for patients to find these trials, if their specific disease is not registered as a condition.
- o Requires sites to update their recruitment status more frequently. BCT only lists trials that are actively recruiting. If an active trial is not listed as open and recruiting, we fail to list it for our users; if we include a trial that is closed, users waste time contacting a research site.
- o Enable alerts for when Phase I/II trials (or other expanded cohorts) transition from Phase I to Phase II. Currently it is not possible for us to determine which phase is open and is particularly problematic when each phase has different eligibility criteria. We suggest encouraging sponsors to document when a Phase I/II trial shifts from Phase I to Phase II in its History of Changes. If CT.gov provides a descriptor field within the History of Changes table, which can be shared through the API, we could view these changes in our daily feed.
- o Enable alerts when new arms open/close in precision medicine trials. Once a trial is included in our registry, we are unable to alert our users when new arms open/close via amendments. This is particularly important for patients who are seeking targeted therapies in a disease-agnostic “basket trials.” We suggest the same solution as described above for Phase I/II trials.
- o Improve the quality of trial site information. We suggest more frequently reminding sponsors to update their recruiting sites coupled with a way for users to alert CT.gov when site information is incorrect. To address the inconsistent registration of site names, we suggest that CT.gov consider the possibility of leveraging NCI’s database of organizations, which CTRP staff curate and update.
- o CT.gov may consider a way of alerting patients when a research site collaborates with local providers to minimize travel burden to a research site. Perhaps CT.gov may provide a filter that enables users to view trials in which research sites allow for local care.

- o Provide a feedback loop for API users to contact CT.gov. It's important for CT.gov staff to be alerted to issues re: data quality and suggestions for improvement. While some of these issues can be fixed in-house, others may need to be passed to sponsors. Regardless, CT.gov needs to be informed and track issues related to sponsor registration.

Suggestions for improving the search experience on the CT.gov website:

While we primarily use CT.gov to access data through the API, this positions as a surrogate user of the website. Consequently, the issues/recommendations we put forth as an API user apply to those who manually search on CT.gov. In this section, we offer additional suggestion that were not covered above both from our own experiences and those relayed to us by patient advocates.

- Provide short instructional videos about how to conduct searches on CT.gov.
- On the advanced form, alert users to whether search terms are combined using “and” or “or” operators or provide an option for either.
- Encourage sponsors to upload their informed consent forms and make it easier to find them. These are important documents for patients as they have been vetted by an IRB for accuracy and health literacy. However, on a recent search for informed consent docs, we found only 3 out of 2293 records for metastatic breast cancer had an attached informed consent. Of these only 1 was actively recruiting patients. Moreover, we had to scroll to the bottom of the record to find the document. We suggest that the informed consent should be more prominently displayed, perhaps within a tab that also includes patient-friendly descriptions of the trial and resources.
- Include a feedback loop through which website users can provide input on their online experience.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our organization relies on ClinicalTrials.gov to extract a broad range of studies across the country that are actively recruiting breast cancer patients. These include intervention studies for treatment, symptom management, and quality-of-life as well as observational studies. Once users match to trials, we offer them options to filter their results by specific categories of interest such as immunotherapy. It would be helpful if sponsors could apply tags from a picklist and that these tags would be available through the API.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

We agree with our collaborators at ACS-CAN that CT.gov adopt a machine-readable data standard for eligibility criteria. In addition to considering mCODE™, we suggest it review more mature coding systems such as SnoMed, Loinc, and RxNorm. Whatever system is adopted, we will be able to map to it on our backend.

We also suggest evaluating the NCI Thesaurus as an alternative vocabulary to MeSH for cancer trials. This may require adopting a different ontology for cancer, but given the number of cancer trials on CT.gov it might be warranted, especially if cancer submissions can benefit from work already done by CTRP curators.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

We suggest evaluating the NCI Thesaurus as an alternative vocabulary to MeSH for cancer trials. This may require adopting a different ontology for cancer, but given the number of cancer trials on CT.gov it might be warranted, especially if cancer submissions can benefit from work already done by CTRP curators.

Attachment: RFI CT.gov Modernization_BCT_FINAL.pdf

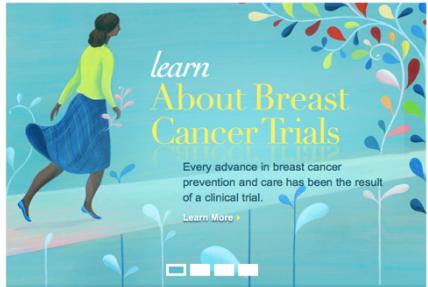
By Electronic Delivery

Patricia Flatley Brennan, RN, Ph.D.
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Re: Request for Information (RFI): ClinicalTrials.gov Modernization

Dear Dr. Brennan:

Thank you for the opportunity to provide input to the RFI for modernization of ClinicalTrials.gov. As a long-term user of the CT.gov API, we at BreastCancerTrials.org are pleased to submit comments based on our experience and in the spirit of helping CT.gov better respond to the needs of the clinical trial community. Launched in 2008, BCT offers a portfolio of direct-to-patient services that educates breast cancer patients



about the potential benefits of clinical trial participation and provides matching tools to help them find trials personalized to their situation. BCT is a program of Quantum Leap Healthcare Collaborative, a non-profit organization whose programs bridge the gap between research and clinical care. It was piloted as a research collaboration between NCI and the UCSF Carol Franc Buck Breast Care Center, with whom it remains closely affiliated.

Built on a non-profit, philanthropic model, BCT does not derive revenue from patient recruitment or monetization of patient data. In 2018, our trusted, non-profit services attracted 80,000 people.

BCT offers four services:

- **BCT Match:** Personalized matching to trials based on a user's self-reported diagnostic and treatment history.
- **BCT Browse:** Searchable access to the BCT Trial Registry via keywords and filters such as Vaccines and Immunotherapy.
- **Metastatic Trial Search (MTS):** A matching engine designed for metastatic breast cancer patients and featured on 23 advocacy group websites.
- **CTMatch API:** Access to our curated registry of trials for use by 3rd parties. We currently support trial matching on the MBC Connect applications sponsored by the Metastatic Breast Cancer Alliance.

RFI: ClinicalTrials.gov Modernization

We have been actively engaged in the activities led by the American Cancer Society Cancer Action Network (ACS-CAN) focused on addressing barriers to clinical trial participation. This includes our attendance at the January 2019 Trial Matching Summit and participation in follow-up committees that are exploring recommendations set forth from the summit.

In an extension of our collaboration with ACS-CAN, we engaged with other stakeholders to discuss the CT.gov RFI and co-signed the joint response. We are also submitting this separate response to amplify the suggestions from ACS-CAN

as well as provide further input based on our own experience using CT.gov data as the backbone of our BCT Trial Registry.

1. Website Functionality. NLM seeks broad input on the [ClinicalTrials.gov](#) website, including its [application programming interface \(API\)](#).

- a. *List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.*

We appreciate NLM's request for unsupported, new uses of the CT.gov website as it develops a long-term strategic plan. However, we hope that in this phase of modernization, CT.gov focuses on improving the quality and accuracy of its data as it pertains to current uses and users.

NOTE: As with ACS-CAN, we are a cancer organization and our suggestions come from a cancer-centric perspective. Despite this limitation, we hope our comments can inform the full scope of CT.gov activities.

- b. *Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.*

- Directory of Resources: It would be a service to its users if CT.gov included a resource section that listed 3rd-party services to assist users seeking trials. This would include links to other clinical trial search or matching engines, such as disease specific applications such as BCT and Metastatic Breast Cancer Trial Search. It could also include educational materials produced by other organizations (such as BCT's Metastatic Trial Talk) and links to advocacy groups that provide supportive services such as trial navigation, insurance counseling, and transportation assistance. This would require internal governance for setting guidelines and vetting applicants.
- Links to 3rd Party Patient-friendly Trial Descriptions: CT.gov trial descriptions include medical and scientific terms that can be overwhelming to consumers searching for trials. The content and layout can even be difficult for providers searching CT.gov at the point-of-care. One solution is to require sponsors to upload patient-friendly trial summaries that adhere to health literacy guidelines. Alternatively, CT.gov can leverage the work of advocacy organizations such as BCT by allowing them to upload their trial summary content into the relevant CT.gov records. BCT recasts trial descriptions in a user-tested, patient-friendly format that incorporates literacy guidelines. It can be made easily available as a link embedded in the CT.gov record. The need for patient-centric trial information aligns with RFI responses from both ACS-CAN and PAIR.
- Study Calendar: BCT lists the number of required visits to a research site. Patients have confirmed that this is important to them when evaluating their capacity for travel. We commit a considerable amount of time to this effort. It would be helpful if sponsors were required to post their study calendars or a high-level summary of study visits.

- c. *Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.*

Our main use of CT.gov is to download trial records through its API. Our process is twofold:

1. Query the CT.gov database broadly to identify records containing the search term "breast."
2. Within those results, apply additional filters that refine the resultant records to those that are most relevant to our users.
3. For each trial in our database we:
 - Curate the text-based eligibility criteria into standardized (SnoMed and Loinc), machine-readable statements that are available for matching.

- Translate the trial title and descriptions into patient friendly language that conforms to a user-tested template and incorporates literacy guidelines. Our descriptions include convenience factors such as number of required study visits and distance from the nearest research site.
- Tag each trial with terms that enable users to filter their trial matching results.
- Integrate trial site locations and contact information.

What works well:

- As the official repository of US clinical research, CT.gov provides access to a wide variety of studies including treatment trials, non-treatment trials, and observational studies, all of which are of interest to our users.
- Availability as a single source of eligibility criteria is essential to our trial curation services that form the heart of our applications.
- Inclusion of sponsor-entered trial content from which we derive our trial summary descriptions.

Suggestions for improving the quality and accuracy of data retrieved through the API:

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The capture of cancer stage is particularly challenging. Many protocol authors use terms like "advanced cancer" or "locally advanced cancer" as a substitute for stage. While context for these terms may be intuitive to a provider, it is not to a machine, patient, or curator. With structured forms, sponsors will be forced to select all permissible stages for inclusion reducing coding errors based on misinterpretation.

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 - Enable alerts for when Phase I/II trials (or other expanded cohorts) transition from Phase I to Phase II. Currently it is not possible for us to determine which phase is open and is particularly problematic when each phase has different eligibility criteria. We suggest encouraging sponsors to document when a Phase I/II trial shifts from Phase I to Phase II in its History of Changes. If CT.gov provides a descriptor field within the History of Changes table, which can be shared through the API, we could view these changes in our daily feed.

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- On the advanced form, alert users to whether search terms are combined using “and” or “or” operators or provide an option for either.
- Encourage sponsors to upload their informed consent forms and make it easier to find them. These are important documents for patients as they have been vetted by an IRB for accuracy and health literacy. However, on a recent search for informed consent docs, we found only 3 out of 2293 records for metastatic breast cancer had an attached informed consent. Of these only 1 was actively recruiting patients. Moreover, we had to scroll to the bottom of the record to find the document. We suggest that the informed consent should be more prominently displayed, perhaps within a tab that also includes patient-friendly descriptions of the trial and resources.
- Include a feedback loop through which website users can provide input on their online experience.

- d. *Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.*

Our organization relies on ClinicalTrials.gov to extract a broad range of studies across the country that are actively recruiting breast cancer patients. These include intervention studies for treatment, symptom management, and quality-of-life as well as observational studies. Once users match to trials, we offer them options to filter their results by specific categories of interest such as immunotherapy. It would be helpful if sponsors could apply tags from a picklist and that these tags would be available through the API.

- 2. Information submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
 - a. *Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.*
 - b. *List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.*

We agree with our collaborators at ACS-CAN that CT.gov adopt a machine-readable data standard for eligibility criteria. In addition to considering mCODE™, we suggest it review more mature coding systems such as SnoMed, Loinc, and RxNorm. Whatever system is adopted, we will be able to map to it on our backend.

We also suggest evaluating the NCI Thesaurus as an alternative vocabulary to MeSH for cancer trials. This may require adopting a different ontology for cancer, but given the number of cancer trials on CT.gov it might be warranted, especially if cancer submissions can benefit from work already done by CTRP curators.

Submission No.: 213

Date: 3/13/2020

Name: Joseph Laakso

Name of Organization: Endocrine Society

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

As noted above, we strongly support opportunities to align reporting activities with existing practices to avoid duplication of effort. For instance, if journals use a clinical trials reporting checklist (e.g., CONSORT) and this either contains or could be made to contain via a more flexible interface, the relevant reporting items such that clinicaltrials.gov could cite or pull this information, that would be an improvement.

Using consensus common data elements (CDE) for outcomes would also be helpful, but we recognize that these are largely field specific. One potential improvement would be the ability to cite relevant CDE standards. If study databases are public or shareable on a more limited basis, we would appreciate being able to link entries as part of the submission process.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We find that the existing features on the website work well for clinical trials with common designs, for example, involving a single drug and a disease outcome. However, in general the site does not work well for the reporting of mechanistic clinical trials or studies evaluating human physiology. Also, studies in rare disorders or others that employ less traditional designs, including, for example, adaptive randomization, are more difficult to enter and entering results is proving most challenging. Also, currently there is no mechanism to easily link to the corresponding published results, that is, data have to be entirely re-entered. The user interface is very challenging to navigate at all stages, as discussed in detail in other sections of our response.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Our members report that the current clinicaltrials.gov interface is challenging for the many different types of study designs that now fall under the definition of a clinical trial. In particular for studies that are not typical clinical trials involving single drugs, our members find that the interface is cumbersome and the tutorials are not adequate. For studies that focus on probing physiology and explore multiple endpoints or outcomes that are not related to lifespan or disease, researchers are required by the

standard clinicaltrials.gov interface to enter outcomes may not correspond with design of the study. Consequently, a great deal of staff time and resources need to be focused on navigating and working out how to report study results on clinicaltrials.gov, including “work-arounds” that make the resulting data less interpretable. Additional templates that offer flexibility for reporting of both the design of studies and the results would be particularly useful. It might also be helpful to have opportunities to provide descriptive results of some studies, and options to refer to publications, if details are contained therein, since peer-reviewed publications are the ultimate goal of these trials. A better process for aligning reporting in the peer-reviewed article and in clinicaltrials.gov would be ideal, for example, laying out criteria for the article that could avoid the need for separate clinicaltrials.gov reporting. That is, if the published article contains certain relevant details, a simple link could suffice.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Funding to support central data entry resources for example via the CTSAs would be helpful. Data entry takes a great deal of time and expertise, and centralized resources would be valuable to more efficiently submit results. In addition, additional staff time or effort is also warranted.

Submission No.: 214

Date: 3/13/2020

Name: Jennifer Prozonic

Name of Organization: Emory University

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**
 - No comments.
 - 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**
 - No comments.
 - 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**
 - The current website is used to adhere to the regulations and policies for ClinicalTrials.gov for investigators at Emory University conducting clinical research.
 - o Improvements could be made to search functionality (e.g., searching for studies by official title often does not render the actual study; only portions of the title will allow for study display, often lending to multiple searches to find the study).
 - o When searching the website to find examples of how certain studies are registered or how outcome measures are described, there is a lot of inconsistency between the standards accepted by the NIH reviewers. Improvements could be made in the consistency and standards for issuing QA review comments as well.
 - o Potential issues exist with transferring of records and the mechanism by which the transfer occurs adds to confusion on the public site. When records are transferred to a different institution, but are not “released” by the

responsible party, the Sponsor listed on the public site remains that of the prior institution. This is problematic as the prior institution cannot access the record and has no control over how well it is maintained. There should be a mechanism to establish the new Sponsor on the public site by the PRS reviewers who are performing the transfer.

- o A log of transferred records separate from deleted records with more details (e.g., date of transfer, etc.) would be helpful.
- o For records that are transferred from one institution to another, a transfer status field on the public site would be helpful.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

- Our use of the system is as an organizational account as an academic medical center for investigators conducting clinical research. The system is utilized for registration and results reporting. No further comments.
- 2. **Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- On the public website, when a study does not have secondary outcome measures or other pre-specified outcome measures, those fields are highlighted in pink on the tabular view of the public site with the words “Not Provided”. The highlight and chosen words imply that the study team is not sharing what these measures are, when it is more likely that the study simply does not have secondary or other pre-specified outcome measures. This concern also applies to the “Publications” and “Collaborators” rows.
- Ability to proactively flag study records with upcoming results that are required to be reported (both applicable clinical trials and NIH-funded clinical trials) at a year, six months, and at results deadline.

- Ability to flag study records (either internally with the organization or with a default system indicator) that will need documents uploaded for adherence to the Common Rule
- Should have a system choice (based on the individual organizational accounts and their use of the system) to whom the mass warning emails are received by (e.g., Emory's warnings should always go to the Responsible Party).
- Easier way to obtain history of transferred records (currently in the "Deleted" section)
- Further standardization between NIH reviewers would be helpful. The consistency of comments, e.g., "advisory" suggestion (up to PI to decide if an edit is needed) should not be changed to "major" issue by another reviewer (to make the change happen) in a subsequent review.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- It would be extremely beneficial to allow interfacing of the ClinicalTrials.gov with different CTMS applications.
- It would also be beneficial to allow for internal notes for the organization and indicators to allow for ways for certain records to be identified for results reporting (e.g., NIH, PCORI, etc.).
- The current system does not identify NIH-funded, interventional studies in a sufficient and user-friendly manner in order to help with reporting. The planning report fields only indicate results information for applicable clinical trials.
- Creation of a tool (when the Responsible Party is an individual) that allows for adding a step prior to the Responsible Party releasing the record for NIH review (a prompt) asking if they are in agreement with the accuracy of the record, etc.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- No comments.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- Inconsistency between records in the system continues to be an issue at times (e.g., when results are submitted and awaiting review, some records are still listed as having “problems” while others do not).
- It would be useful to have an internal PRS component to denote study records that will require results due to the funding source, when studies are not ACTs (NIH defined clinical trials, PCORI, any other circumstance when results are required). This can be an internal field that can be included on the planning report.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

- Information could be displayed as “on time” with latest update notation prominently noted for results, etc.
- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**
- Make more room/ flexibility for the description of variables and measuring units for innovative/highly specialized studies that do not necessarily have clear scales due to the study having pioneering research.
- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**
- No comments.

Submission No.: 215

Date: 3/13/2020

Name: Vojtech Huser

Name of Organization: [Not provided]

Attachment: ctg-comments-person.docx

Request for Information (RFI): ClinicalTrials.gov Modernization

Notice Number: NOT-LM-20-003

Key Dates

Release Date: December 30, 2019

Response Date: March 14, 2020

Issued By

National Library of Medicine (NLM)

Purpose

Introduction

The purpose of this Request for Information is to solicit public input to guide the National Library of Medicine (NLM) in planning infrastructure enhancements aimed at users and submitters of ClinicalTrials.gov as part of a multi-year modernization initiative.

Background

ClinicalTrials.gov is the world's largest public clinical research registry(1) and results database (2), providing information on more than 320,000 clinical studies and over 40,000 results on a wide range of diseases and conditions. More than 145,000 unique visitors use the public website daily to find and learn about clinical studies, resulting in an average of 215 million pageviews each month(3).

ClinicalTrials.gov is maintained by NLM on behalf of the National Institutes of Health (NIH) and enhances transparency across the clinical research enterprise in support of U.S. legal requirements (e.g., 42 CFR Part 11)(4), the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information(5), and other policies, such as those of other U.S. Federal agencies(6)and international entities(7). The potential benefits of registration and results reporting include greater public availability of information about ongoing and completed clinical studies(8). This information may help individuals find and compare clinical studies for which they may be eligible to enroll. Maintaining this database of searchable records of studies and their results helps enhance public trust in clinical research and can:

- honor the contribution of people who volunteer to participate in clinical trials to advance medical knowledge;
- encourage complete, unbiased, and timely reporting of individual studies;
- provide a more complete set of studies to inform medical and other decisions;
- provide insight into the clinical research enterprise to improve study focus, design, and reporting; and
- help funders and researchers identify and address key research needs.

Study sponsors and investigators are responsible for ensuring that their studies listed on ClinicalTrials.gov follow all applicable laws and regulations for the scientific and ethical conduct of research studies in humans. Studies listed on ClinicalTrials.gov are not evaluated by NLM for scientific validity or conformance to ethical, legal, and policy requirements. However, NLM staff conduct a limited quality control review of information submitted to ClinicalTrials.gov for apparent errors, deficiencies, or inconsistencies(9-11).

NLM is embarking on a modernization initiative to update the technological infrastructure underlying ClinicalTrials.gov, enhance its public-facing components, and deliver a modern user experience with a platform and services that continue to accommodate growth and enhance efficiency. We aim to gather information to help maximize the value of ClinicalTrials.gov to its many users, while continuing to provide essential services to support existing legal and policy requirements. This RFI is not intended to modify existing legal and policy requirements for clinical trial registration and results reporting.

NLM will host a public meeting on April 30, 2020, to provide an open forum for further eliciting detailed input on topics of interest identified in responses received through this Request for Information (RFI).

75-Day Comment Period

Comments must be received no later than March 14, 2020.

Submitting Responses

Comments received, including name and affiliation of commenter, will be posted without change after the close of the comment period. Please do not include any proprietary, classified, confidential, or sensitive information in your response.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers to provide support for any ideas identified in response to it. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the U.S. Government shall arise as a result of a response to this request for information or from the Government's use of such information.

Information Requested

NLM is requesting public comment to guide efforts to enhance and better support the users of ClinicalTrials.gov, particularly within the topic areas outlined below. Response to this RFI is voluntary, and

respondents are free to address any or all topics listed below, and other relevant topics, for NLM and NIH consideration:

web

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its

application programming interface (API).

a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

No comments



b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. Link to Pubmed: Current linking is not complete. There are publications in pubmed that contain an NCT in abstract, but are not linked. The current algorithm is linking the first such publication but often does not link all subsequent PMIDs mentioning the NCT

2. Link to IPV:



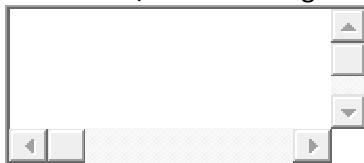
c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I download XML of the trials. The current ability to download is not optimal. A database format of the information is much more convenient for analysis. NLM should directly provide database like download (just like the one provided here <https://aact.ctti-clinicaltrials.org>. Relying on third party for this seems not necessary.



d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

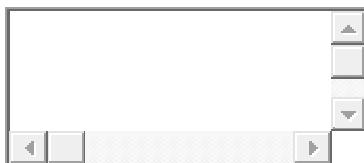
I download/use wide range of studies. I also focus on observational studies and registries.



2. Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

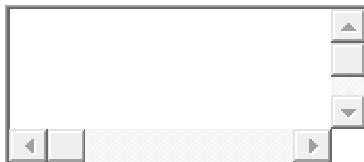
a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Currently, only PDF format for providing additional study artifacts is supported. (e.g., annotated CRFs, study protocol). PDF format is not machine readable and does not satisfy the A in FAIR. It should do a 180degree turn and encourage trial record administrators to submit machine readable format (e.g., .RTF or .DOCX or .HTML for protocol). For example, dbGaP converts all informed consents into HTML to allow standardization across studies in the repository.



b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

CTG should be active in the field of standards for clinical research. It should not introduce own formats (e.g., own XML format for trial) but instead contribute to ongoing efforts to develop international standards (e.g., CDISC CTR-XML). CTG should pioneer adoption of a standard for representing Case Report Forms and Common Data Elements used by a study and support deposit of this data (in results database) using non PDF and standard formats. Even if that standard is CSV file with columns pre-defined. See CONSIDER statement at <http://w3id.org/CONSIDER> for more context.



c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

CTG should adopt a different standard than MeSH for annotating the condition in the trial. Meaningfull use and EHR standards do not use MeSH. Adopting same terminology as for EHR would allow harmonization and compatibility of health data and study registries.

CTG should adopt a formal standard for clinical drug (and other interventions (e.g., device) used in the study as intervention. When providing study registration data, study record administrations should be

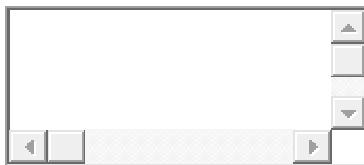
presented with RxNorm terms (NLPed from entered free text). So keep current free text, but simply offer users what terms were detected and allowed advanced users to specify a coded intervention.

CTG should better harmonize registration and results data. For study arms, when submitting results, study record administrator is forced to update registration data (to keep them harmonized). But for other elements (namely reporting of Adverse events), result groups and registration groups can differ. This makes analysis difficult. (see attached emails)



d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

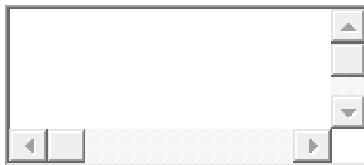
No comments



e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

To increase the quality, CTG can rank current submitters by organization and present this ranking directly on their website. Academic prestige will drive improvements. See 2015 STAT investigation and link here

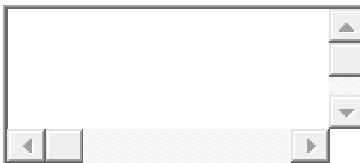
<https://www.statnews.com/2019/11/13/more-results-published-clinical-trials-database-data-quality/>



3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

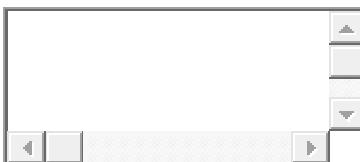
a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Keep current free text option but in many fields, offer advanced users to specify a standard term.



b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

SNOMED CT for conditions and devices and drug ingredients
RxNorm for drug ingredients



References

1. Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on Trial Registration 11 Years after the ICMJE Policy Was Established. *N Engl J Med.* 2017;376(4):383-91 (Available at <https://www.nejm.org/doi/full/10.1056/NEJMsr1601330>).
2. Zarin DA, Fain KM, Dobbins HD, Tse T, Williams RJ. 10-Year Update on Study Results Submitted to ClinicalTrials.gov. *N Engl J Med.* 2019;381(20):1966-74 (Available at <https://www.nejm.org/doi/full/10.1056/NEJMsr1907644>).
3. Trends, Charts, and Maps (Available at <https://clinicaltrials.gov/ct2/resources/trends>).
4. FDAAA 801 and the Final Rule webpage (Available at <https://clinicaltrials.gov/ct2/manage-recs/fdaaa>).
5. NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information; NOT-OD-16-149 (Available at <https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html>).
6. Key U.S. Policies (Available at <https://clinicaltrials.gov/ct2/manage-recs/resources#KeyUSPolicies>).
7. Key International Policies (Available at <https://clinicaltrials.gov/ct2/manage-recs/resources#InternatPolicies>).
8. What Is the Purpose of Trial Registration and Results Submission? (Available at <https://clinicaltrials.gov/ct2/manage-recs/background#WhatIsThePurpose>).
9. ClinicalTrials.gov Protocol Registration Quality Control Review Criteria (Available at <https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf>).
10. ClinicalTrials.gov Results Quality Control Review Criteria (Available at <https://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf>).
11. PRS Guided Tutorials (Available at <https://prsinfo.clinicaltrials.gov/tutorial/content/index.html#/lessons/cMcBAshEQIFPfY3TZmzUrO6y7QS2M2>).

Inquiries

Please direct all inquiries to:

ClinicalTrials.gov Information Team

National Library of Medicine

Email: register@clinicaltrials.gov

Supplementary materials or responses can be submitted via upload. Max file size: 100 MB

Drop files or click here to upload

Please provide the following information, if you wish (optional).

Name

Vojtech Huser

Email Address

Name of Organization

Submission No.: 216

Date: 3/13/2020

Name: Raj Bandaru

Name of Organization: RnD Consulting LLC

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

There are several usecases that CT.gov currently supports partially and could be improved with additional and better data. Some new uses would be in enabling trial simulations, synthetic control arms etc. which cannot be done effectively with the level of data currently available in CT.gov.

Another use case is with respect to patients finding studies to participate or even just following clinical studies, at the moment with the approach of data feeds into CT.gov, the view on clinical trials is static and very few of the studies share site level information, which sites, location etc. to make it accessible to patients.

I also use ct.gov for trial design and feasibility modeling, as well as landscape assessments to support drug development strategy and trial design. All these are partially supported with data from CT.gov now and mostly via other sources, either historical patient level trial data or Real world data sources (EMR/claims).

In addition I think CT.gov can be very valuable to patients looking for studies to decide on trials if one could link and show in the same space SAEs, audit findings for sites etc. I have worked with some clients to develop such augmented ct.gov dashboards that in real time combine and hyperlink to other databases. Synonym searches works okay on CT.gov, but search can be enhanced using Medra/OMIM/Snomed ontologies and ICD-9/ICD10 codes will be a valuable functionality to have. Another area where CT.gov could also help significantly is in improving quality and reducing risk in clinical studies by sharing statistics on risks/findings etc.

Having access to patient level data would be better but I can understand in most cases due to IP and privacy concerns it may not be as easy to share this. Perhaps there are certain data elements like biomarker status, etc. that can be shared at the patient level and will vastly benefit clinical research.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

As mentioned in the previous 1a. Patients searching CT.gov will find it really valuable if they could also see data on how the sites are doing, a little more around the recruitment, and links to reported SAEs/ FAERS database, audit findings and trials issues are important as well. This type of data currently does not really exist and even for sponsors where I do site selection and recruitment optimization we rely on other data sources such as Trinetx, Citeline (Trialtrove), metrics champion consortium etc. Linking other data sources at FDA, NIH into CT.gov can be very valuable and of course the NLM (pubmed).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I recently consulted on the FDA sponsored Rare disease cures accelerator platform initiative for the Critical Path Institute and generated through the CT.gov API, a landscape assessment of clinical studies for the rare diseases and the status of these, the various sponsors working on the different rare diseases etc. This was an interesting exercise that helped them draft the proposals and architect the platform.

Prior to this I also used CT.gov, as head of data sciences at Bill and Melinda Gates Medical Research Institute to identify and assess sites in Africa and understand their performance with respect to latitude (as a correlate of BCG vaccine efficacy). This work helped us to design the clinical study (David Kaufman CMO and Alex Schmidt, CSO).

Prior to this at Sanofi, my team regularly used data from CT.gov for landscape assessments, site selection, feasibility analysis and recruitment optimization etc. More recently I have also been working with the Tufts Center for Drug Development (Prof. Ken Kaitlin and Ken Getz) to explore topics on patient burden in clinical studies and CT.gov has been a very valuable resource.

I have relied on and used CT.gov for several trial design projects when I worked in Pharma (Takeda, Biogen, Vertex, Novartis, AstraZeneca and Sanofi) and also for trial feasibility and optimization analysis for numerous studies.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

As a biostatistician I worked mostly on Ph 1 thru Ph 3 oncology studies (while at Novartis and Biogen), I also worked on other indications at Vertex, Takeda, Sanofi and AstraZeneca. Most of this work was to support trial design and protocol/statistical analysis plan authoring and CT.gov was a valuable resource to understand and compare/benchmark against other studies that were being done.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

When I worked in the pharma, this function was done by our data management and programming teams or contracted out, now I consult to various pharma to help them with data deidentification and redaction. At Sanofi my team developed rules based automated solutions which I have subsequently been developing into more machine learning approaches that can speed up data processing for sharing via CT.gov. If there were some standard online pipelines that allows submitters to process their raw data, interactively gate/mask and select parts of the data they want to share on CT.gov, run some quality checks etc. that will ensure more compliance and more frequent sharing of data from trial sponsors.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

It would be great to enhance the PRS registration to include roles at different hierarchy with more trusted users/ submitters (KOLs, known investigators) who can login and review and submit comments on the studies. At the moment there is no way to annotate submissions with comments from users. Capturing user and patient comments (anonymously) with clinical trials will be a valuable source of data for patient engagement and for sponsors and regulatory bodies to know how trials are progressing and when to intervene. Having KOLs and trusted submitters provide comments on clinical studies will be a great discussion forum and allow more open and broader scientific and ethical discussions on clinical studies. Currently there are a number of clinical studies that are being done with very low ethics oversight, linking to IRB review process will be very valuable.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

At Sanofi my team developed rules based automated solutions which I have subsequently been developing into more machine learning approaches that can speed up data processing for sharing via CT.gov. If there were some standard online pipelines that allows submitters to process their raw data, interactively gate/mask and select parts of the data they want to share on CT.gov, run some quality checks etc. that will ensure more compliance and more frequent sharing of data from trial sponsors.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Currently the most useful information for me is inclusion and exclusion criteria which aren't always available. In addition the sites, planned enrollment is useful for my other use cases. Current CT.gov data is static and provides only a one time update and status of clinical studies. Being able to see more progression on the studies from start up to enrollment and completion, having that timeline view of studies can be very helpful in landscape analysis to show studies that are lagging, having recruitment issues etc. Several sponsors I work with now develop internally or buy (trial networks, gobalto etc.) platforms to do this, but not all sponsors, academic research institutions can afford this. the data is in CT.gov anyways and if we could stand up such a view on the studies it would be very valuable and could potentially be a source of subscription.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

One should be able to see not only the data uploaded by the submitter for any study but also show some statistics on what data has not been loaded, this is something one can easily develop smart machine learning algorithms to predict how much and what data is expected simply based on the trial design and indication and number patients to be enrolled/ enrollment status etc. Showing what was updated in CT.gov, vs what was collected and what was submitted for regulatory submissions can incentivize sponsors to submit more complete information. A periodic conference where high quality and high compliance submitters are recognized and awarded will be another method. In addition for

those submitting data (by volume) an exchange of enhanced access to data and services, input/KOL comments could be incentives to submit data. This could also be barriers to submission, but this can be avoided by submitters opting out during submission for open or public vs private commenting and feedback etc.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

Enforcing standards on users can inhibit the submission, on the other hand as described in 1c. Providing an intelligent and automated data ingestion module that can infer and process/transform/load data will be very valuable to users and ensure high data quality, raise quality queries in real time and generate a quality score associated with each submission. This can be used by users when searching for trials as an additional attribute.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Standards are always evolving and new ones are being created. CT.gov should aim at designing more intelligent, standards agnostic platform that can consume data in any standard. This will not only reduce reporting burden, but also reduce maintenance and effort in validating data on CT.gov. Such a system will also be scalable and extensible to consume new sources in the future very easily.

Submission No.: 217

Date: 3/13/2020

Name: [Not provided]

Name of Organization: Duke University School of Medicine

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- Currently the public site has a History of Changes where a tracked change view is available. Adding this functionality to the PRS would reduce the time it takes to review a record and decrease the potential for errors. Information submission is often a collaborative effort with multiple users entering data into the system. At a minimum it would be very helpful for the Responsible Party to be able to view any changes since the last submission. Ideally, any users on the Access List would be able to view changes since the record was last saved.

o Currently it can take 10-15 minutes to identify which changes have been made when a record is updated and 30 minutes to review changes to results submissions. It is helpful that the RP can view which sections have been changed prior to release, but this has limited utility when a user edits multiple sections. We would expect this time to be significantly reduced

- The “Problems” flagged in the records list is very helpful in identifying study records that need attention. However, there is often a delay in flagging records that meet the “problem” criteria which makes it more difficult for users and administrators to identify and follow-up on problem records.

o For example, if an “anticipated” primary completion date is in the past, there is an Error within the record but the record doesn’t have a “problem” in the problem list. This record is then omitted from some reports, and it won’t be obvious to a user unless they open that specific record.

- Some institutions require an NCT# during the study start-up process. Adding the option to notify PRS Administrators when a new NCT# is assigned (in addition to the RP and Last Updater) would streamline our process and save time.

- Currently the system has a column for “all results expected”, but sometimes there are outcomes due in the interim. Adding due dates for any secondary outcomes with an “anticipated reporting date” to the Planning Report would assist with compliance and reporting.

- The information available in the Document Upload section is very helpful. Adding information about redaction would provide this important information for those not as familiar with the redaction criteria provided in the regulations.

- Managing PRS comments can be complicated, particularly for users not experienced with the PRS. As administrators we often find it helpful to save the PRS Review Comments as a PDF and distribute them to the study team working on the record. The following suggestions would help users navigate this

part of the process (especially for results submissions, which tend to have multiple comments in a module that has multiple sections to navigate):

- o Adding a checkbox or comment field to indicate when a comment has been addressed would be especially useful when multiple users are addressing comments. An alternative suggestion is to include a succinct list of comments within the Results Section so users can easily see what needs to be addressed (in addition to embedding the comments within the record).
- o When PRS Comments are issued for results submissions, it would be easier to review the comments if the results section was at the top of the Review Comments preview (rather than the entire record summary).
- o Occasionally a second round of PRS Comments may be issued that identifies additional comments that were missed during the first review. This creates an inefficient workflow where PIs and statisticians may need to re-review data and update the record again. Errors should certainly be corrected, but it would be more efficient if all comments were listed in the first release of comments.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- The system “notes” that have been added have been very helpful, particularly for infrequent users (for example, the note outlining the information expected for scales in the Outcome Measure description field). Adding similar notes for the Outcome Title in the Protocol Section may help prevent some of the PRS Comments issued for outcome measures during registration.
- The download/upload option for SAEs/AEs has been helpful for some users with a high rate of adverse events. It would also be helpful to have this option available for other modules.

Attachment: CT.gov RFI_Signed.pdf

March 13, 2020

ClinicalTrials.gov Information Team
National Library of Medicine
register@clinicaltrials.gov

Re: Response to RFI: Clinical Trials.gov Modernization NOT-LM-20-003

Thank you for the opportunity to provide feedback on this exciting modernization project.

The Duke Office of Clinical Research provides oversight for the 1700+ studies registered in the Duke University Health System ClinicalTrials.gov account. In addition to providing guidance on related regulation and policy, we also support investigators, regulatory staff, and statisticians with registration, record maintenance, and results submissions in ClinicalTrials.gov. As daily users of the Protocol Registration and Results System (PRS) we are acutely aware of the strengths and limitations of the PRS' administrative functions, and we often receive feedback from our research community who utilize the PRS and public site.

Duke has a strong commitment to research transparency and we consistently encourage our investigators to utilize ClinicalTrials.gov as a method of sharing their research with the public. However, many study teams are not frequent users of the system and the complex regulations and requirements of the system can be overwhelming and time-consuming to navigate. Below we outline some specific enhancements we feel would help increase efficiency and compliance, provide clarity for end users (especially those who are not frequent users), and improve the quality of data provided.

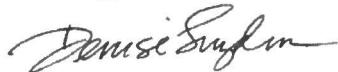
- Currently the public site has a **History of Changes** where a tracked change view is available. Adding this functionality to the PRS would reduce the time it takes to review a record and decrease the potential for errors. Information submission is often a collaborative effort with multiple users entering data into the system. At a minimum it would be very helpful for the Responsible Party (RP) to be able to view any changes since the last submission. Ideally, any users on the Access List would be able to view changes since the record was last saved.
 - Currently it can take 10-15 minutes to identify which changes have been made when a record is updated and 30 minutes to review changes to results submissions. It is helpful that the RP can view which sections have been changed prior to release, but this has limited utility when a user edits multiple sections. We would expect this time to be significantly reduced.
- The “**Problems**” flagged in the records list are very helpful in identifying study records that need attention. However, there is sometimes a delay in flagging records that meet the “problem”

criteria which makes it more difficult for users and administrators to identify and follow-up on problem records.

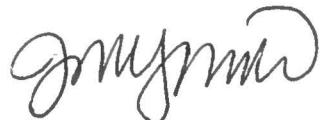
- For example, if an “anticipated” primary completion date is in the past, there is an Error within the record but the record doesn’t have a “problem” in the problem list. This record is then omitted from some reports, and the error is not obvious to a user unless they open that specific study record.
- Some institutions require an NCT# during the study start-up process. Adding the option to notify PRS Administrators when a **new NCT#** is assigned (in addition to the RP and Last Updater) would streamline our process and save time.
- Currently the system has a column for “all results expected”, but sometimes there are outcomes due in the interim. Adding due dates for any secondary outcomes with an **“anticipated reporting date”** to the Planning Report would assist with compliance and reporting.
- The information available in the Document Upload section is very helpful. Adding information about **redaction** would provide this important information for those not as familiar with the redaction criteria provided in the regulations.
- Managing PRS comments can be complicated, particularly for users not experienced with the PRS. As administrators we often find it helpful to save the PRS Review Comments as a PDF and distribute them to the study team working on the record. The following suggestions would help users navigate this part of the process (especially for results submissions, which tend to have multiple comments):
 - Adding a checkbox or comment field to indicate when a comment has been addressed would be especially useful when multiple users are addressing comments. An alternative suggestion is to include a succinct list of comments within the Results Section so users can easily see what needs to be addressed (in addition to embedding the comments within the record).
 - When PRS Comments are issued for results submissions, it would be easier to review the comments if the results section was at the top of the Review Comments preview (rather than the entire record summary).
 - Occasionally a second round of PRS Comments may be issued that identifies additional comments that were missed during the first review. This creates an inefficient workflow where PIs and statisticians may need to re-review data and update the submission again. Errors should certainly be corrected, but it would be more efficient if all items to be addressed were listed in the first release of comments.
- The system “notes” that have been added are very helpful, particularly for infrequent users (for example, the note outlining the information expected for scales in the Outcome Measure description field). Adding similar notes for the Outcome Title in the Protocol Section may help prevent some of the PRS Comments issued for outcome measures during registration.
- The download/upload option for SAEs/AEs has been helpful for some users with a high rate of adverse events. It would also be helpful to have this option available for other modules.

ClinicalTrials.gov has undergone many enhancements in the 8 years since we have centralized our disclosure efforts, and we are grateful for the opportunity to provide input on future improvements to help reach the mission of providing this vital information to the public.

Sincerely,



Associate Dean for Clinical Research



ClinicalTrials.gov Manager

Submission No.: 218

Date: 3/13/2020

Name: Jason Resendez

Name of Organization: UsAgainstAlzheimer's

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

see attached comment letter

Attachment: TrialsGov Comments_UsAgainstAlzheimer's.pdf

UsAgainstAlzheimer's

March 14, 2020

Dr. Patricia Flatley Brennan
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Dear Dr. Brennan -

UsAgainstAlzheimer's (UsA2) is pleased to have this opportunity to provide comments in response to the National Library of Medicine's efforts to modernize ClinicalTrials.gov. Powered by our personal experience and the millions of families touched by Alzheimer's, UsA2 presses for greater urgency from government, industry, and the scientific community in the quest for an Alzheimer's cure—accomplishing this through effective leadership, inclusive collaboration, advocacy, and strategic investments. As part of our commitment to address Alzheimer's disproportionate impact on communities of color, we launched the Alzheimer's Disease Disparities Engagement Network (ADDEN) in 2016 to address disparities in Alzheimer's through culturally tailored brain health promotion, research collaborations, and public policy analysis. ADDEN comprises a national network of research institutions, patients, caregivers, health system stakeholders and community-based organizations.

First, the UsA2 wishes to commend the National Library of Medicine for undertaking a process to modernize ClinicalTrials.gov that has included a wide range of stakeholder input opportunities. This effort is vital given the growing importance for clinical research recruitment to address diseases like Alzheimer's. Alzheimer's research is in dire need of participants, and ClinicalTrials.gov is an essential source of knowledge for research stakeholders, participants, and families.

Improved research, education and literacy is critical for underrepresented communities at greater risk of Alzheimer's. African Americans are at least twice as likely as non-Hispanic white Americans to develop the disease, while Hispanic Americans are 1.5 times as likely.¹ Despite these higher risk profiles, Hispanic Americans and African Americans are less likely to receive a diagnosis from a provider or to participate in research when compared to non-Hispanic whites. With this in mind, UsA2 is pleased to contribute to national and local efforts to diversify participation in Alzheimer's related research. We feel that important changes to ClinicalTrials.gov are needed to promote equitable access to research opportunities for all

¹ Barnes LL & Bennett DA. Alzheimer's disease in African Americans: Risk factors and challenges for the future. Health Affairs (Project Hope) 2014;33(4):580–586. <https://doi.org/10.1377/hlthaff.2013.1353>

communities, including communities who are most comfortable seeking health information in a language other than English. With this in mind, we recommend the following actions be taken to modernize ClinicalTrials.gov

1. We recommend that the ClinicalTrials.gov platform be updated to include a search function that enables users to search for research studies that accept participants in languages other than English. There is currently no way to search ClinicalTrials.gov for trials that enroll non-English speakers. This change would make the platform more user friendly for families seeking research opportunities in their native languages. For example, according to Alzheimer's Disease Centers Latino Special Interest Group, 70 percent of Latino participants enrolled in Alzheimer's Disease Center studies reported Spanish as their primary language.² This data underscores the importance of prioritizing language accessibility across the research enterprise.
2. We recommend the website be translated into multiple languages.
3. We recommend the Library of Medicine review the site language and layout to ensure it is written at a health literacy level (e.g. 4th - 6th grade) that would make the information accessible to the general public across varying degrees of educational attainment.

As we continue to build on the work of ADDEN to address the underrepresentation of racial and ethnic minorities in research, we look forward to working with the National Library of Medicine to advance this mission through public comments and the implementation of changes. ClinicalTrials.gov is a critical portal for the healthcare community to access information on clinical research opportunities and it's vital that this information be accessible to all communities.

Thank you for this opportunity to comment,

Jason Resendez
Co-Lead, Alzheimer's Disease Disparities Engagement Network (ADDEN)
Executive Director, LatinosAgainstAlzheimer's
UsAgainstAlzheimer's

Stephanie Monroe,
Co-Lead, Alzheimer's Disease Disparities Engagement Network (ADDEN)
Executive Director, AfricanAmericansAgainstAlzheimer's
UsAgainstAlzheimer's

² Perales-Puchalt, J., Shaw, A., McGee, J. L., Moore, W. T., Hinton, L., Resendez, J., ... Vidoni, E. D. (2019). Preliminary Efficacy of a Recruitment Educational Strategy on Alzheimer's Disease Knowledge, Research Participation Attitudes, and Enrollment Among Hispanics. *Hispanic Health Care International*. <https://doi.org/10.1177/1540415319893238>

Submission No.: 219

Date: 3/13/2020

Name: Meg Johnson

Name of Organization: UMass Center for Clinical & Translational Science/UMass Medical School

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Example website: www.conqueringdiseases.org - for clinical trial sites to advertise trials to patients, connect them to study teams and analyze the site traffic information. The site provides information on the trials in a very simplified manner. Patients can search for trials and send request to be contacted directly to the study teams.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

-Proactive and Enhanced Notifications: Users recommended updating the system to send proactive notices and reminders for when annual reviews, updates, and results reporting will be coming due. This would also eliminate the need for PRS administrators to develop their own systems to proactively review records and alert Responsible Parties. Enhancements to format and content of system notifications are also requested as they are often overlooked by busy Responsible Parties requiring additional prompts from PRS administrators.

-Identification of Non-ACTs with Results Reporting: Users requested updating functionality to permit them to identify all results reporting requirements for non-Applicable Clinical Trial (ACT) studies. The current system does permit filtering to identify NIH grants, but does not permit sorting to clearly identify the NIH grants that are subject to NIH registration and results reporting requirements. We are requesting adding the ability to flag studies which fall under NIH registration and results reporting policy to enable PRS administrators to more readily identify the registrations for which results reporting will be required.

-Designation and Display of “Problem Records”: Currently, the “Problem Records” report displays all records together, regardless of whether a record is “entry in process” or truly overdue for update, update release, or results reporting. Separation of “in process” records from “Problem Records” would allow local PRS Administrators to focus on true compliance issues, e.g. overdue items, and better determine true compliance rates.

-Enhanced Help Features: The current “help” features contains excellent guidance and information, but we find it is rarely accessed by those doing the entry. As many fields are frequently misunderstood or misinterpreted (see response to Information Submission, below), our institution has moved to use of a separate entry guide to support users. Updating this feature to a “hover over” or similar guidance (e.g. question mark link) at each individual data element would enhance clear understanding of that is being asked and better support End Users.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

NIH-Clinicaltrials.gov Interface to Reduce Duplicate Entry: Users requested an interface between NIH systems and the clinicaltrials.gov registration that would permit import of grant submission information into clinicaltrials.gov, to enhance efficiency and support compliance with NIH policy.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

NIH-Clinicaltrials.gov Interface to Reduce Duplicate Entry: Users requested an interface between NIH systems and the clinicaltrials.gov registration that would permit import of grant submission information into clinicaltrials.gov, to enhance efficiency and support compliance with NIH policy.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

-Access to a standard list or library of common instruments used in outcomes measurement: Adding this feature will provide a consistent standard approach which is beneficial to both institutions and central PRS administrators.

-Flexibility in defining arms and outcomes: Frequently, Responsible Parties and End Users advise that for many studies, the study aims and outcomes may be fluid—particularly with studies containing exploratory aims. End Users often have a difficult time separating aims from outcome and understanding what is expected, especially on the first pass.

--Enhancements to format and guidance on Time Frames: many studies have fluid time frames which do not appear to fit well within the current format or expectations. Updates to format and guidance is requested, especially with regard to non-drug or device trials.

-Outcomes: End Users/Responsible Parties of non-drug/device studies frequently misunderstand what is expected in the Adverse Event reporting requirement.

-Enhancements to better support entry for non-drug/device studies.

-Brief Summary/Detailed Description: In study description, Users often copy and paste information from their grant and/or Informed Consent document to reduce time entering data and do not access the help and definitions. In the end, this frequently creates quality issues in the submission which require additional time to correct. Enhanced guidance on what is expected, or changes to formatting to prompt users to enter more appropriate information, is requested.

-Responsible Party Transfer/Affiliation: Given the fluid nature of Responsible Party affiliation, institutional affiliation and administration of records can be problematic at times—especially with investigator-initiated work where there is no external funding. As registration records are registered under institutional accounts, enhanced rules, guidance and flexibility on record transfer, change in affiliation and account deactivation is requested.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

-Access to a standard list or library of common instruments used in outcomes measurement: Adding this feature will provide a consistent standard approach which is beneficial to both institutions and central PRS administrators.

-Flexibility in defining arms and outcomes: Frequently, Responsible Parties and End Users advise that for many studies, the study aims and outcomes may be fluid-particularly with studies containing exploratory aims. End Users often have a difficult time separating aims from outcome and understanding what is expected, especially on the first pass.

-Enhancements to format and guidance on Time Frames: many studies have fluid time frames which do not appear to fit well within the current format or expectations. Updates to format and guidance is requested, especially with regard to non-drug or device trials.

-Outcomes: End Users/Responsible Parties of non-drug/device studies frequently misunderstand what is expected in the Adverse Event reporting requirement.

- Enhancements to better support entry for non-drug/device studies.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

-Access to a standard list or library of common instruments used in outcomes measurement: Adding this feature will provide a consistent standard approach which is beneficial to both institutions and central PRS administrators.

-Flexibility in defining arms and outcomes: Frequently, Responsible Parties and End Users advise that for many studies, the study aims and outcomes may be fluid-particularly with studies containing exploratory aims. End Users often have a difficult time separating aims from outcome and understanding what is expected, especially on the first pass.

--Enhancements to format and guidance on Time Frames: many studies have fluid time frames which do not appear to fit well within the current format or expectations. Updates to format and guidance is requested, especially with regard to non-drug or device trials.

Attachment: Institutional Reponse to CTGov_AH MJ 2.docx

March 12, 2020

In response to the Request for Information (RFI): Clinicaltrials.gov Modernization (NOT-LM-20-003), the UMass Center for Clinical & Translational Science/University of Massachusetts Medical School (UMMS) submits the following input:

1. **Website Functionality.** NLM seeks broad input on the [ClinicalTrials.gov](#) website, including its [application programming interface](#) (API).
 - a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.
 - b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.
 - c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.
 - d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

UMMS Response: Within our organization, respondents overall commented that the user interface and system is outdated and should be updated to maximize functionality.

Recommendations include:

- **Proactive and Enhanced Notifications:** Users recommended updating the system to send proactive notices and reminders for when annual reviews, updates, and results reporting will be coming due. This would also eliminate the need for PRS administrators to develop their own systems to proactively review records and alert Responsible Parties. Enhancements to format and content of system notifications are also requested as they are often overlooked by busy Responsible Parties requiring additional prompts from PRS administrators.
- **Identification of Non-ACTs with Results Reporting:** Users requested updating functionality to permit them to identify all results reporting requirements for non-Applicable Clinical Trial (ACT) studies. The current system does permit filtering to identify NIH grants, but does not permit sorting to clearly identify the NIH grants that are subject to NIH registration and results reporting requirements. We are requesting adding the ability to flag studies which fall under NIH registration and results reporting policy to

enable PRS administrators to more readily identify the registrations for which results reporting will be required.

- **NIH-Clinicaltrials.gov Interface to Reduce Duplicate Entry:** Users requested an interface between NIH systems and the clinicaltrials.gov registration that would permit import of grant submission information into clinicaltrials.gov, to enhance efficiency and support compliance with NIH policy.
- **Designation and Display of “Problem Records”:** Currently, the “Problem Records” report displays all records together, regardless of whether a record is “entry in process” or truly overdue for update, update release, or results reporting. Separation of “in process” records from “Problem Records” would allow local PRS Administrators to focus on true compliance issues, e.g. overdue items, and better determine true compliance rates.
- **Enhanced Help Features:** The current “help” features contains excellent guidance and information, but we find it is rarely accessed by those doing the entry. As many fields are frequently misunderstood or misinterpreted (see response to Information Submission, below), our institution has moved to use of a separate entry guide to support users. Updating this feature to a “hover over” or similar guidance (e.g. question mark link) at each individual data element would enhance clear understanding of what is being asked and better support End Users.

2. ***Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).***

- a. *Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.*
- b. *Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.*
- c. *Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.*
- d. *Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.*
- e. *Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.*

UMMS Response: We anticipate that NLM and the central PRS staff has conducted or will conduct an analysis of high-volume registration errors and mistakes to target areas for system improvement. Our response is separated into Responsible Party/End User (End User meaning a study team member who is supporting the Responsible Party with PRS registration and reporting) feedback and Institutional PRS Administrator feedback.

- **Responsible Party/End User:** The most frequent feedback we received from our community (Responsible Parties and other End Users) related to:

- Difficulty registering studies with multiple aims, aims with their own primary and secondary outcomes, and/or multiple arms into the current system registration and results reporting parameters—particularly when some aims may be exploratory and fluid. System enhancements and enhanced guidance to better support registration of complex trials is requested.
 - Defining outcomes for qualitative or fluid measures, such as focus groups and informant interviews can be challenging. Greater flexibility or guidance on how to enter these outcomes on registration is requested.
- **Institutional PRS Administrator:** common issues which will benefit from system enhancement include:
 - **Release Process:** Improvement to the review and release process: Responsible Parties will frequently miss the final step of submitting for PRS review. It is reasonable to assume that this step is missed due to the placement of the “submit” button. Revision of the review and release prompts and mechanism is requested.
 - **Alignment of Help and Definitions Features:** As outlined above, End Users often misunderstand what is required at each data element, and do not access the “definitions” or “help” features within the system. Common errors encountered include: Primary/Secondary Completion, Oversight (including FDA applicability as it’s often read as only applying to studies involving an IND/IDE), and Collaborators. Enhancements to these wording and their definitions is requested.
 - **Enhancement to the formatting/labeling of data fields:** Several fields are often missed on first pass by End Users, e.g. Study Official, Secondary ID, Locations. It is reasonable to assume that these fields are missed because of how they are formatted. Enhancements to formatting and wording is requested.
 - **Entry of Outcomes Measures:** Access to a reference list or library of common, validated instruments with the description content as required by clinicaltrials.gov (scale, interpretation of high score, low score) would make results reporting more efficient, and less error-prone, for institutions. Furthermore, entry of timeframe is one of the most frequent errors for our Responsible Parties and End Users. For many studies, it is difficult for study team to convert study outcome timeframes from the protocol to the required clinicaltrials.gov format. Refinement or redefinition of this data element is recommended to reduce frustration for studies which may not fit the standard drug-study mold.

3. ***Data Standards.*** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- a. *Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.*
- b. *List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.*

UMMS Response:

Many of our responses for (2), above, carry through to (3), Specifically:

- **Access to a standard list or library of common instruments used in outcomes measurement:** Adding this feature will provide a consistent standard approach which is beneficial to both institutions and central PRS administrators.
- **Flexibility in defining arms and outcomes:** Frequently, Responsible Parties and End Users advise that for many studies, the study aims and outcomes may be fluid—particularly with studies containing exploratory aims. End Users often have a difficult time separating aims from outcome and understanding what is expected, especially on the first pass.
- **Enhancements to format and guidance on Time Frames:** many studies have fluid time frames which do not appear to fit well within the current format or expectations. Updates to format and guidance is requested, especially with regard to non-drug or device trials.
- **Outcomes:** End Users/Responsible Parties of non-drug/device studies frequently misunderstand what is expected in the Adverse Event reporting requirement.
- **Enhancements to better support entry for non-drug/device studies.**

Additionally:

- **Brief Summary/Detailed Description:** In study description, Users often copy and paste information from their grant and/or Informed Consent document to reduce time entering data and do not access the help and definitions. In the end, this frequently creates quality issues in the submission which require additional time to correct. Enhanced guidance on what is expected, or changes to formatting to prompt users to enter more appropriate information, is requested.
- **Responsible Party Transfer/Affiliation:** Given the fluid nature of Responsible Party affiliation, institutional affiliation and administration of records can be problematic at times—especially with investigator-initiated work where there is no external funding. As registration records are registered under institutional accounts, enhanced rules, guidance and flexibility on record transfer, change in affiliation and account deactivation is requested.

Submission No.: 220

Date: 3/13/2020

Name: [Not provided]

Name of Organization: PRA Health Sciences

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Is it possible to link clinicaltrials.gov with the Mychart system? That way patients could see the clinical trial results from their Mychart portal? Perhaps it would also be a possibility for them to search for clinical trials in which they might be eligible directly from their portal.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

- Advanced search is useful.
- On the public site, the definition icon should be available for all terms, such as masking and primary purpose, as we feel this would help lay readers.
- It's great that the study protocol and SAP are made public along with the results submission, but it is rather difficult to find. If a patient was looking at the trial results, they would have to know to go into the registration record to view the protocol and SAP. It may be better to move these documents to the results section or make them viewable from both the registration and the results tabs.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

- Our primary use of clinicaltrials.gov includes the registration and results reporting of clinical trials on behalf of our clients. One aspect that is difficult is fitting necessary information into registrations for observational studies. Even though this is not required by the final rule, many sponsors have policies that require the registration of observational studies.

- The registration of expanded access studies could be simplified.
- We also use the system for performing portfolio reviews/looking for accepted examples of endpoints to guide current drafting practices (post-final rule).

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- In the adverse events section, it would be useful to have an option that fills out all empty fields with '0'.
- It would reduce time if we could duplicate changes made to an arm title or description throughout the disclosure. There should be an option to copy these changes to other endpoints/ sections of the disclosure.
- A warning message when number of participants is not equal in different sections of the results disclosure.
- Provide the document or criteria the reviewers use to QC disclosures (if it is not the document that is already public).
- Provide an error message once a study is registered and becomes recruiting for Non-IND studies that are missing IRB information.
- Provide a “warning” for missing IND serial numbers.
- Add capability for results (outcome measures) to sort/select fields in a view— for example, for all outcome measures include only endpoint title, reporting groups, number analyzed, analysis population description. This view could be used to compare Ns and analysis population descriptions across the endpoints, to check if they are consistent— extend to include participant flow, baseline characteristics and AEs if possible.
- Increase baseline study-specific characteristic footnote limit to 1000 characters, since usually this is same information that is in outcome measures description (which has limit of 1000 characters).
- In prior version of ClinicalTrials.gov, you were able to start a new search from almost any page. Now it seems you have to “return to list/start over” before you can begin a new search. The old version was better in this respect.
- It would be nice if tips about how to make bullets and sub-bullets were provided in the PRS eligibility section.
- Numbering of outcome measures for 1) PRS data entry view/ClinicalTrials.gov “Study Results” tab versus 2) PRS “preview view”/ClinicalTrials.gov “Study Details” tab (Registration) is not the same, for same record. 1) For PRS data entry and ClinicalTrials.gov Results tab, measures are numbered consecutively beginning with “1” for first primary measure, and continue that way consecutively into and through secondary measures. 2) For PRS “Preview” and ClinicalTrials.gov “Study Details”, after primary are listed (1, 2....), numbering begins again at “1” for first secondary measure. (Based on review of record with Results posted). It might be better if numbering was consistent across views of same record.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- It would reduce time and improve accuracy if AEs could be uploaded via Excel (if saved in a common format). XML requires additional expertise and effort that is not always available. Is this a possibility?

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- Consider adding pre-populated, standard Outcome Measure titles for sponsors to pick from. Implementing this will help ensure uniform endpoint submissions for “standard” endpoints and minimize rejections. Include templated framework/wording for Measure Descriptions for tools/scores-on-a-scale, etc.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

- More detailed review criteria as there seems to be discrepancy from reviewer to reviewer.
- Might be helpful to have the “top 10” most used links/documents grouped together (in addition to wherever else they appear), such as Registration Data Elements, Results Data Elements, Helpful hints, Review Criteria.
- NLM Major Comments List is helpful.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

- Ref ‘Results Submission “Success:” Industry and Non-Industry Orgs’ - it would be useful to have this kind of information more public, maybe a section on the public website.
- Leader boards for different submitters as no financial sanctions are currently being issued.
- Recognition in the “Hot off the Press” blog or NLM daily bulletins.
- Maybe adding a statement in a different color on the public site stating results/registrations were submitted accurately and on time.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

- More guidance for medical writers to help develop writing standard for Protocols/SAPs from a disclosures perspective.
- Is it possible to present data in a graph format? e.g. displaying data from PK endpoints. Would be easier to decipher for a lay reader.

- Possibly NLM could provide example endpoint descriptions for common endpoints, such as PK parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, CL), oncology endpoints (Survival, Time to Progression, Complete Response).

Submission No.: 221

Date: 3/13/2020

Name: Lucia Speroni

Name of Organization: Illumina, Inc.

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The main use is to search for clinical trials on topics of interest. Here are some suggested improvements:

- Create alert for search criteria/study: Currently, an RSS feed has to be set up by the user to receive updates on new study records meeting a search criteria. A preferred system to receive alerts would: (1) allow to create alerts for a search criteria or for a particular study, (2) allow to customize alerts per field, e.g. alert when a new publication was indexed to a study, (3) email updates (see the “Create Alert” feature in Pubmed.gov as an example).

- Advanced search: The fields currently available under “Eligibility Criteria” are “Age”, “Age Group”, and “Sex”. Please consider including a field for “Other terms”.

- 2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

- Include a Column, and corresponding “Filter” in “Advanced Search”, named “Submission Quality”. The system will rank the quality as high, intermediate, or low.

- Enable a feature for users to flag inaccurate/missing information.

Submission No.: 222

Date: 3/13/2020

Name: Brian Alper

Name of Organization: EBSCO Clinical Decisions

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Attached is a description of the Evidence Resource, EvidenceVariable Resource, and Statistic DataType found within the the FAST HEALTHCARE INTEROPERABILITY RESOURCES (FHIR) standard that will be especially useful for repositories like ClinicalTrials.gov to structure data for research results to enable interoperability with other systems for communication of research results.

Attachment: RFI ClinicalTrials-gov Modernization.docx

To the National Library of Medicine

Regarding Request for Information (RFI): ClinicalTrials.gov Modernization, Notice NOT-LM-20-003

We are pleased to share a data standard for the computable expression of evidence and statistics-- highly relevant and suitable for this RFI to improve the management, interoperability, and use of information content for reporting and sharing results data from repositories like ClinicalTrials.gov.

Health Level Seven International (HL7) is a standards development organization. **Fast Healthcare Interoperability Resources (FHIR)** is a standard for health care data exchange, published by HL7. The National Institutes of Health (NIH) is supporting the use of FHIR through multiple initiatives (<https://datascience.nih.gov/fhir-initiatives>), including the NLM's exploration of FHIR-compliant API development for the database of Genotypes and Phenotypes. NIH is encouraging researchers to explore the use of the FHIR standard to capture, integrate, and exchange clinical data for research purposes and to enhance capabilities to share research data.

FHIR has primarily been developed to support the electronic exchange of electronic health data (which may take the form of observations of individual persons such as patients or research participants) and was not previously developed to support the electronic exchange of research results (which may take the form of statistical summaries of data).

In 2017 members from overlapping technology committees in multiple leading organizations in evidence-based medicine communities (Guidelines International Network, Cochrane, and the Grading of Recommendations Assessment, Development and Evaluation [GRADE] Working Group) expressed a desire to work together towards interoperability standards for efforts of research results analysis, systematic review development, guideline development, clinical decision support, and related activities.

In 2018 we recognized FHIR as an ideal standard to enable and support interoperability between the evidence-based medicine and patient care communities. An HL7 project was approved to extend FHIR resources to evidence-based medicine knowledge assets (**EBMonFHIR**), and this project was sponsored by the HL7 Clinical Decision Support Work Group and cosponsored by the HL7 Clinical Quality Information as well as the HL7 Biomedical Research and Regulation work groups.

Our vision is for repositories like ClinicalTrials.gov to structure their data to a universally accepted standard that enables a more rapid uptake of research results in research, policymaking, clinical systems, and decision support.

To achieve this vision, with nearly two years of weekly meetings and five 2-day Connectathons, and active participation from many (including EBSCO Clinical Decisions division of EBSCO Information Services, Johns Hopkins University, University of Colorado, McMaster University, Dynamic Content Group LLC, Duodecim Medical Publications Ltd. [a publisher of the Finnish Medical Society], and MAGIC [a Norwegian non-profit research and innovation program]) we have established a model that can be used to **express evidence and statistics in computable form**.

The **Evidence Resource** structure can be viewed at <http://build.fhir.org/evidence.html> and a simple summary description of this structure can be considered:

1. **Metadata elements**, which can include who created the resource and related artifacts such as journal article citations;
2. **variableDefinition elements**, which include the variableRole (eg, population, exposure, or measured variable), the definition of what was observed, the definition of what was intended, and directnessMatch (an optional element that can be used to express concern when the observed variable does not match the intended variable);
3. **synthesisType and studyType elements**, which can code the type of evidence (eg, meta-analysis of randomized trials);
4. **statistic and distribution** (ordered group of statistics) **elements**, which are described below; and
5. **certainty element**, which provides explicit specification of the certainty of the evidence and reasons for uncertainty.

The **EvidenceVariable Resource** structure can be viewed at <http://build.fhir.org/evidencevariable.html> and supports explicit definitions of the variables using one or more characteristics.

The **Statistic Datatype** structure can be viewed at <http://build.fhir.org/statistic.html> and a simple summary description of this structure can be considered:

1. **statisticType element**, which classifies the statistic (eg, relative risk);
2. **quantity element**, which includes value, comparator (eg, greater than or equal to), and unit of measure;
3. **sampleSize element**, which has subelements to account for variations such as numberOfParticipants and knownDataCount; and
4. **attributeEstimate element**, which can handle many statistics about the statistic (eg, confidence interval, p value, heterogeneity measure).

Furthermore, we have developed a robust information model to support expressions for many types of evidence and statistics. Computable expression with a CodeableConcept datatype is used for many elements across this model, including:

- Evidence.variableDefinition.variableRole
- Evidence.variableDefinition.directnessMatch
- Evidence.synthesisType
- Evidence.studyType
- Evidence.certainty.rating
- Evidence.certainty.certaintySubcomponent.type
- Evidence.certainty.certaintySubcomponent.rating
- EvidenceVariable.characteristic.definitionCodeableConcept
- EvidenceVariable.characteristic.method
- Statistic.statisticType
- Statistic.attributeEstimate.type
- Statistic.attributeEstimate.estimateQualifier.type

We have mapped code sets and value sets to existing statistical ontologies and other resources where available, but this has not been fully mapped before. Ultimately, we will need to add codes and value sets as use cases show the need. For example, when reporting research results it is important to report

the precise scale used for measurement or classification. This could be supported efficiently if the measurement scales are already coded. For an example related to reporting research in stroke care we found the modified Rankin scale has LOINC code (75859-9) but the ASTRAL score does not.

We have also developed data entry forms to enable a researcher to enter data in understandable terms and have it automatically converted to JSON or XML expressions in the FHIR format. We have not yet created this for scaled systems or others not directly working on the EBMonFHIR project. We are currently working on publishing the first instances of computable evidence artifacts.

The EBMonFHIR project is an open project (project website <https://confluence.hl7.org/display/CDS/EBMonFHIR>, open meetings occur on Thursdays at 9 am Eastern) and NLM participation is welcome to adapt and further develop FHIR Evidence and related resources to meet the needs for ClinicalTrials.gov.

Sincerely,

Brian S. Alper, MD, MSPH, FAAFP, FAMIA

Chief Medical Knowledge Officer, EBSCO Information Services

Founder of DynaMed

Lead, EBMonFHIR project

Submission No.: 223

Date: 3/13/2020

Name: Joanne Salcido, PhD

Name of Organization: Pediatric Brain Tumor Foundation (PBTF)

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

I am on the leadership team at the Pediatric Brain Tumor Foundation (PBTF). We use ClinicalTrials.gov in two distinct and important ways. For one, we mine this database to respond to queries by affected families searching for open therapeutic clinical trials for which their child may be eligible to enroll. The results need to be sorted through since the search yields spurious content at times. The goal is to provide a comprehensive list for parents' discussion with the child's medical team. Second, we access ClinicalTrials.gov to better understand and characterize the clinical trial landscape and trends segmented by a number of parameters including enrollment criteria, therapy class, Phase, clinical trial status, geographic location. A primary goal is to help identify areas of relative lack of trial focus or potential areas of logistical improvement for trial collaboration and execution.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

The Pediatric Brain Tumor Foundation (PBTF) is interested in tracking all records that are inclusive of or exclusively for children and teenagers diagnosed with any type of CNS tumor types across the range of therapy types (interventional or observational) and geographical locations. We are also interested in biomarker/diagnostic and quality of life studies (interventional or observational). The detailed analyses of the landscape that we undertake is currently painstakingly laborious. An example of the outcome of such analyses conducted with collaborators at Children's National Health System is submitted herein as a PDF of the poster presented at the 2018 International Symposium on Pediatric Neuro-Oncology (ISPNO). Our analyses would be greatly facilitated if each record had additional classifiers as downloadable fields. Specifically, fields to categorize therapeutic trials by the following key parameters: 1) type of therapy under investigation (e.g., immunotherapy, chemotherapy, targeted therapy (and subtypes), radiation), 2) indication as to whether monotherapy versus combination therapy, 3) number of study sites (e.g., single site, 2-5 sites, 6-10 sites, 11+ sites), 4) whether or not the trial is being conducted through a clinical trial consortium, 5) disease status (newly diagnosed, relapsed/recurrent, both), 6) study Phase, and 7) target enrollment.

Attachment: Clin Trial Landscape_Ped CNS Tumors_ Children's National and PBTF_2018 ISPNO.pdf



Children's National

The current landscape of therapeutic clinical trials in pediatric and adolescent brain tumors

Joanne Salcido¹ PhD, Sandeepkumar Kuril² MD, Eugene Hwang² MD

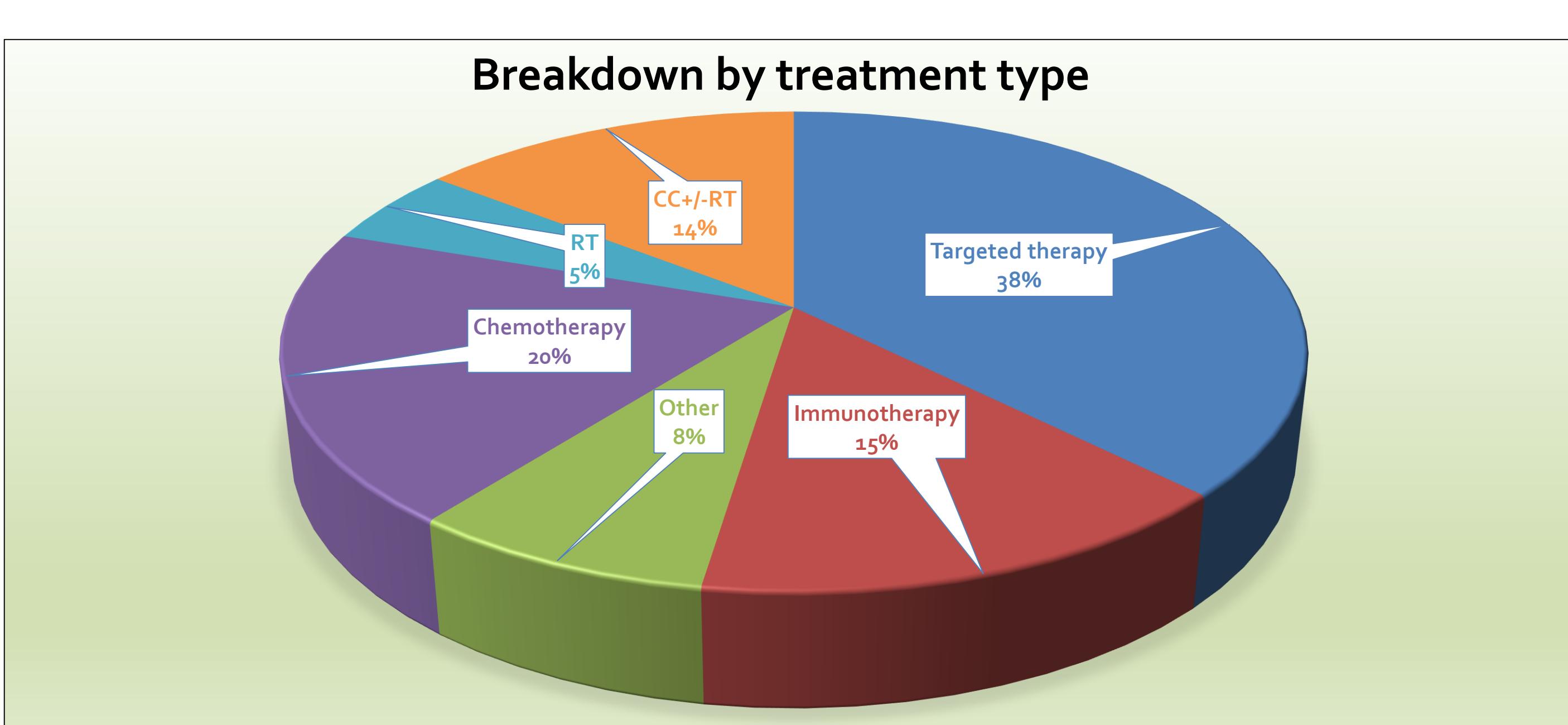
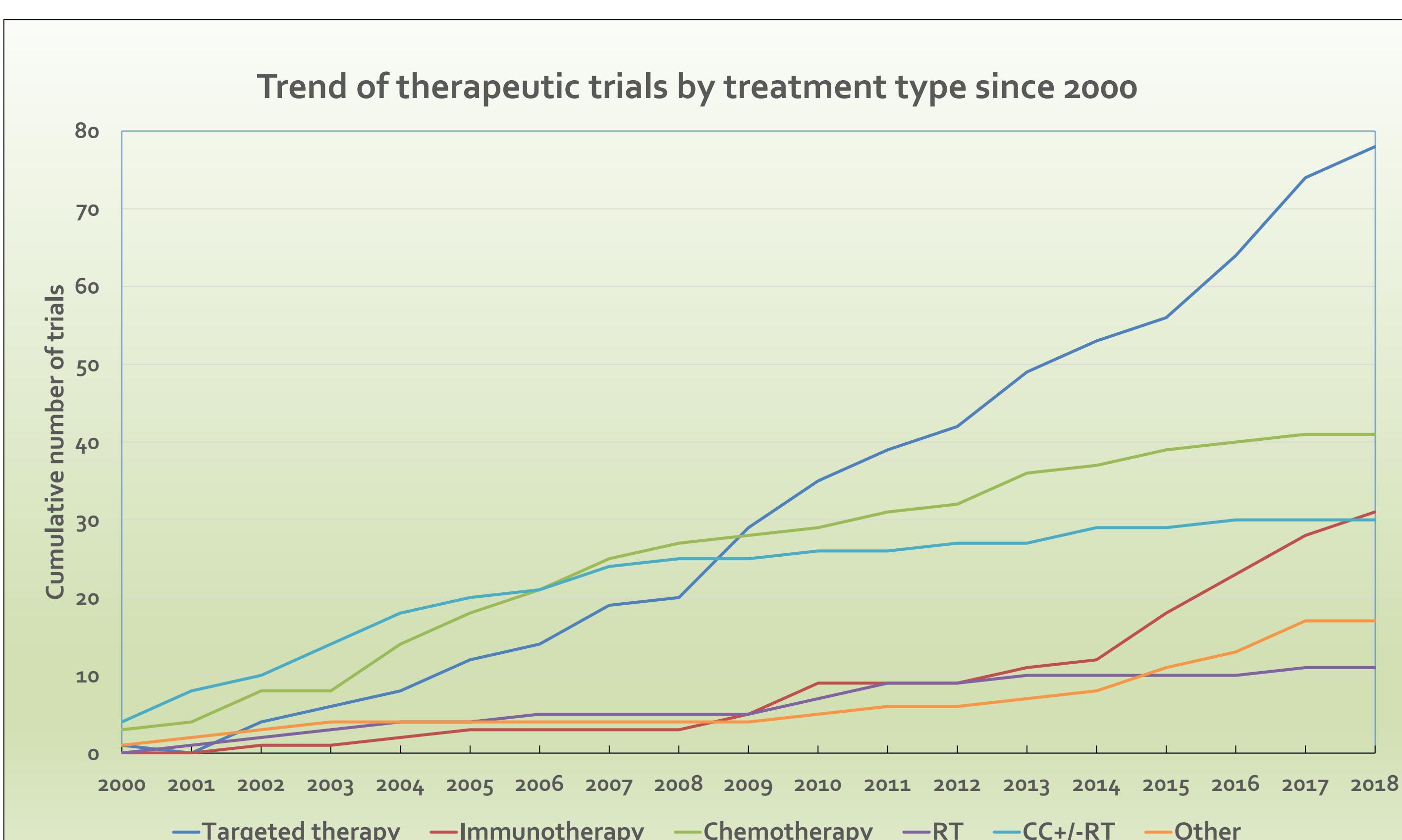
1. Pediatric Brain Tumor Foundation 2. Division of Neuro-oncology, Children's National Health System

Background

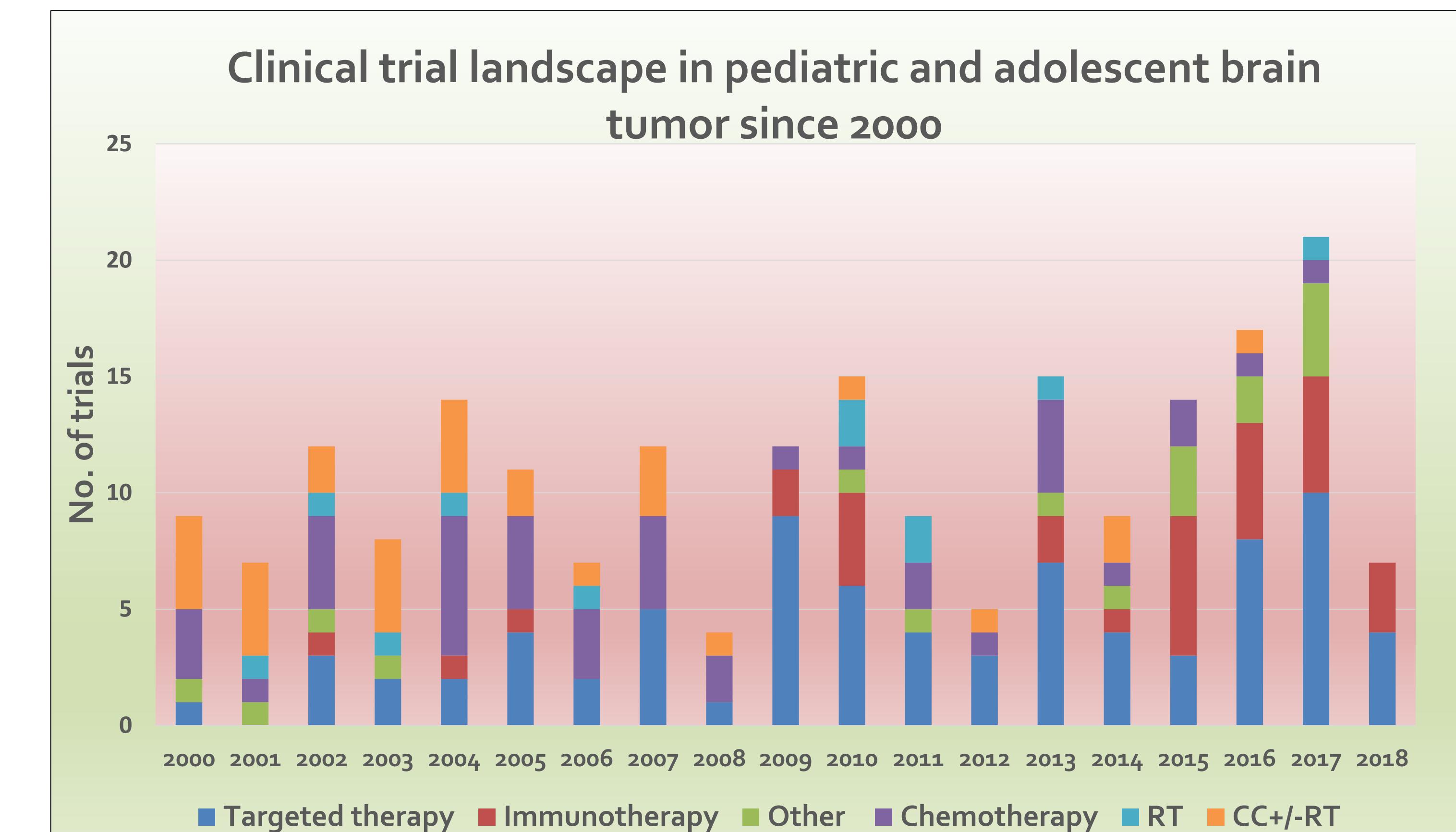
- Despite substantial investment in clinical trials for pediatric brain tumors, significant improvements have been slow for most CNS malignancies. In order to better understand the landscape, we searched records in clinicaltrials.gov for therapeutic trials enrolling children diagnosed with a CNS tumor over the past 18 years (i.e., from January 2000 through March 2018).

Results

- A total of 208 clinical trials were identified.
- They were categorized into
 - a) targeted therapy (n=78, 37.5%)
 - b) immunotherapy (n=31, 14.9%)
 - c) chemotherapy only (n=41, 19.7%)
 - d) radiation only (n=11, 5.2%)
 - e) combination chemotherapy with/w/o radiation (n=30, 14.4%)
 - f) other therapies (n=17, 8.1%).



Results



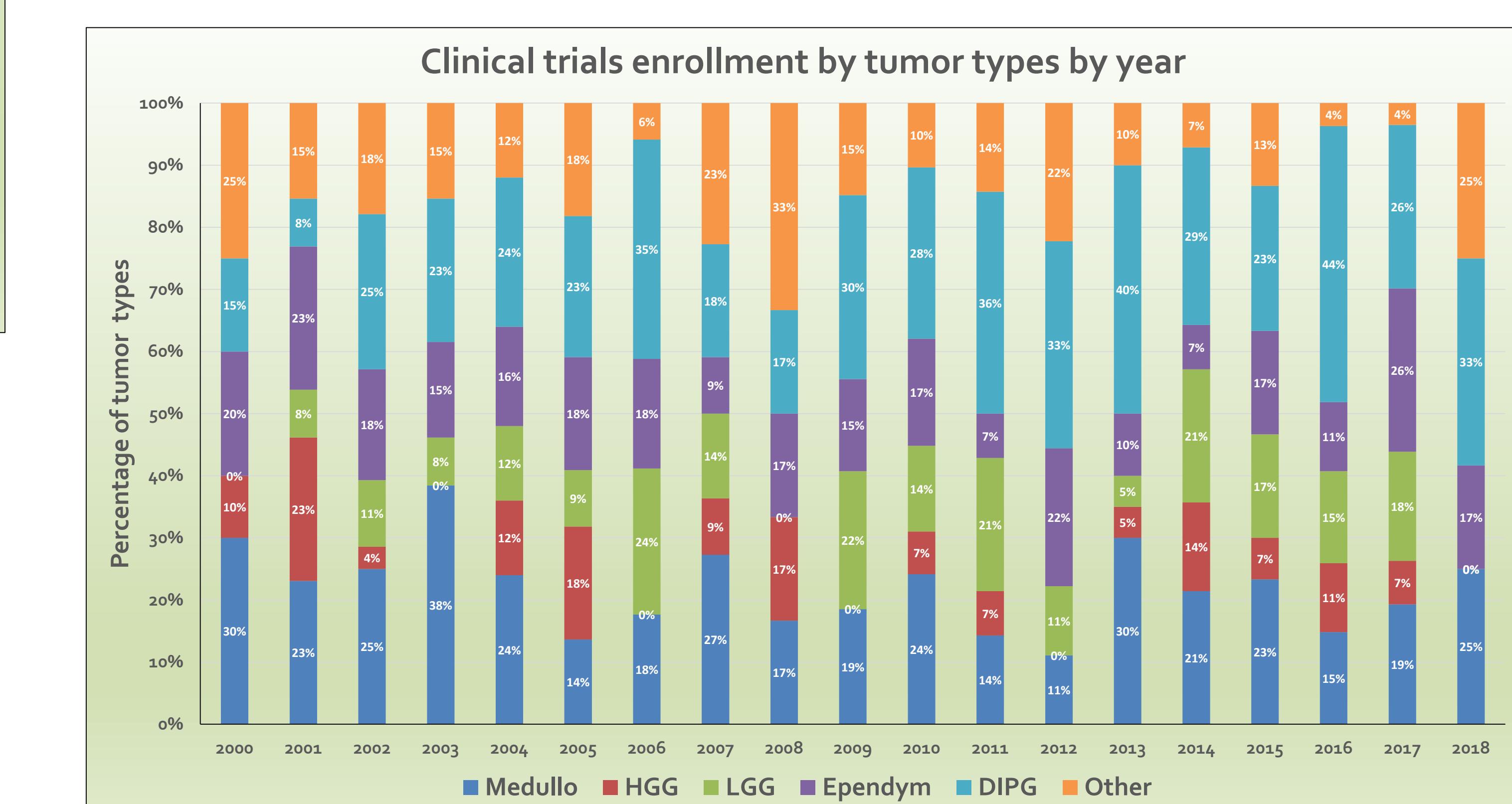
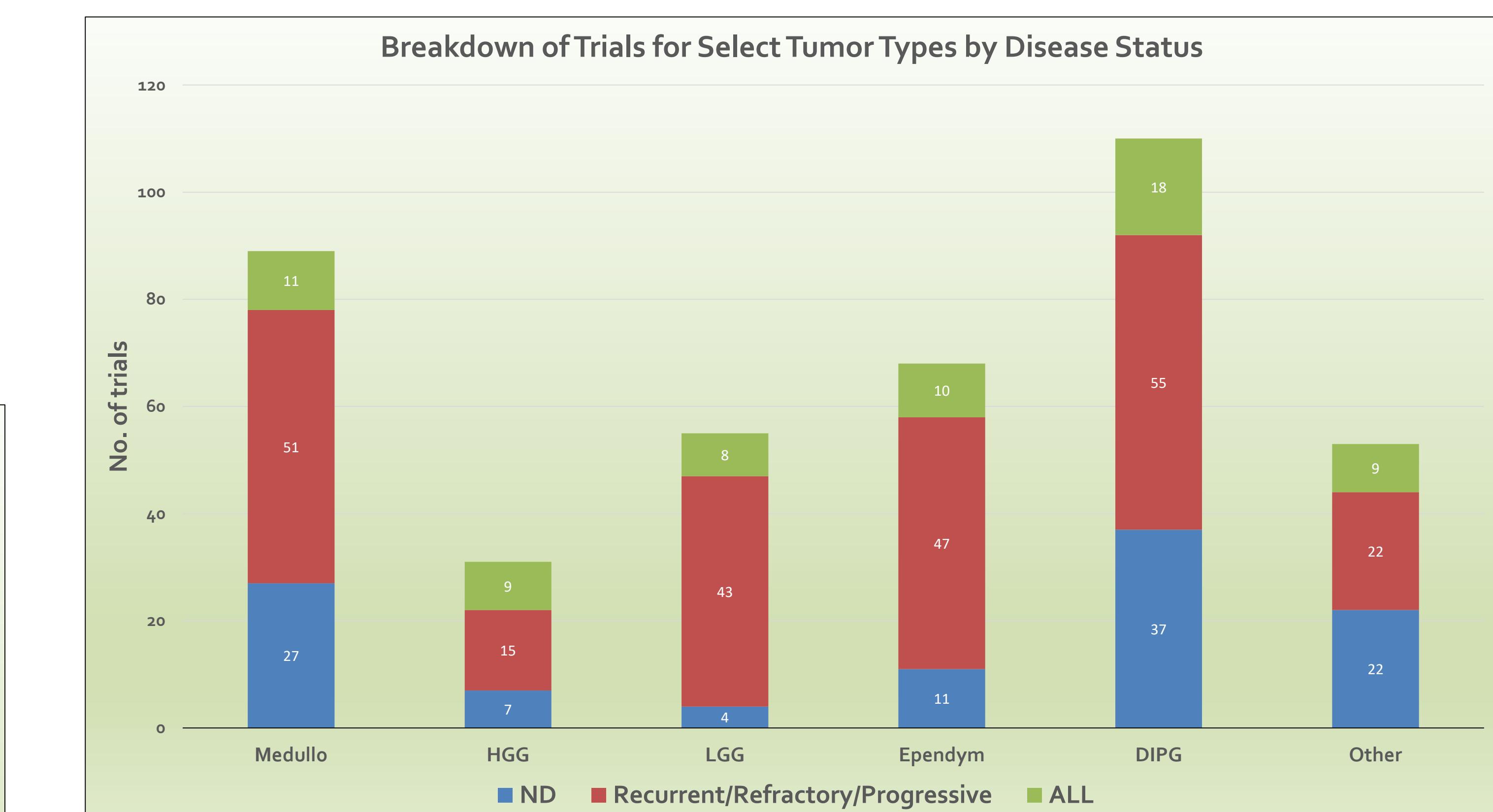
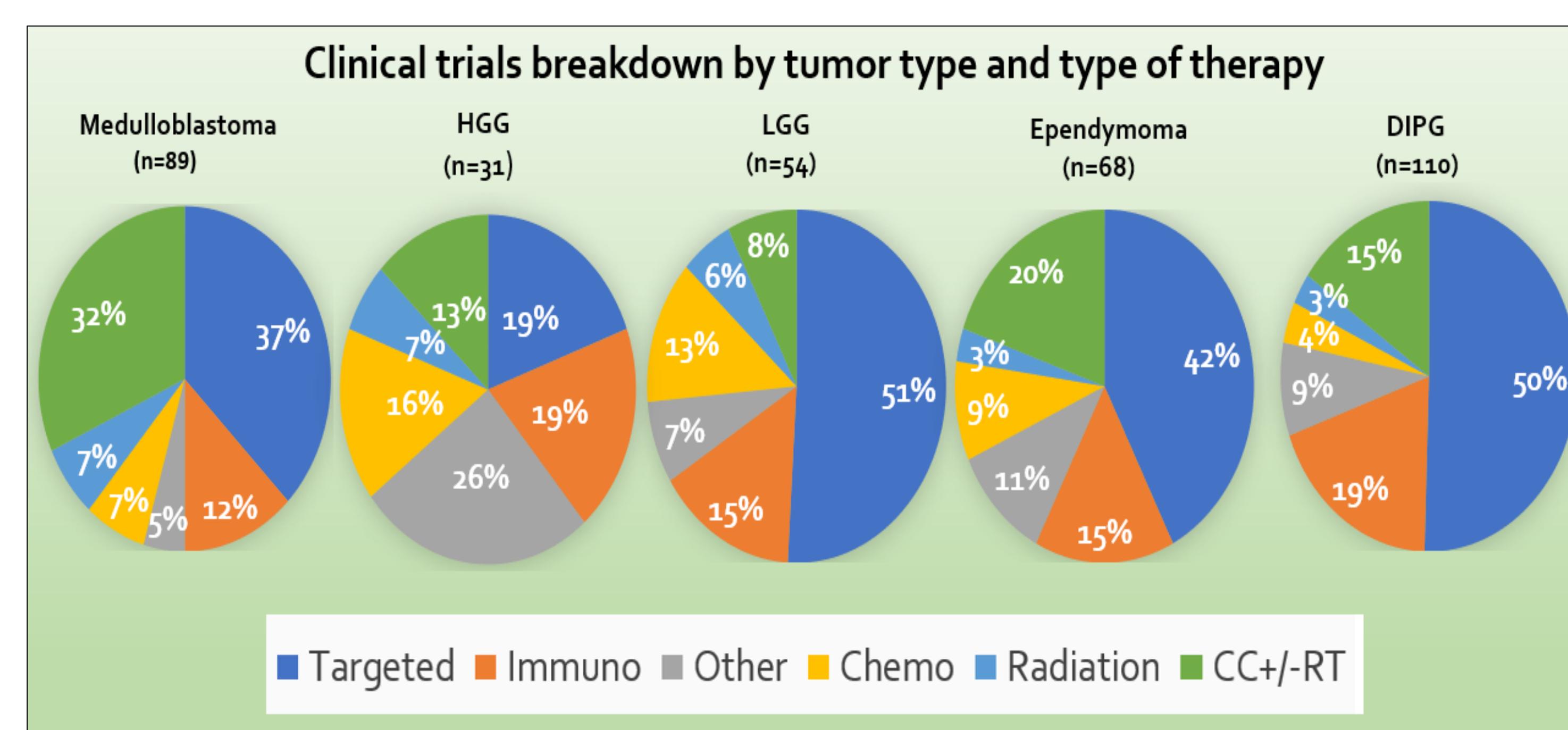
The majority of the trials were:

- Phase 1 (n=90, 40%) or phase 2 (n=103, 45%)
- 40% were conducted through a consortium
- 36%, 13%, 11% and 36% of clinical trials were at a single site, 2-5 sites, 6-10 sites, and ≥ 11 sites, respectively.

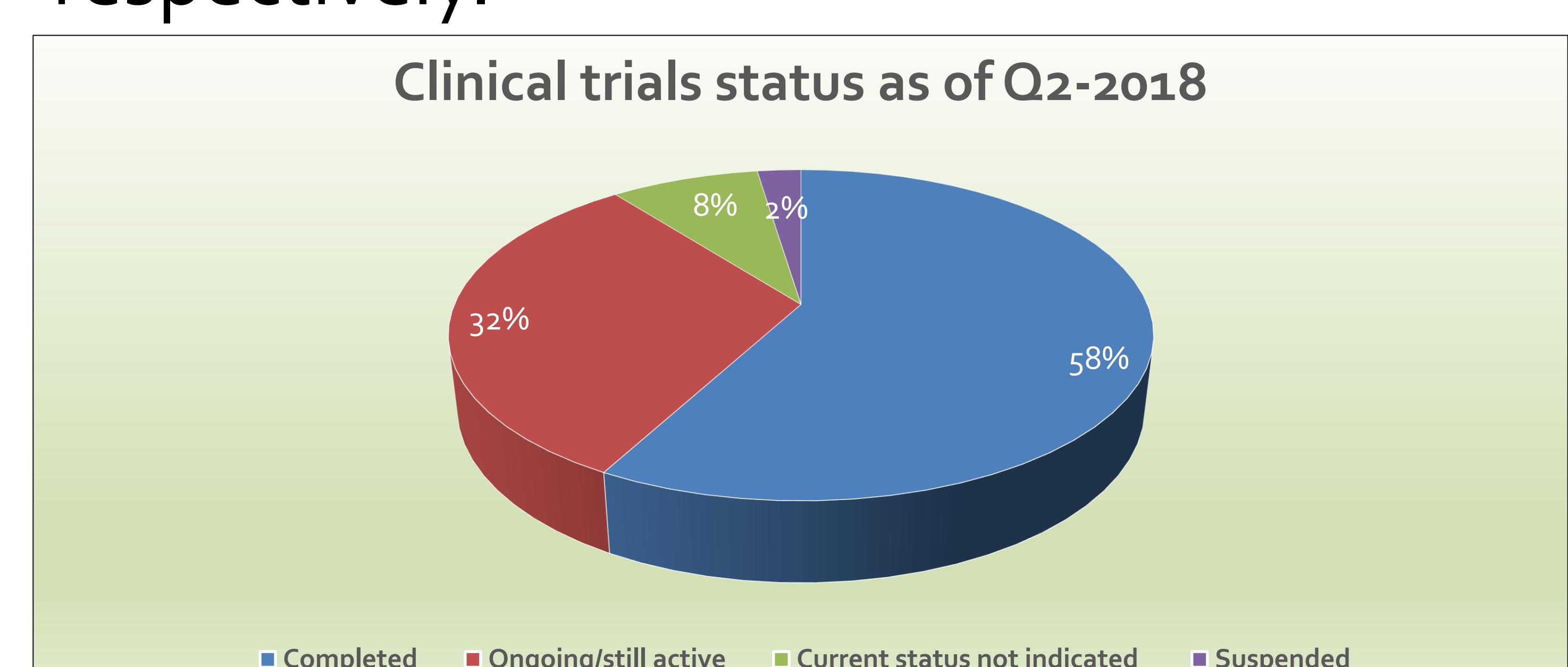
Results

The trials enrolled patients with:

- Medulloblastoma (n=89, 19%)
- High grade glioma (excluding DIPG) (n=31, 21%)
- Low grade glioma (n=55, 12%)
- Ependymoma (n=68, 14%)
- Diffuse intrinsic pontine glioma (n=110, 23%)
- Miscellaneous brain tumors (n=53, 11%) (graph not depicted here)



Clinical trial status (completed, ongoing, not indicated, and suspended) is noted in the below figure. indicated, and suspended, respectively.



Conclusion

- This landscape provides physicians, patients/families and foundations a summary of pediatric brain tumor clinical trials over the past one and a half decades.
- It may help identify areas of relative lack of trial focus or potential areas of logistical improvement for trial execution and collaboration.

Submission No.: 224

Date: 3/13/2020

Name: Jennifer Graff and Richard Willke

Name of Organization: National Pharmaceutical Council and ISPOR

Attachment: NLM ClinicalTrial RFI 031320 final.pdf

March 14, 2020

Dr. Rebecca Williams, PharmD, MPH
Acting Director, ClinicalTrials.gov
National Library of Medicine

Submitted electronically via https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Request for Information: ClinicalTrials.gov Modernization (NOT-LM-20-003)

Dear Dr. Rebecca Williams,

We, the undersigned, applaud ClinicalTrials.gov as it celebrates its 20th anniversary and seeks input on how it may best serve the research community in the years to come as part of the National Library of Medicine roadmap for modernization. Over the past two decades, there has been a growing interest in using data from clinical practice, referred to as real-world data (RWD), as well as transforming these data into real-world evidence (RWE) to inform decision-making. Several federal agency initiatives in the United States provide funding to improve the generation and quality of RWD¹ or to evaluate the potential use of RWE for regulatory or reimbursement decision-making.^{2,3}

In parallel, the types of studies registered on ClinicalTrials.gov have diversified. As of March 5, 2020, over 69,000 studies (21%) are observational studies—a type of RWE.⁴ We commend the inclusion of these studies, however some of these studies have unique characteristics due to the use of secondary data which could make it harder to use the current version of the study registry, but for reasons we enumerate here would benefit from registration. For example, concerns exist that study investigators could change study outcomes, modify inclusion and exclusion criteria, or alter the analytic approaches, ultimately cherry-pick findings rather than publishing results from pre-specified analyses.⁵ Recognizing these challenges, several groups have developed recommendations regarding the transparency of observational studies and specifically hypothesis-evaluating treatment effectiveness (HETE) studies.^{6⁷8} Over the past year, the Real-World Evidence Transparency Partnership, a joint collaboration to establish a culture of transparency for study analysis and reporting of RWE HETE studies, was formed and outlined recommendations.⁹

One of the challenges is the ease of registering HETE studies on existing study registration sites. Study sponsors and investigators of HETE studies must modify study details when submitting information to the Protocol Registration and Results System, increasing the potential for errors and inconsistencies. For example, researchers must determine if the “Study Start Date” field should report the start of the pre-index observation period or the study index date. In other cases, for RWE studies, researchers often have good reasons to evaluate RWD sources prior to study initiation (e.g., to assess the data quality or completeness) or to inform the study design (e.g., feasibility counts, patterns of care, or treatment switching). The ability to describe the degree to which data exploration and analyses were conducted before the pre-specified analysis plan or the rationale for modifications are decided could improve the credibility of the reported findings. Finally, disincentives to register HETE studies exist due to 1) the broad availability of secondary data sources and 2) the ease with which researchers may be able to quickly start a parallel research effort on similar data to get results in a similar timeframe if given enough information. Enabling researchers to select **when** information is released (e.g., immediately, after the study analysis, or after a specified time period) and **which users** (e.g., regulators vs. other researchers) have access at various time points could promote the need for confidentiality and intellectual

property protection while also ensuring transparency. A more fit-for-purpose registration for RWE HETE studies would improve the consistency and accuracy of the information submitted.

The goals of ClinicalTrials.gov modernization and a more fit-for-purpose registration site for HETE studies are not mutually exclusive. While ClinicalTrials.gov was originally designed as a repository for patients to find information regarding clinical trials, the goals outlined for ClinicalTrials.gov apply to all studies.

| Benefits of ClinicalTrials.gov Modernization¹⁰ | Benefits of HETE RWE Inclusion |
|--|--|
| <ul style="list-style-type: none">• honor the contribution of people who volunteer to participate in clinical trials to advance medical knowledge; | <ul style="list-style-type: none">• honor the contribution of people who <i>volunteer data</i> to advance medical knowledge |
| <ul style="list-style-type: none">• encourage complete, unbiased, and timely reporting of individual studies; | <ul style="list-style-type: none">• encourage complete, unbiased, and timely reporting of individual studies; |
| <ul style="list-style-type: none">• provide a more complete set of studies to inform medical and other decisions; | <ul style="list-style-type: none">• provide a more complete set of studies to inform medical and other decisions; |
| <ul style="list-style-type: none">• provide insight into the clinical research enterprise to improve study focus, design, and reporting; and | <ul style="list-style-type: none">• provide insight into real-world clinical research and <i>learning health systems</i> to improve study focus, design, reporting and use in real-time decision-making; and |
| <ul style="list-style-type: none">• help funders and researchers identify and address key research needs. | <ul style="list-style-type: none">• help funders and research identify and address key research needs |

The availability of RWD and the use of RWE to guide decision-making are likely to grow in the next two decades. Broader flexibility to include evolving data sources and study designs such as RWE could streamline the site for investigators and improve the value of the information found on ClinicalTrials.gov for the people who rely on it. The Real-World Evidence Transparency Partnership shares the goals of increasing public trust in research and hopes to continue this critical dialogue. Thank you for the opportunity to provide comments on the Modernization of ClinicalTrials.gov.

Sincerely,

Jennifer S. Graff, PharmD
Vice President, Comparative Effectiveness Research,
National Pharmaceutical Council

Richard J. Willke, PhD
Chief Science Officer
ISPOR

- ¹ The Office of the National Coordinator for Health Information Technology. Draft 2020-2025 Federal Health IT Strategic Plan. Available at: https://www.healthit.gov/sites/default/files/page/2020-01/2020-2025FederalHealthIT%20StrategicPlan_0.pdf. Accessed March 1, 2020.
- ² 114th Congress. H.R.34 - 21st Century Cures Act. Published 2016. Available at: <https://www.congress.gov/bill/114th-congress/house-bill/34>. Accessed March 1, 2020.
- ³ 84 FR 42044. Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals
- ⁴ Trends, Charts, and Maps. Available at <https://clinicaltrials.gov/ct2/resources/trends>. Accessed March 4, 2020.
- ⁵ National Academies of Medicine. Examining the Impact of Real-World Evidence on Medical Product Development: Proceedings of a Workshop Series. February 6, 2019. Available at: <https://www.nap.edu/download/25352#>. Accessed March 1, 2020.
- ⁶ Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1033-1039
- ⁷ National Pharmaceutical Council and Academy Health. Six Ways to Make Real-World Evidence Methods More Transparent. May 20, 2019. Available at: <https://www.npcnow.org/blog/six-ways-make-real-world-evidence-methods-more-transparent>. Accessed March 5, 2020.
- ⁸ Duke Margolis Center for Health Policy. Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision-Making, and Demonstrating Their Credibility. November 25, 2019. Available at: https://healthpolicy.duke.edu/sites/default/files/u31/non-interventional_study_credibility_final.pdf. Accessed March 5, 2020.
- ⁹ ISPOR. Improving Transparency in Non-Interventional Research for Hypothesis Testing—WHY, WHAT, and HOW: Considerations from The Real-World Evidence Transparency Initiative. Draft White Paper. September 18, 2019. Available at: https://www.ispor.org/docs/default-source/strategic-initiatives/improving-transparency-in-non-interventional-research-for-hypothesis-testing_final.pdf?sfvrsn=77fb4e97_6. Accessed March 5, 2020.
- ¹⁰ National Library of Medicine. Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003). December 30, 2019. Available at <https://grants.nih.gov/grants/guide/notice-files/NOT-LM-20-003.html>. Accessed March 4, 2020.

Submission No.: 225

Date: 3/13/2020

Name: Priyesh Ved

Name of Organization: NET ESOLUTIONS CORP. (NETE), an NTT DATA Company

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The NIH Research Portfolio Online Reporting Tools (RePORT) application provides a central point of public access to reports, data, and analyses of NIH research. RePORT updates its links to ClinicalTrials.gov monthly using ClinicalTrials.gov bulk downloads of Other Study ID Numbers (grant numbers).

The NIH Internal Research Portfolio Online Reporting Tools (iRePORT) is an internal NIH reporting portal. Users can combine a variety of widgets showing different facets of an NIH application portfolio that a user is interested in. The Clinical Trials widget shows a list of clinical trials associated to projects in the selected portfolio. It combines data from NIH RePORTER and an NIH RPPR grant system (OD eRA). The widget links to the study record detail page at ClinicalTrials.gov.

The NIH Portfolio Analysis Reporting Data Infrastructure (PARDI) project involves integrating data from multiple Data Sources and grant records into a couple of data stores. The project is organized into modules that roughly align with the data sources. The Clinical Trials (CT) module downloads all available data from ClinicalTrials.gov and loads it into these stores weekly. PARDI supplies its data to other downstream NIH IC systems.

All three projects have been developed under a contract by NET ESOLUTIONS Corporation (NETE) for the Office of Extramural Activities at the National Institutes of Health (NIH) / US DHHS. Brian Haugen (NIH OD) is a business owner for both systems.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The RePORT and PARDI applications download the entire ClinicalTrials.gov data in XML format. While this works well for repopulating Clinical Trials data, it amounts to deletion of the entire data set and repopulating data set from scratch, temporarily bringing the data offline.

Potentially, ClinicalTrials.gov bulk download feature can be improved by offering incremental downloads, that is updates since a particular date.

Additionally, if a system consuming ClinicalTrials.gov needs to do a fuzzy search of ClinicalTrials it has to develop its own capabilities. ClinicalTrials.gov providing an ability to find clinical trials using fuzzy search could improve functionality of downstream systems.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

It is not easy to specify data elements on case report forms— question-value-pairs often called trial items— precisely and consistently, since it requires not only knowledge about the medical domain but also about additional constraints, like conventions of value coding, units of measurement, normal ranges, or conceptual relations. Furthermore, specifying a clinical trial is a concerted effort involving many people with different backgrounds. Physicians initiate a new trial after identifying a new scientific problem, biometrists help to write the study protocol and ensure that all relevant parameters are recorded, database programmers set up a database for storing trial items and consistency rules, and data managers design report forms based on the specification. In order to coordinate that effort a lot of communication is required, especially in academic institutions focusing on noncommercial trials where people involved in specifying a trial often work in different departments. Another issue is the interoperability of software used. As people involved in the process may use different software stacks lacking interoperability there is a risk that changes cannot be propagated and have to be made manually in every single document or program.

Yet another point is that with the clinical problem varying from trial to trial even experienced biometrists will have difficulties in keeping abreast of all items and item variants used. This may lead to incomplete or inconsistent specifications delaying the overall specification process or, even worse, affecting the subsequent analysis of trial results. There are initiatives to define global item libraries (Clinical Data Acquisition Standards Harmonization (CDASH)) or disease-specific local core-data sets, still they cover only a fraction of the required items and lack some semantics, too.

An application of Semantic Web standards to ClinicalTrials.gov can enrich the relational data with standard-based semantic metadata and ontology, enabling rich, reasoning queries on it.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

- 1. Clinical Data Acquisition Standards Harmonization (CDASH):**

<http://www.cdisc.org/standards/cdash/index.html>. The Clinical Data Interchange Standards Consortium (CDISC) is a standard developing organization (SDO) dealing with medical research data linked with healthcare, to “enable information system interoperability to improve medical research and related areas of healthcare”. The standards support medical research from protocol through analysis and reporting of results and have been shown to decrease resources needed by 60% overall and 70–90% in the start-up stages when they are implemented at the beginning of the research process.

CDISC standards are harmonized through a model that is also a HL7 standard and is the process to becoming an ISO/CEN standard.

2. Resource Description Framework (RDF) is a family of Semantic Web (W3C) specifications originally designed as a metadata data model. ClinicalTrials.gov can benefit from Semantic Web technologies in numerous ways. The graph-based model of RDF is much more flexible and conceptually closer to the problem domain than a traditional relational approach (which requires a lot of mapping tables and has few possibilities of explicitly specifying relations or inheritance).

3. Web Ontology Language (OWL) has expressive constructs that allow checking for valid domain and range values (not only primitive data types) without additional programming. It is easily extensible, at least for a knowledge engineer, so that modifications can be made without necessarily recompiling the source code. The availability of reasoners allows checking for inconsistencies and classifying objects based on their properties rather than on explicit statements. Furthermore, the application can support the user in the process of item specification through reasonable assumptions, e.g. that blood pressure should have a measurement unit that is a Pressure Unit.

A very important issue is searching and navigating ClinicalTrials.gov repository. Advanced, and full-text search might not be sufficient. On the one hand, many labels, descriptions and definitions can contain the search string without being conceptually related to the search item. On the other hand, the set of search results can nevertheless be very large. An advanced search interface can combine textual search with semantic search.

Attachment: NETE_NOT-LM-20-003_RFIResponse_13March2020.docx

COVER PAGE

March 13, 2020

ClinicalTrials.gov Information Team

Department of Health and Human Services (HHS) / National Institutes of Health (NIH) / National Library of Medicine (NLM)
8600 Rockville Pike, Bethesda, MD 20894

Email: register@clinicaltrials.gov

RE: Request for Information (RFI): No. NOT-LM-20-003, for “ClinicalTrials.gov Modernization” for HHS / NIH / NLM

To Whom It May Concern:

NET ESOLUTIONS CORPORATION (NETE), an NTT DATA Company, welcomes the opportunity to respond to this Request for Information (RFI): No. NOT-LM-20-003, for “**ClinicalTrials.gov Modernization**,” for HHS / NIH / NLM.

| | | |
|---|-------------------------------------|---|
| 1 | Organization Name | NET ESOLUTIONS CORPORATION (NETE), an NTT DATA Company |
| 2 | DUNS Number | 01-063-9917 |
| 3 | Company Address | 8180 Greensboro Drive, Suite 900, McLean, Virginia 22102 |
| 4 | Authorized Company Point of Contact | Primary: Mr. Priyesh Ved Director Company Address (please see above) Telephone: (703) 893-6383 ext. 212 Fax: (703) 995-4721 E-mail: priyesh@nete.com Secondary: Mr. Mark Pak Director BD and Compliance / Corporate Counsel Company Address (please see above) Telephone: (703) 893-6383 ext. 245 pakm@nete.com |
| 5 | Business Size | Large Business |
| 6 | Socio-economic Status | N/A |
| 8 | Contract Vehicles | <ul style="list-style-type: none">• NITAAC CIO-SP3 Small Business (Contract No. HHSN316201200160W), (5-Year Recertification Date was July 14, 2017, and we are no longer Small Business but classified as OTHER (OTHER THAN SMALL) on CIO-SP3 SB)• GSA IT Schedule 70: Contract No. GS-35F-0526V – SIN 132-51, Large Business• Business and Professional Support Services (BPSS) II contract holder; Contract No. 75N98019D00014• GSA Professional Support Services: Contract No. GS-00F-187CA – select SINs Small Business (Currently Small Business on PSS/MOBIS-AIMS contract awarded July 1, 2015; SB until 5-year Recertification Date is June 30, 2020)• CMS SPARC IDIQ until 2022; Contract No. HHSN-500-2016-00049I |

NETE has provided industry leading organizational management and technology-related consulting services and solutions to government agencies and commercial organizations since 1999. We approach consulting from a multidisciplinary and solution-oriented perspective with a management team that includes subject matter experts (SMEs) from across different sectors to ensure our services and solutions meet our clients' needs and are delivered on-time and on-budget. Simply put, our multidisciplinary and solution-oriented approach, coupled with our highly-skilled and talented workforce, management infrastructure, and competitive rates, position NETE to be the right choice for providing NLM with high-quality and exceptional planning and support services identified in this RFI. Thank you for the opportunity.

Sincerely,

R.H. Suthar

Rahul Suthar,
Chief Operating Officer



NETE Certifications



COMPANY INFORMATION

Established in 1999, NETE provides administrative and technical program support and analysis, web application design, product launch / rollout, operations / logistics support services, Agile methodology, software customization, technical and analytic projects, communications products support services, and a wide range of other IT support services to agencies and NIH Institutes and Centers (ICs) across the Federal Health IT space, including supporting the HHS, NIH, Centers for Medicare and Medicaid Services (CMS), Health Resources and Services Administration (HRSA), Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), National Science Foundation (NSF), General Services Administration (GSA), U.S. Department of Agriculture (USDA), Department of Veterans Affairs (VA), Department of Energy (DOE), Environmental Protection Agency (EPA), and Department of Defense (DoD).

Given the depth and breadth of our knowledge and experience, we are prepared to provide website development and modernization to the National Library of Medicine (NLM). We have forged a solid reputation as a highly responsive and Agile solutions provider in a variety of high-value areas, including technical, logistics, administrative, operational, and managerial requirements. NETE employs a Program Management Methodology (PMM) grounded in the Carnegie Mellon Software Engineering Institute (SEI) Capability Maturity Model (CMM) practices and the project management principles espoused in the Project Management Institutes' (PMI) Project Management Body of Knowledge (PMBOK®).

We are proud to promote this "NETE Experience," through our team of Information Technology (IT) SMEs, led by Program Managers (PMs) and Senior PMs, who consistently elevate metrics to optimize production, maximize efficiencies, and create room for innovation. They bring extensive knowledge, relevant certifications (e.g., Project Management Institute (PMI) Project Management Professional (PMP) certification), and years of successful and proven hands-on experience in program and project development from conceptual planning to completion; hands-on experience and demonstrated ability to provide guidance and supervision to complex management tasks; and proven ability to control schedule, resources, and project funds.

NETE has over 75 active and completed contracts across the Federal Health IT space, including HHS Operating Divisions (OPDIVs) and NIH ICs. Across these contracts we have gained experience in the various task area requirements outlined by NIH in this RFI. Below we present some of our most relevant experience which aligns with these task areas.

Submission No.: 226

Date: 3/13/2020

Name: Nancy Smider

Name of Organization: Epic

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Please see attached document.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Please see attached document.

- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

Please see attached document.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Please see attached document.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Please see attached document.

Attachment: Epic Response to RFI on ClinicalTrials.gov Modernization (NOT-LM-20-003) - Submitted.pdf

March 13, 2020

Submitted electronically at: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Re: Request for Information (RFI): ClinicalTrials.gov Modernization (NOT-LM-20-003)

Thank you for the opportunity to submit input regarding the modernization of ClinicalTrials.gov.

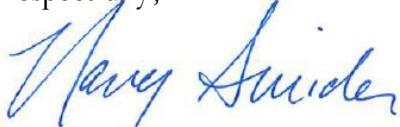
Epic is an electronic health record (EHR) developer based in Wisconsin. We provide the EHR platform for many of the most advanced healthcare research organizations in the United States. We estimate that, when all of our current customers are fully rolled-out, 65-75% of the U.S. population will have an Epic health record. Our software also features tools specifically designed to facilitate research study execution as well as participant recruitment both at the point of care and through our MyChart patient portal.

We are excited that you are undertaking an initiative to update the technological infrastructure underlying ClinicalTrials.gov. Among the numerous potential benefits is the opportunity to increase participation in clinical trials by making it easier for prospective participants and their care teams to identify relevant trials via both self-initiated searches as well as more automated matching toolsets.

Our comments focus on ideas that could make study information in ClinicalTrials.gov more accessible to a broader audience and provide better support for interoperability between ClinicalTrials.gov, EHRs, and research systems. Our extensive experience developing software to help support the research mission of our customers and to enable interoperability not just across clinical systems, but also between clinical and research systems, informs our input.

Thank you for your commitment to modernizing healthcare research in this country. We appreciate your consideration of our comments.

Respectfully,



Nancy Smider, PhD

Director, Research Informatics

Epic

Commentary on NOT-LM-20-003

Below is our input for specific items in the RFI (organized by item). We are not commenting on all items.

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

(d) Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our customer community (U.S. and international) relies on having baseline access to information about a wide range of studies, and the ability to filter them on an array of criteria. We appreciate that ClinicalTrials.gov already contains a number of useful filters. However, it remains a significant challenge to use **study site** as a filter in a systematic way. Today on ClinicalTrials.gov multiple studies performed at the same site often use different variations of their site name making it difficult, for example, to search for all recruiting studies at that site. From the perspective of an individual who might be searching for trials relevant to their condition, being able to filter quickly to studies of interest based on information such as recruitment status and also whether your healthcare organization is an enrolling site would be helpful.

Further, we encourage ClinicalTrials.gov to consider using unique and persistent study site codes (rather than simply relying on free text names). Doing so would better facilitate interoperability of study information between ClinicalTrials.gov and other software systems (<https://www.hl7.org/fhir/researchstudy.html>).

2. Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

(b) Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

We strongly support NLM's desire to improve the interoperability of its platform as part of this modernization initiative. In particular, we encourage NLM to adopt standards-based APIs to support information exchange between ClinicalTrials.gov, EHRs, and research systems.

A number of EHRs, including ours, provide native research functionality including study recruitment and study execution features. NLM should leverage interoperability standards already in use in production environments by clinical healthcare IT systems (EHRs) supporting integrations with clinical trials management systems (CTMSs) and electronic data capture systems (EDCs). Leveraging those standards could enable information exchange between all of these types of systems and ClinicalTrials.gov. Standards-based interoperability would ensure systems can not only consume information from ClinicalTrials.gov, but could also streamline the effort required of researchers to keep information in ClinicalTrials.gov more up to date and accurate (e.g., study status). Specific standards NLM should consider adopting to facilitate more efficient and effective PRS registration and updates include:

- FHIR ResearchStudy resource (<https://www.hl7.org/fhir/researchstudy.html>)
- FHIR ResearchSubject resource (use for ClinicalTrials.gov may be limited)
(<https://www.hl7.org/fhir/researchsubject.html#ResearchSubject>)
- Integrating the Healthcare Enterprise (IHE) Retrieve Process for Execution (RPE)
- Integrating the Healthcare Enterprise (IHE) Clinical Process Content Profile (CRPC)

Although the IHE research interface profiles have been in use for more than a decade to support interoperability between EHRs and CTMSs, a range of platforms are now rapidly adopting research-specific FHIR APIs.

(c) Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

We strongly recommend ClinicalTrials.gov support inclusion of a participant-friendly study title and description approved by an IRB or other appropriate patient-centered review body. Today, most trials contain complex technical formal titles and descriptions, which can be intimidating and confusing to potential participants in search of opportunities. Providing study names and descriptions that are more easily understandable by non-researchers could result in greater participant engagement and interest. Our customer community has reported that displaying audience-appropriate study descriptions in their patient portals increases positive responses to research opportunities from potential participants. Interoperability standards for study information could also be extended so that the participant-friendly titles and descriptions are shareable across systems in addition to the long and short formal titles and descriptions commonly supported today.

An increased focus on participant-friendly study information would reinforce the notion of “community conscious” approach to research information as highlighted in The NLM synopsis of the 2017-2027 Strategic Plan:

“A library is only as effective as the users it reaches. Smart community engagement is therefore critical to assuring NLM’s resources most effectively reach our wide range of audiences —from

librarians to researchers and clinicians, from teenagers to their parents, from policymakers to healthcare professionals.”¹

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- (a) Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specific in the study protocol and analysis plan.

We appreciate NLM’s desire to structure and represent information using existing standards. In particular, alignment with interoperability standards included in ONC’s health IT certification program would rapidly enable data exchange between ClinicalTrials.gov, EHRs, and research systems. Interoperability standards in ONC’s certification program include standard reference terminologies (e.g., RxNorm, SNOMED-CT, LOINC, HCPCS, CPT, ICD-10), all of which have already been heavily adopted in the healthcare space to support clinical interoperability. Additionally, requiring that study submitters specify inclusion and exclusion criteria using the United States Core Data for Interoperability² (USCDI) standard where feasible would be a strong starting point that reinforces harmonization across federal agencies.

We recognize that USCDI will not cover all types of inclusion/exclusion criteria, or the complexity of temporal logic some studies require. To address some of these current limitations, it will also be necessary to optionally extend criteria specification based on domain specific standards (e.g., the Common Oncology Data Elements eXtensions³ – CodeX – recently launched as an HL7 FHIR accelerator) and/or to allow additional free text description until the standards can support this information in computable ways.

Adopting existing interoperability standards, already required by the ONC health IT certification program and widely used in the United States, would provide a robust approach for representing study inclusion and exclusion criteria in a manner that would better support more efficient and cost-effective patient-trial matching.

- (b) List names and references to specific standards and explain how they may be useful in improving data quality, enabling re-use of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

¹U.S. National Library of Medicine. Synopsis of A Platform for Biomedical Discovery and Data-Powered Health: Strategic Plan 2017-2027 (March 2018). Available from: https://www.nlm.nih.gov/pubs/plan/lrp17/NLM_StrategicReport_Synopsis_FINAL.pdf

² <https://www.healthit.gov/isa/united-states-core-data-interoperability-uscdi>

³ <https://www.hl7.org/codex/>

As noted in our prior responses, we believe that leveraging the standards referenced in ONC certification, along with emerging FHIR standards for research, could improve consistency within ClinicalTrials.gov and enable interoperability that would reduce burden on research teams. Adopting these standards could improve the ability of ClinicalTrials.gov to provide useful representations of key data (e.g., codified inclusion/exclusion criteria) and keep key study information (e.g., study status) up-to-date without requiring duplicative manual effort in multiple system by study teams. Specifically, we recommend NLM consider adoption of the following standards in ClinicalTrials.gov:

- USCDI
- CodeX
- FHIR ResearchStudy resource
- FHIR ResearchSubject resource (depending on full range of use cases)

Terminologies:

- RxNorm
- SNOMED-CT
- LOINC
- HCPCS
- CPT
- ICD-10

Submission No.: 227

Date: 3/13/2020

Name: Kathy Riley

Name of Organization: Pediatric Brain Tumor Foundation

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

From the family support perspective:

1. The website functions well but requires a level of scientific sophistication beyond the reach of almost all lay people searching for a clinical trial for a loved one.
2. Consider offering a patient version and a professional version. The National Cancer Institute provides excellent examples of how to carry out this recommendation: see <https://www.cancer.gov/types/brain>
3. Include a simple, introductory paragraph written in lay language on the home page explaining how to make the best use of the site. This would improve patient/family access.
4. Define important terms directly on the home page (see below for examples of essential terms that need to be explained) or make the Glossary of Common Site Terms more visible on the home page:

Study Status - Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, etc.

Study Types - Interventional, Observational, Patient Registries, Expanded Access

Study Phase - Early, Phase 1, Phase 2, Phase 3, Phase 4

5. Define scientific terms within the Glossary definitions instead of using links that require users to open a pop-up menu.
6. The navigation bar at the top of the home page (find studies, about studies, resources, etc.) contains valuable information but is not prominent enough to be noticed.
7. Invite lay people, not just professionals, into the modernization process early.

Submission No.: 228

Date: 3/13/2020

Name: Sandra A. Brown

Name of Organization: University of California San Diego

Attachment: RFI ClinicalTrials.gov Modernization.pdf

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March 13, 2020

Notice Number: NOT-LM-20-003

Release Date: December 30, 2019

Response Date: March 14, 2020

Issued By National Library of Medicine (NLM)

Subject: Request for Information (RFI): ClinicalTrials.gov Modernization

Dear ClinicalTrials.gov Information Team,

The University of California San Diego appreciates the opportunity to comment on the National Library of Medicine ClinicalTrials.gov Modernization Request for Information (RFI), released December 30, 2019.

UC San Diego is one of the largest research institutions in the country, with over \$1.35B in sponsored research funding in the last fiscal year. Of that, over \$495M came from the Department of Health and Human Services. UC San Diego's School of Medicine is the only medical school in the San Diego region and has been named a Top 5 public medical school for NIH funding. UC San Diego has over 670 ClinicalTrials.gov records with more than 800 users, of which 277 are responsible parties under UC San Diego.

Below we provide comments and suggestions that we hope will improve the efficiency, accuracy and quality of ClinicalTrials.gov.

Website Functionality

In addition to registering and updating clinical trials and entering results information for Applicable Clinical Trials as required by federal regulations and other policies, UC San Diego also uses ClinicalTrials.gov to search for similar study types, which allows our research community to see examples of previous studies with similar protocol that have made it through the PRS review system.

UC San Diego uses UCLA's PRS Record Oversight and Compliance Management system (PROCoM) to manage our records. Every night, all data from our PRS system is uploaded into the PROCoM system. The system then allows the UC San Diego administrator to send automated emails based on problem flags to specific records and keeps statistics on the activity of the institution's PRS account. PROCoM

has a variety of functions that make managing and tracking records more maintainable. The ability of PROCoM to allow email communications with the responsible parties and those associated with the records saves administrative time and makes keeping our records in compliance much more efficient.

In the future, it would be helpful to link a study team member to the Open Research Contributor Identification (ORCID) number and profile since ORCID is a subset of the International Standard Name Identified (ISNI) and interoperable with other ID systems.

Information Submission

A few areas where we feel improvements are most needed in the submission process are:

PRS Review:

- *ClinicalTrials.gov assistance:* While the register@clinicaltrials.gov email is a useful tool, there are often questions that need an immediate response. Consider the following suggestions for improvement:
 - Offer assistance by telephone.
 - Provide an online chat function with filtered topics. Complex issues can be directed to the ClinicalTrials.gov email.
 - Offer an option on the website to schedule a teleconference with the PRS team (particularly for complex issues, which will be more expedient than sending emails back and forth).
- *Enhanced clarifications in the ClinicalTrials.gov emails responses:* ClinicalTrials.gov should provide the study team and PRS administrators more detailed responses which outline what needs to happen with a record. For example, when ClinicalTrials.gov sends an email that indicates there are PRS comments, it would be helpful to list either the module the comments are in, the number of overall comments and/or the comments themselves. This will facilitate the researcher response by giving them a snapshot of what the issues are so they can forward or assign to the most appropriate member of their team and streamline the process.
- *Reviewer comments:* Sometimes it is unclear how to view PRS reviewer comments. It is common for a researcher to click the “PRS reviewer comments” section and have it populate in another window. This requires two windows to be open — one with the reviewer comments and one to make the actual changes to the record. It would be helpful to have the reviewer comments populate in the same window where the responses are entered.

Record Management:

- *Never released records:* Our institutional PRS account has some records that are particularly old, dating back to 2012. These records were created, but never approved and released. It would be beneficial if, after a fixed period of time, the PRS system would automatically delete a record that was never submitted for approval and release. This would allow the institution to focus on more significant problem records by cleaning up the records under the institutional PRS account and reducing the number of overall problem flags.
- *Institutional accounts:* It would save time if there were an online mechanism that allowed PRS administrators to transfer records between institutional PRS accounts without having to email ClinicalTrials.gov first.
- *Deleting submitted records:* It would be more efficient and less burdensome on both the ClinicalTrials.gov PRS administration and the institutional PRS administrators if there was an

option for the institutional PRS administrator to delete and unregister a record after the record has gone through a PRS review cycle but prior to an NCT number being assigned.

- *Ability to mark system-identified probable Applicable Clinical Trials (pACTs) as non-Applicable Clinical Trials (ACTs):* The current system automatically identifies trials that may be ACTs as pACTs based on the data elements entered. A manual review by the organization's administrators can confirm that some studies are not ACTs. There is currently no way to indicate that some marked as pACTs are not ACTs, so the records are marked with problems and the system triggers submission of results.

Account Management:

- *Organization PRS administrator functionality:* Like many institutions, UC San Diego has a team of PRS administrators who manage records. The ability to assign or categorize a record to a specific organization administrator would aid in the internal review and follow-up process. It would also be helpful if the organization's administrators could record internal notes that are available to the public or the PRS team for each record so that the review and/or follow-up process is more efficient when a record is subsequently reviewed.
- *Email alerts for change of email address:* Sometimes researchers will leave the institution and not notify the PRS administrator to transfer the record to their new institution. Typically, the researcher will update their email to another institution's email or a personal account, and continue to manage the record while not being associated with our university. Offer the PRS administrator an option to set up an email notification if users under the PRS account change their emails.
- *Read-only access:* Currently, only a history of changes that have gone through a PRS review is available on the public site. Changes that have not been submitted cannot be viewed without record access. Without being on the access list, department administrators or other study team members cannot see pending changes that have not been reviewed. It would be useful to create read-only access for department administrators or other study team members that allows them to see any changes made to the record that may not have gone through a PRS review. This will create a layer of oversight for groups and departments.
- *Record owner:*
 - The PRS administrator is the only person who can currently change a record owner. This poses an issue when record owners leave the institution as most of times study coordinators are the ones who start the study record and are listed as a record owner. When previous record owners are still listed as current, our communications do not reach the necessary parties. We also need a new contact for the study besides the responsible party, otherwise the record remains in noncompliance. It would be helpful if the responsible party could manage their own records and change the record owner themselves, rather than having to reach out to a PRS administrator to make the change.
 - Because only record owners or responsible parties can grant access, we find that some study teams will instead give someone access to act as a record owner. It would be helpful to allow anyone who has access to the record to grant others access as well.
- *Changing passwords:* To help protect user accounts, it would be helpful if ClinicalTrials.gov required new members to change their password at first login.

In order to better align the PRS submission process with our own processes, it would be helpful to allow uploads of major data fields from electronic IRB systems and larger clinical research management suite (CRMS) applications such as Velos or RedCap.

To enhance information quality and content submitted to the PRS, it would be helpful to include an NIH clinical trial identifier like the FDAAA Applicable Clinical Trial (ACT) indicator. Since NIH has a broader definition of what a clinical trial is, it is important researchers are aware that if their study is a clinical trial it may subsequently require the posting of results. Related, the problem flag for “late results” only populates if a study is deemed to be an ACT or probable ACT (pACT), which may exclude certain NIH-funded clinical trials from receiving a notification that they are required to post results. If there was an indication that a study is a clinical trial but not necessarily an ACT or pACT, it would allow more researchers to be notified that results must be published. It would also allow institutions to track records more efficiently, helping to facilitate compliance with the ClinicalTrials.gov entry requirements.

Useful Submission-related Informational Materials:

- The Results Data Entry Modules are extremely helpful to our research community. As a large institution, our researchers conduct complex studies and it is beneficial to have examples of how to clearly outline the participant flow for crossover studies or factorial studies. Similarly, it can be difficult to input the protocol designs as the design may not fit the standard template. It would be helpful if the study design options are expanded to include different studies, such as imaging and observational studies.
- It would be useful to have the ability to include key graphs and images from manuscripts in the results section to aid both the public and research community in understanding the results.
- The definitions link at the top of the website is extremely helpful when trying to determine the best way to enter information, but it is not visible when actually entering the information. It would be good to include the glossary windows like those that are available on the public site next to each key field. The definitions should also include examples.
- One great feature of ClinicalTrials.gov is that the person entering results can copy and paste the pre-specified and approved arms and outcome measures from the protocol section when they are entering results. It would be more helpful, however, if this option was always available and not just when first entering results. Sometimes a party may enter the outcome measures and copy the arms from the protocol section, save the information and then decide to delete the arms and start over. In this instance, they cannot copy the arms from a different section where they had been previously entered. The option to copy arms from other sections of the record should always be available throughout the study results section.

To recognize the efforts of timely submissions, it would be useful to provide an update once or twice a year to PRS administrator with statistics of their accounts. It would be helpful if ClinicalTrials.gov provided the average number of PRS reviews an institution goes through before a record is made public, the average number of days a record is late to publish results for an institution, and the most common PRS comments left on a review for each institution. This data will help PRS administrators provide education and training to their research community.

Data Standards

Rather than requiring data entry by the responsible party, allow them to simply upload the study’s statistical analysis plan and protocol and then have the ClinicalTrials.gov system abstract the applicable

information for each specified field. This would reduce the administrative burden on the researchers and their study teams.

Thank you again for the opportunity to comment.

Sincerely,



Sandra A. Brown, Ph.D.
Vice Chancellor for Research
Distinguished Professor of Psychology and Psychiatry
University of California San Diego

Submission No.: 229

Date: 3/13/2020

Name: Wendy Smith Begolka

Name of Organization: National Eczema Association

Attachment: NEA Comments to NLM NOT-LM-20-003 RFI ClinicalTrialsgov Modernization
SUBMITTED.pdf



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CHIEF EXECUTIVE OFFICER
Julie K. Block

March 13, 2020

Patricia Flatley Brennan, RN, PhD
Director, National Library of Medicine
Bethesda, MD 20894

RE: NOT-LM-20-003; Request for Information (RFI): ClinicalTrials.gov Modernization

Dear Director Brennan,

The National Eczema Association (NEA) appreciates the opportunity to provide input on the modernization of clinicaltrials.gov on behalf of over 31 million U.S. adults and children living with atopic dermatitis and other forms of eczema.¹ NEA is the largest U.S. patient advocacy organization dedicated to raising eczema awareness, promoting education, and supporting innovative research that will yield more and better treatments with the goal of improved patient outcomes. As such, many in the eczema patient/caregiver community turn to NEA for information on treatments in development, the latest science, and on clinical trials. We offer these comments regarding our organizational interaction with the clinicaltrials.gov website as well as suggestions for enhancing its content to more fully address the needs of the eczema community.

The NEA website is visited by over 5.4 million visitors per year and serves as a robust source of information and resources for people affected by eczema. Within the NEA website is a portal listing of eczema clinical trials, available at: <https://nationaleczema.org/research/clinical-trials/>. This webpage is populated and updated weekly using an automated process that retrieves key trial information from clinicaltrials.gov. Our NEA website resource is well-visited averaging 50 people per day in 2019 and supports the need to provide this valued information to eczema community, yet importantly, positions NEA to provide an extended reach for clinicaltrials.gov to individuals that might not otherwise be familiar with or comfortable using it.

Our site's relevance and accuracy rely on the ability to retrieve high quality data from clinicaltrials.gov. We have identified a significant limitation of the retrieved data related to study locations, as this basic information is often listed inconsistently across trials, hindering the ability to display a user/map-friendly address as well as the ability of patients and caregivers to find trials of relevance to them by location. As this data is provided by the clinical trial

¹ Hanifin JM, Reed ML, Eczema P, Impact Working G. A population-based survey of eczema prevalence in the United States. *Dermatitis*. 2007;18(2):82-91.

investigators, we would recommend this field be formatted to require the input of clinical trial site locations in a standardized address format.

We know from focus groups, public meetings, and other feedback from our community that accessibility and convenience are major factors in determining if a clinical trial is appropriate for them. Trial site location is one of the first and critical pieces of information patients and caregivers search for. Enhancing this field as suggested would allow this information to be presented by clinicaltrials.gov and organizations such as ours in a visually helpful way (such as an interactive map), with the goal to facilitate greater patient engagement in clinical trials. As we are experiencing an unprecedented acceleration in drug development and clinical trials for eczema, this singular change can have an immediate impact in dissemination of clinical trial information to potential participants.

While we recognize that the clinicaltrials.gov website must provide information in manner that spans multiple patient/caregiver demographics and disease spaces, we would welcome an opportunity to discuss the value of providing greater specificity to the available clinical trial information in both function and content. As limited research has been conducted to assess eczema-specific clinical trials awareness, attitudes, and motivators and barriers to participation, NEA is currently developing a survey on this topic to administer in Spring 2020. We would welcome an opportunity to share our findings with you to further inform the clinicaltrials.gov modernization efforts. We see this upcoming survey as a unique opportunity to discover eczema-specific clinical trial behaviors, attitudes, and needs, as well as potentially confirm those already noted in the literature that apply to other diseases.

Thank you for the institute's efforts to modernize and improve clinicaltrials.gov, and for considering NEA's comments as part of this process. If we can be of further assistance, please contact Wendy Smith Begolka, MBS, NEA Vice President, Scientific & Clinical Affairs at wendy@nationaleczema.org.

Sincerely,



Julie Block
President & Chief Executive Officer



Wendy Smith Begolka, MBS
Vice President, Scientific & Clinical Affairs

Submission No.: 230

Date: 3/13/2020

Name: Francine Lane

Name of Organization: TrialScope

Attachment: CTGOV RFI Reponse - TrialScope.docx

ClinicalTrials.gov Modernization RFI

Data entry screen: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

1. Website Functionality.

NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

- a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.
1. Provide the ACT flag for Final Rule studies on the public facing ClinicalTrials.gov website and the data download. Researchers, journalists, and industry critics are currently applying their own methodologies to public data to determine disclosure compliance. However, these interpretations can be inconsistent leading to compliant sponsors being marked as non-compliant, and organizations that are struggling with compliance to dismiss assessments that correctly identify problems.
 - a. Consider making the pACT flag for statute studies public as well (on ClinicalTrials.gov and the download). The classification based on public data of trials that fall under the FDAAA statute is more complex and error prone.
 - b. Since publishing the pACT flag identify trials that are ‘probable’ applicable trials, it might be useful to add an accuracy probability (i.e. if key data is missing, then accuracy probability will drop). We understand this is not perfect, especially for older studies. However, various organizations are already publishing their assessments based on public data with less knowledge (and access to additional information) than your team. It would paint a clearer picture for the public of which studies fall under the regulation. You could provide a disclaimer as well.
2. Publish the product approval status on ClinicalTrials.gov – by connecting the NCT numbers listed in form 3674 to the record on ClinicalTrials.gov. Understanding which trials have supported product approvals is of public value and help organizations better manage their results disclosure requirements. For clinical trials of approved products, it would be ideal to include the product approval status and the date of the initial approval of the product of any use.
3. Include the QC cycle count between the ‘study_first_submitted’ and the ‘study_first_submitted_qc dates’ as well as between the ‘results_first_submitted’ and the ‘results_first_submitted_qc dates’. This information would allow establishing QC benchmarks and reduce the number of QC cycles. It is currently already possible (though cumbersome) to derive the number of QC cycles for initial results disclosures based on changes to the public data (tracking the number of submissions cycles and changes to the ‘Results Submitted to ClinicalTrials.gov’ and ‘Results Returned after Quality Control Review’ dates on the ClinicalTrials.gov public site.
 - a. *NOTE: An alternative to adding the cycle information would be to preserve the information that is currently available in trials where results are pending – at least in the data that is These pending results show each submission and return cycle until the results record is made*

public, at which point the information is removed (it would also mean adding this cycle information for the initial study submission)

- b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.
- c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.
- d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

2. Information submission.

NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

1. New API to query the ‘State of the record in PRS’
 - a. Use case
 - i. Query the state of one or more study IDs on PRS
 1. Return State of the record on PRS (In progress, entry completed, approved, released, PRS review, public) for each study
 2. Return date/time of last record release
 3. For each study that has QC Comments (note: some data already available in record download API, but having it available in a lighter API would reduce the need to download entire study XML)
 - a. Return sum of Major comments per study, including 0
 - b. Return sum of Advisory comments per study, including 0
 - c. Return expected due date for comments
 - d. Return URL to view QC Comments
 - e. Return list of QC comments by field/XML context
 4. For each study that does not have QC Comments
 - a. Return message that study has no active QC Comments
 2. New API to validate record data
 - a. Use case
 - i. Submit study record for validation

1. Return validation portion of the upload success API
2. Uploaded changes for validation are not preserved/updated on PRS and cannot be released
3. Include the Release Success/Fail in the Successful Upload Responses when using the API
 - a. Use Cases:
 - i. Study is successfully uploaded without releasing
 1. Upload success is returned with validation messages (as today)
 2. No 'Release successful' message
 - ii. Study is successfully uploaded and released
 1. Upload success is returned with validation messages
 2. Release success message returned
 3. State of the record on PRS (In progress, entry completed, approved, released, PRS review, public)
 - iii. Study is successfully uploaded, and release fails (e.g. due to ERRORS)
 1. Upload success is returned with validation messages
 2. Release failed message returned
 3. State of the record on PRS (In progress, entry completed, approved, released, PRS review, public)
4. New API to get the Release Receipt
 - a. Use Cases:
 - i. Query single record immediately after uploading and releasing
 1. Release receipt PDF with the study ID and date/time (or some other indicator of version)
 - ii. Query one or more records periodically
 1. Release receipt PDF with the study ID and date/time (or some other indicator of version)
5. Add IDs to Location collection so that updates can be made on specific sites
 - a. Facilities:
 - i. <facility>
 - ii. **<facilityID/>**
 - iii. <name/>
 - iv. <address/>
 - v. </facility>
6. Include the ability to upload documents (protocol, protocol & SAP, Informed consent, etc.) in the upload API
 - a. Use Cases
 - i. Upload changed record without documents
 1. Upload record as today
 - ii. Upload changed record with documents
 1. Include documents in API
 2. Return upload success message
 3. Return release success message (if applicable)
 - iii. Upload unchanged record with documents (e.g. update doc versions)
 1. Include documents in API

2. Return upload success message
 3. Return release success message (if applicable)
 7. Add data entry tips on PRS as another category of validation messages rather than within the data entry form UI so they can be automatically returned and up-to-date in vendor systems (see also validation API)
- b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.
- c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.
- d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.
- e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

3. Data Standards.

NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.
- b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Submission No.: 231

Date: 3/13/2020

Name: Francine Lane

Name of Organization: DIA Innovative Clinical Trials Working Group

Attachment: CTGOV RFI Reponse - DIA Innovative Clinical Trials Working Group.docx

1. Website Functionality.

NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

- a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Adaptive clinical trials are not easy to identify, especially if there are multiple studies that are related.

- Ability to search ClinicalTrials.gov on Umbrella, or Master Protocol, etc.
 - Link as keywords
 - Reference to other similar words as many users won't know what words to search
- Create a field for Plain-language Summaries at the top of the Results tab/display (external link), but not to have them intermingled with other general links
 - Possibly with a disclaimer that it is an external link/NLM is not responsible for content – contact sponsor with issue with the link
- Create a prominent place on each page to display the acronym/glossary list. All terms should have hover accessibility each time these terms and acronyms are used. The acronym/glossary list should also be printable, and possibly available at the side of each web page, so it is easy to refer back while reading the content in a study record.
 - There should also be the option to view the Glossary list by letter, or categories to make it easier and more useful. Topics could include categories like body, therapy, type of studies, biomarker, etc.
- *Test at key points with patients, sponsors, clinicians, etc.*

- b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

2. Information submission.

NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

This is a bit general, but many organizations are looking for guidance, preferences, or best-practices on how to register these studies (please see our recommendations on content submission).

Some specific questions that we have discussed are:

- What types of studies are better registered as single studies and which are better as multiple studies (e.g. by study design)
- What are recommendations around timing of results for adaptive studies that are registered as a single study – the Primary Completion Date may continuously get pushed out as the study evolves, but that is not in the spirit of the law.
- Challenges and recommendation to keep the scientific integrity of the study intact while disclosing results sooner.

c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- Recommendations:
 - Ability for sponsors to register and disclose results on adaptive trials as one study or as sub-studies at the sponsor discretion depending on preserving the trial integrity as needed
 - Identify adaptive clinical trials as a separate 'type' with sub-types (similar to EAP) – that are searchable on the ClinicalTrials.gov website
 - Example: Type = Adaptive
 - Subtype to refine such as (in screen shot below, Master Protocol would be below Interventional)
 - Master Protocol – Umbrella or
 - Master Protocol - Platform or
 - Master Protocol – Basket or
 - Master Protocol - Hybrid

- o Indication if registration as single or multiple studies
 - A way to link master and sub-studies – possibly similar to expanded access trials (if registering as separate studies)
 - Register the ‘screening’ protocol in a way that **doesn’t require results or sites** (currently, it is difficult to register an interventional screening protocol in a way that doesn’t require results (Currently, using N/A for intervention/Phase, or submitting screening protocol as an observational trial are the options that have been identified, but don’t seem to be a great option in all cases)

Example to Facilitate Search for Adaptive Trials

In the **Study Type** of the **Advanced Search**: Have a Type = Adaptive Study (Master Protocol) and under Interventional Studies have sub-types which have Umbrella, Platform, Basket

Current on CTgov

The screenshot shows the CTgov search interface with the following search parameters:

- Condition or disease: [empty input field]
- Other terms: [empty input field]
- Study type: All Studies (highlighted in yellow)
- Study Results: All Studies (highlighted in blue)
- Status: Observational Studies
 - Patient Registries
 - Expanded Access Studies

Recommended Changes in Red

Study Type:

Interventional Studies (Clinical Trials)

--**Basket**

--**Platform**

--**Umbrella**

Observational Studies

--Patient Registries

Expanded Access Studies

Adaptive Studies (Template where we can enter Master/Screening similar to Expanded Access)

- o Indication if registration as single or multiple studies
 - A way to link master and sub-studies – possibly similar to expanded access trials (if registering as separate studies)

In the Protocol Registration Record, the text below is currently available for studies w/ Expanded Access.



Example to Facilitate Linking to Master Protocol

For an Adaptive Trial, recommend the creation of a Template for Adaptive Study (Master Protocol) and have similar text in the same location as EA and similar message w/ the link to the Master Protocol. The Master Protocol can then specify the sub-studies associated with the current study being viewed.

Adaptive Trial: A master protocol associated with study is available. [More info...](#)

- Register the ‘screening’ protocol in a way that **doesn’t require results or sites** (currently, it is difficult to register an interventional screening protocol in a way that doesn’t require results (Currently, using N/A for intervention/Phase, or submitting screening protocol as an observational trial are the options that have been identified, but don’t seem to be a great option in all cases))
- This will be similar to Expanded Access that does not require site locations or results.

Example presentation- Similar to Expanded Access

Interventional/Observational Study requires the Recruitment Status

ClinicalTrials.gov Identifier: NCT04228588

Recruitment Status  : Recruiting
First Posted  : January 14, 2020
Last Update Posted  : January 14, 2020

See [Contacts and Locations](#)

Expanded Study: No Recruitment Status (showing that EA Status is Available)

ClinicalTrials.gov Identifier: NCT00244686

Expanded Access Status  : Available
First Posted  : October 27, 2005
Last Update Posted  : January 13, 2020

d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

3. Data Standards.

NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

- a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.
- b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Different organizations/consortiums working on these types of trials. They should be monitored to update with current practices

- FDA – Adaptive Trials (statistical design) & Master Protocol-guidance issues
 - [Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry](#)
 - [Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; Draft Guidance for Industry](#)
- EMA – Adaptive Trials guidance issues
 - [CTFG Recommendations of initiation and conduct of complex clinical trials](#)
- CTTI – disclosure and how to operationalize – www.ctti-clinicaltrials.org

Submission No.: 232

Date: 3/13/2020

Name: Sue Buff

Name of Organization: [Not provided]

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

As a volunteer advocate within the Parkinson's disease (PD) community, I maintain a website called PDTrialTracker.info to help create greater awareness of the PD trial pipeline with the goal of facilitating patient collaboration in research (in areas of trial design, recruitment, etc.) PDTrialTracker.info analyzes data downloaded from ClinicalTrials.gov to give a big picture view of the pipeline and also provides pre-filtered, direct links to ClinicalTrials.gov so users can drill down into more detail about specific trials. One of the goals of PDTrialTracker is to help introduce users unfamiliar with ClinicalTrials.gov to its many features and to get them comfortable using it directly. The ClinicalTrials.gov site provides an important public service, and it's invaluable to have the registry information freely available to the public. As the ClinicalTrials.gov platform continues to evolve, in both form and function, it will become even more widely used and beneficial to the patient, research and funding communities. Thank you for your efforts on this project!

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

It would be helpful to have a more direct link between ClinicalTrials.gov and PubMed to identify existing publications for those trials whose status = "Completed". Currently, if a study is registered as "Completed" on ClinicalTrials.gov, the "More Information" section of the trial page will provide links to publications automatically indexed to the study by its NCT Number. I believe the links to PubMed from ClinicalTrials.gov show abstracts for both the study publication itself, as well as other studies which reference this study.

However, if a study abstract/publication exists, but does not include the NCT number within it, the publication will not be automatically indexed to the relevant study page on ClinicalTrials.gov.

So a possible workaround for this could be a policy recommendation asking sponsors to include a trial's NCT number in their publications of trial results.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I currently use the website to identify both ongoing and completed trials for Parkinson's disease. The existing search tools (basic, advanced, and expert) are very helpful for identifying trials of interest across a host of parameters. The interactive map tool is a great way to get a global snapshot of trial activity with the ability to drill down into trials by region.

- A new feature suggestion within the Search results page would be to allow sorting by column headers. Currently, I rely on downloads to Excel to do this, but it would be nice to be able to do this directly on ClinicalTrials.gov.

-Another feature suggestion is to allow creation of multiple saved trial lists (or trial portfolios, where a portfolio is a set of NCT's). Currently a user can save trials to one list that is accessible from the "Saved Studies" button on the Home Page. Having more than one saved trial list, with ability to name each one, would be invaluable for maintaining and sharing groups of trials that have certain characteristics (e.g., recruiting Phase 2 for disease x in city y as of date z).

- The Home Page is straightforward and uncluttered, which makes it user-friendly. And the ability to Search by country/state/city/distance was a great feature addition in the last big update of the site, as it is esp. helpful for patients/clinicians who might be looking for recruiting trials in their area. An additional enhancement would be to display the filters that appear on the left-hand side of the Search results page directly on the Home page itself, so one can more efficiently search for trials of interest.

Submission No.: 233

Date: 3/13/2020

Name: Dr. Ting-Chao Chou

Name of Organization: MSKCC/PD Science LLC

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

[To Replace the original submission dated on 3.12.2020. This March 13, 2020 version is the same with typing and grammar errors corrected]

Date: March 13, 2020

Input Report in Response to RFI of March 6, 2020 Webinar

From NLM/NIH and SBIA/FDA Regarding the Modernization Program

Functionality, Informatics and Standard [modernizingClinicalTrials.gov]

Notice Number: NOT-LM-2-20-003

Input Report Submitted by Ting-Chao Chou*, Memorial Sloan-Kettering Cancer Center, New York, NY 10065 [*Present address: PD Science LLC, 599 Mill Run, Paramus NJ 07652-1754] Tel: 201-251-8812 (O), 201-561-2576 (C) E-mail: dtchou99@gmail.com

"The ClinicalTrial.gov Modernization and How to Provide Input" presented in the Webinar on 3.6.2020, summarized by Dr. Rebecca J. Williams of NLM, NIH was insightful and extremely important for governmental regulatory affairs and public information. This is a welcome event for the major coordinated efforts between NIH (via NLM) and FDA (via CDER-SBIA) to update, improve, modernize the drug-evaluation and development. The FDA announced of "Modernizing the New Drugs Regulatory Program: Reorganization Approved" on 9.26.2019, was also a great major initiative.

Looking into the modernizing ClinicalTrial.gov, the concerned issues are much broader than the administrative framework, and far beyond described in the present RFI by NLM/NIH and by previous FDA Announcements and SBIA's, CDER's RFIs. However, they are all inter-connected. This Input Submitter likes to make this Input Report in a broader spectrum to include the very basic fundamental issues, as indicated in the followings:

In Slide No. 35 of the 3.6.2020 NLM Webinar indicated that the RFI is not intended to modify the existing legal and policy requirements for clinical trial registration and results submission.

In this Juncture, this Input Submitter respectively requests that Dr. R. J. Williams of NLM/NIH forwards this Input Report to the FDA's SBIA, CDER, BDER, OCP Officers and Advisory Committee Members of FDA and NIH, for a broader review and discussions for the ongoing Governmental Innovation and Modernization or Reorganization Programs.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. The ClinicalTrials.gov web site functionality and API are well designed and working properly. However, the modernization initiative for enhanced efficiency and transparency is limited by extrinsic factors such as NIH's specific-project for specific-aims policy, while, unintentionally, neglecting general fundamental biologic principle; and FDA's PK-ADME-oriented approach for drug-evaluation with numerous, disconnected, specific-guidelines, while neglecting the basic drug dynamics for efficacy and toxicity determination that is common to all drugs. For drug evaluation research, a general quantitative algorithm-based e-analysis and indexed conclusions should be established. In the absence of clear central guiding scientific principle/doctrine, and the clear and exact Scientific Definitions of key scientific terms, such as "PD", "synergy" and "additive effect of two drug" and "minimum number of dose-data points for clinical trials", it will be not difficult to manage or execute administrative regulatory tasks. To collect/receive large number of clinical trials protocols, and dealing with big volumes of data/results with ambiguous definitions or guidance, are not necessarily, useful to public, and even un-analyzable by professional bio-medical experts. For example, it is impossible to determine synergy if using single-dose of any drug, in vitro, in animal or in clinical trials, regardless of how accurate is the assay, how many time has repeat the study, and how much time or resources has spent. Therefore, "Design" is a serious matter and "Theory" is critically important for data analysis. For another example: All single-dose clinical trials are disqualify for PD analysis. PD explicitly requires two or more doses. If we use 2- or 3-dose-data points for clinical trials, it is important to know exactly, how to conduct PD data analysis with automated computer simulation, to achieve quantitative/indexed conclusions.

Therefore, this Input Submitter proposes a unique remedy using the innovative new approach of emphasizing the fundamental functional dynamics and informatics first, and then deal with numerous of individual cases. This will greatly improve efficiency and cost-effectiveness. The central scheme present here, is the mass-action law based biodynamics, pharmacodynamics and bioinformatics (MAL-BD/PD/BI). This mathematically derived theory/algorithm provides basic parameters and exact definitions that are essential for streaming effective and efficient regulations. The lack of definitions in key scientific terms and the deficiency in providing unified guidance reduces the overall functionality, informatics and standard that NLM seeks.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

2. The submitter of this Input Report has been working on MAL-PB/PD/BI functional dynamics theory, algorithm, and computer software for 45 years with over 430 publications, with over 32,250 citations, in over 1,500 journals, encompassing nearly all disciplines of biomedical sciences. The unified MAL theory has proven useful in applications in vitro, in cells and in animal studies, and in clinical trials, for the protocol design and quantitative data analysis/simulation/diagnosis using very small number of dose-effect-data points by automated computer simulations. [General Reviews] Refs: [1]. Chou, Pharmacol. Rev. 58:621-681, 2006; [2]. Chou & Talalay, Adv. Enz. Regul. 22: 27-55, 1984; [3]. Chou, Cancer Res. 70: 440-446, 2010; [4]. Chou, Integr. Biol. 3: 548-559, 2011; [5]. Chou, Synergy 1:3-21, 2014; [6]. Chou & Martin, CompuSyn software, 2004, PD Science LLC (www.combosyn.com) (Free download upon registration since 2012).

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

3. This Input Submitter is a pharmacologist, theoretical biologist, and cancer researcher, not a ClinicalTrials.gov site user/sponsor for FDA applications. However, this Input Submitter is the MAL-PD theory initiator, developer, who derived the PD-unified Median-Effect Eq. (MEE), and, with P. Talalay, derived the Combination Index Eq. (CIE) which defines synergism ($CI<1$), additive effect ($CI=1$), and antagonism ($CI>1$). The References used the MAL-based clinical trial protocol-design, (including animal studies *in vivo*), with computerized data analysis/simulation are: Ref. [7]. Chou, Leuk. Lymph. 49: 2059-2080, 2008; [8]. Chou, Am. J. Cancer Res. 1: 925-954, 2011; [9]. Mildvan et al. Antivir. Ther. 1: 77-88, 1996; [10]. Fu et al. Synergy 3: 15-30, 2016; and [11]. Chou et al. Synergy 9: 100049, 2019. Using the MAL-CI method, anti-HIV clinical trials, AZT+IFN, used only 10 data-points with 3-doses each drug, and constant- ratio combos, quantified synergy with computer simulation, using only 36 patients [9]. [For ten dose-data-points, A, B, A+B for 3+3+3 (+1 control)]. Similarly, anti-cancer combinations (Taxotere+T607) against colon carcinoma HCT-116 xenografts in nude mice, showed synergism, with experiment using 10 dose-data points, with 66 animals [10, 11].

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

4. The MAL-BD/PD/BI is a proven general theory, obtained following system-analysis that derived (and published) over 300 reaction-rate equations over 15 years. The MAL theory is effective, simple, efficient, quantitative and applicable in general bio-systems, regardless of the followings: (i). *In vitro*, *in vivo*, in animal or in human; (ii). Drug type: Chemicals, biologics, natural products, or biosimilars; (iii). Drug' Unit: nM, ug/ml, mg/Kg, IU, Rad, multiple-of-infection, oxygen tension, pH, etc. (since all units cancelled-out due to ratio relativity), and (iv). Mechanism or mode of actions of single drug (or drug combination in mixture): Competitive, noncompetitive, uncompetitive; exclusive or non-exclusive; sequential, ordered, ping-pong, or random mechanisms (See [1-4]).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

5. The general MAL parameters [m and Dm], as the Universal Functional "Identity-Tag", can also be considered as the Bioinformatics BI-Tag, under defined experimental conditions. Thus simplifying and streamlining the regulatory needs to deal with the complex biological variability and diversity. [See 1, 4, 5, 6]. The unified general MAL dynamics principle, can effectively solve broad spectrum of biomedical problems, including those in clinical trials and clinical sciences, as well as drug synergy quantification, as indicated in tens of thousands of bio-scientific papers in over one thousand journals. The RFI from ClinicalTrials.gov for Functionality, Informatics and Standard are closely inter-related.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

6. The prevailing sponsored research or grant supported project are for specific subjects for specific aims, thus, most priorities are disease-specific, organ-specific, tissue-specific, drug-specific, but neglect the general fundamental dynamic theory and parameters, as the common denominator, to simplify complex biological system with unified MAL dynamics and informatics. The single general theoretical article introducing the CI theory, algorithm and computer simulation /quantitation of drug combination synergism [2], has 6,532 citations in 1,287 biomedical journals internationally, as of March 10, 2020, was referred to as "Makes History" (Elsevier News Release, 3.16.2016). However, FDA regulatory guidelines have not yet provided the definition of "synergism" or "antagonism" and the quantitative method to quantify them, although drug combination is widely employed in treating the most dreadful diseases such as cancer and AIDS.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

7. Since 2017, this Input Submitter has voluntarily provided FDA six Public Comments via Regulations.gov and Federal Register. And presented two Public Hearing at FDA at White Oak Campus on 10.2.2017 and on 5.7.2019, and a FDA Public Meeting on 11.7.2019 for "Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs". The topic of this submitter's presentation was, "Mass-action law Pharmacodynamics (MAL-PD) for Quantitative Biomedical R&D, and Efficient Drug-Evaluation Guidance: Computerized Data Analysis of Single Drug and Drug Combinations in Vitro, in Animals and in Clinical Trials". All the above details are available upon request with the FDA-Docket ID Numbers and the Comments Tracking Numbers of Comments. The feedbacks from FDA for these subjects are pending.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

8. The contents of this Input Report are open to public. They are not proprietary, classified, confidential, or sensitive information. The pertinent contents, in addition to present at FDA, also presented at JHU, Baltimore (4.8.2019); at USUMS, Bethesda (10.2.2017); and will be presented at EB-2020 (ASBMB and ASPET) in San Diego, and AACR-2020, in San Diego; AI and Big Data in Cancer: From Innovation to Impact, in Boston; and the International Synergy Forum, in Bonn, Germany. [Some of these Conferences are postponed or cancelled, due to COVID-19 pandemic].

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

9. This Input Submitter is sincerely willing to provide further details of the MAL-BD/PD/BI theory and applications, especially those related to clinical trials protocol design and computerized data

analysis. This Input Submitter wish to work closely with the teams of FDA and NIH, for the modernization projects. This Input Submitter is 81 years old, and is in good health. Since retirement and established PD Science LLC, in 2013, there are 13,336 new citations for the scientific work. The End

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Please Note: The above InPut Report dated March 13, 2020 (With typing and grammar errors corrected) is to replace the same original submission dated on March 12, 2020.

Attachment: Suppl. Mater.InPut Report.ChouTC Illustra.54 Slides.MAL-Dynamics. FDA.NIH. NLM ClinicalTrials.gov Webinar3.6.2020 [NOT-LM-2-20-003].pdf

Supplementary Materials

For ClinicalTrials.gov Webinar March 6, 2020: Modernization and How to Provide Input

To accommodate growth and enhance efficiency [Notice No. NOT-LM-20-003]

Speaker: Dr. Rebecca J. Williams, NLM/NIH

Date: March 13, 2020

InPut Report: Submitted By: Ting-Chao Chou*, Ph.D.

Memorial Sloan-Kettering Cancer Center, New York, NY

10065 [*Present Address: PD Science LLC, Paramus NJ

07652-1754 Tel: 201-251-8812 E-Mail: dtchou99@gmail.com

PDF Illustrative Summary Slides for Broader Innovation and Modernization

Mass-Action Law Based Functional Biodynamics, Pharmacodynamics and Bioinformatics: Theory, Algorithms and Simulations for Cost-Effective Econo-Green Biomedical R&D and Computerized Drug Evaluations in Cells, Animals & Clinical Trials (54 PDF Slides)

[Please Share These Slides with NIH/NLM and FDA/SBIA/CDER, OCP Officers, and the Advisory Committee Members of NIH and FDA for Review and Discussions]

Biology

Complexity

Diversity

Simplicity

Integration

The Mass Action “Law” & “Dynamics”

- ▶ BioDynamics (BD): “Doctrine of The Median”
- ▶ Pharmacodynamics (PD): Median-Effect Eq. & Combination Index Eq.
- ▶ Mass & Action: “Dose” and “Effect” Are “Interchangeable”
- ▶ All PD Dose-Effect “Curves” Can Be Transformed Into “Straight Lines”
- ▶ Functional Dynamics: Dose-Effect Dynamics at Constant Temperature, Constant Atmosphere and Constant Oxygen/CO₂ Tension & pH⁶¹⁰

New Conceptual Path

System Analysis with “Combinatorial Analysis and Pattern Analysis” of the Mass-Action Law”, and with “Mathematical Induction – Deduction” to Derive the Unified General Median-Effect Equation (MEE) (*via >300 Reaction Rate Equations*), as Algorithm, for Computer Simulation.

Then, Using the “Unified Theory” as the “Largest Common Denominator” to Simplify the Complex Biological Systems, for Functional “Dose” & “Effect” Pharmacodynamics (PD), Biodynamics (BD) and Bioinformatics (BI)

[This Unique System Analysis/Math Approach Is New in Bio-Medical Sciences]

IN SEARCH OF TRUE “SIMPLE” DEFINITION

GENERAL PHARMACODYNAMICS (PD):

$$F_a/F_u = (D/D_m)^m$$

“SYNERGY”: $C_l < 1$

A Dedication to the Int'l Synergy Keynote Forum – 2018 Bonn, Germany

March 9 – 10, 2018

Median Effect Equation

[T.C. Chou, J Theor Biol 59: 253-276, 1976. Eqs. 35 & 36]

Unified General Theory for Pharmacodynamics (PD) [Doctrine of The Median]

Hyperbolic (1st order) $m = 1$, or Sigmoidal (Higher order) $m > 1$ (or $m < 1$). The Derivations & Prove took ten years (1966-1976): *System Analysis, Pattern Analysis, Combinatory Analysis* [Derivation of >300 Reaction Rate Equations]:

[Dose & Effect Are Interchangeable] [Two-Data Point Theory]

[Low Dose-Risk Assessments for Carcinogens, Radiation]

[Conservation of Lab Animals, and Reduce Patients in Clinical Trials]

$$\frac{fa}{fu} = \left[\frac{D}{Dm} \right]^m$$

- fa = Fraction affected, e.g., fractional inhibition
- fu = Fraction unaffected; fu = (1-fa)
- D = Dose required to produce fa [The Beauty of “Relativity” Ratio: Dimensionless Quantity]
- Dm = The median-effect dose. i.e. ED₅₀, IC₅₀
- m = Dynamic Order; Sigmoidicity or Shape of Dose-Effect Curve

The Median-Effect Plot (Chou Plot)

$$\log(fa/fu) = m(\log D) - m(\log Dm);$$

Plot: $x = \log(D)$, $y = (fa/fu)$; ($y = ax + b$, for a Straight Line)

Slope: m ; and x -Intercept: $\log(Dm)$

[Dose-Effect Curve Linearization]

[Econo-Green Bio-Res.] [Small Size Experiment]

The Unified PD/BD/BI Theory of The Mass-Action Law

Derivation of Major Biochemical and Biophysical Equations from the Median-Effect Equation

[Chou T.C. Pharmacol. Rev. 58: 621-681, 2006; Fig. 4]

Henderson-Hasselbalch equation

$$\log [H^+] = \log K_a + \log \frac{[HA]}{[A^-]}$$

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

**“Doctrine of the Median”
for Bio-dynamics (BD):**

D_m: Half Affected

K_m: Half Saturated

K_a: Half Ionized

K: Half Occupied

K_d: Half Bound, Half Free

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m} \right)^m$$

The Median-Effect Equation

Chou, J. Theor. Biol. 59: 253-276, 1976

$$f_a/(1-f_a) = (D/D_m)^m$$

$$f_a = [1 + (D_m/D)^m]^{-1}$$

$$\log [(f_a/(1-f_a))] = m[\log(D) - \log D_m]$$

$$\log [(f_a)^{-1}-1]^{-1} = m \log(D) - m \log D_m$$

$$f_a/f_u = D/D_m$$

Hill equation

$$\log [v/(V_{max}-v)] = n \log(S) - \log(K)$$

Michaelis-Menten equation

(Lineweaver-Burk Plot)

$$v/V_{max} = [1 + (K_m/S)]^{-1}$$

The Unified Median-Effect Equation of MAL:
“Derived” (Proven) from
the Mass-Action Law.

[The four major
Equations in
*Biochemistry and
Biophysics* are the *Special
Cases* of the Unified
PD/BD/BI Theory].

[If ME Eq. were wrong,
then textbooks would
need to be revised]

Scatchard equation

$$\frac{[L]_b}{[L]_f} = \frac{n[M]_t}{K_d} - \frac{[L]_b}{K_d}$$

Blogs Home

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HOT: one equation to lead the way to greener biomedical sciences

05 May 2011

By [Francesca Burgoyne](#)



In this HOT Perspective article **Ting-Chao Chou** from the [Memorial Sloan-Kettering Cancer Center, New York](#) presents his vision for a new era of smarter, greener biomedical research and drug discovery.

The algorithm of the **median-effect equation** based on the **mass-action law**, along with experimental design and computer simulation, should allow a significant reduction in the number of data points required to yield useful bioinformatics on the relationship between dose and effect. He poses that a theoretical minimum of a mere two data points are required to construct dose-effect curves – if they are accurately determined. This unified theory, he believes, should pave the way for more efficient, cost-effective research and ethical clinical trials.

This HOT article received glowing reports from our referees and is featured on the front cover of our latest issue – [Issue 5](#). Why not take a look – it's currently **free** to access:

The mass-action law based algorithms for quantitative econo-green bio-research

Ting-Chao Chou

Integr. Biol., 2011, **3**, 548-559 [Published by Royal Society of Chemistry, Cambridge, UK]

DOI: 10.1039/C0IB00130A 6177480

615



Chou, Ting-Chao

Get A Badge

ResearcherID Labs

ResearcherID: B-4111-2009

Other Names: T.C. Chou; TC Chou

URL: <http://www.researcherid.com/rid/B-4111-2009>

My URLs: www.combosyn.com

https://en.wikipedia.org/wiki/Ting-Chao_Chou

<http://scholar.google.com/citations?user=xjcodA8AAAAJ&hl=en>

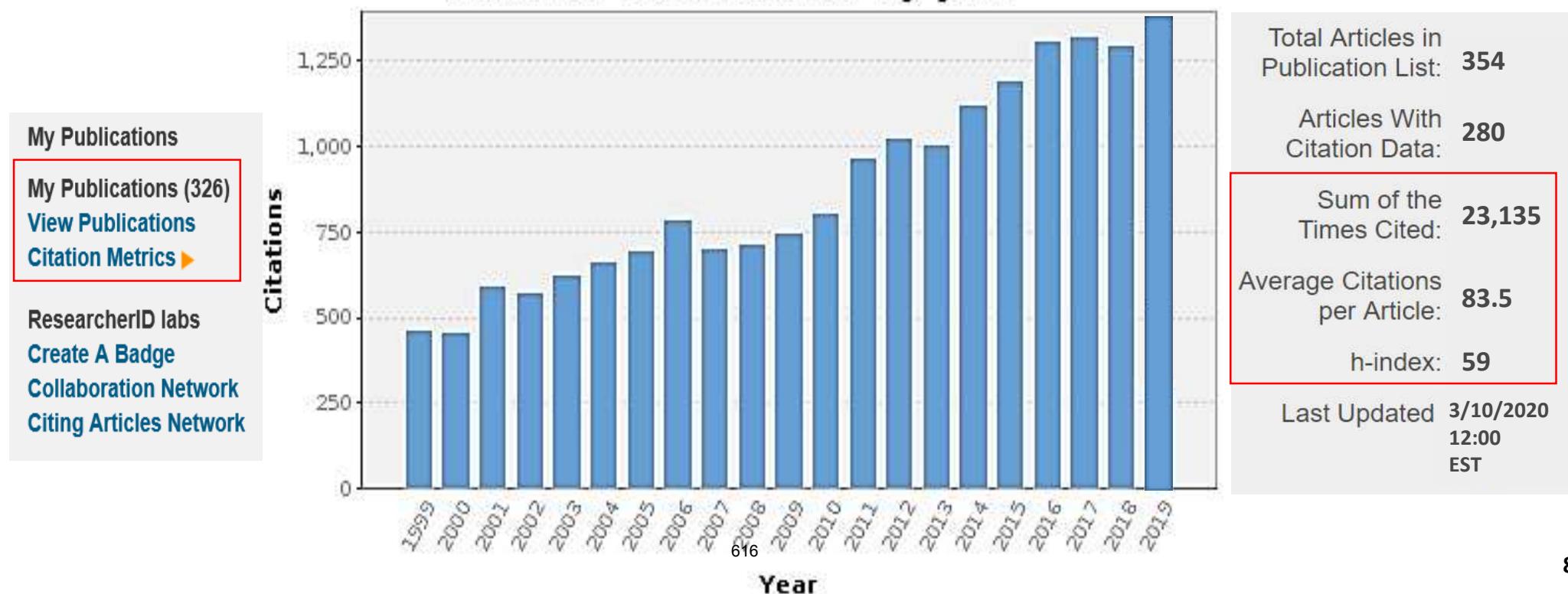
My Institutions ([more details](#))

Primary Institution: Memorial Sloan-Kettering Cancer Center

Sub-org/Dept:

Role: Researcher (Academic)

Citation Distribution by year



Ting-Chao Chou – Google Scholar Citations

PD Science LLC

Verified email at PDScience.org - [Homepage](#)

[Pharmacodynamics](#) [Theoretical Biology](#) [Philosophy of Biology](#) [Biological Control](#)
[Pharmacokinetics](#)

[As of 03.10.2020]

TITLE

CITED BY

YEAR

[Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors](#)

6532

1984

TC Chou, P Talalay

Advances in enzyme regulation 22, 27-55

Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug-combination studies (vol 58, pg 621-681, 2006)

3364

2006

TC Chou

Pharmacological Reviews 58, 621-681

Drug combination studies and their synergy quantification using the Chou-Talalay method

2846

2010

TC Chou

Cancer research 70 (2), 440-446

Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection

1007

2000

TW Baba, V Liska, R Hofmann-Lehmann, J Vlasak, W Xu, S Ayehunie, ...

Nature medicine 6 (2), 200-206

Analysis of combined drug effects: a new look at a very old problem

559

1983

TC Chou, P Talalay

Trends in Pharmacological Sciences 4, 450-454

Computerized quantitation of synergism and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design

537

1994

TC Chou, RJ Motzer, Y Tong, GJ Bosl

JNCI: Journal of the National Cancer Institute 86 (20), 1517-1524

Synergism and antagonism in chemotherapy: The median-effect principle and the combination index for quantitation of synergism and antagonism

485 *

1991

TC Chou

Academic Press, San Diego

Generalized equations for the analysis of inhibitions of Michaelis-Menten and higher-order kinetic systems with two or more mutually exclusive and nonexclusive inhibitors

442

1981

TC CHOU, P Talalay

European Journal of Biochemistry 115 (1), 207-216

617

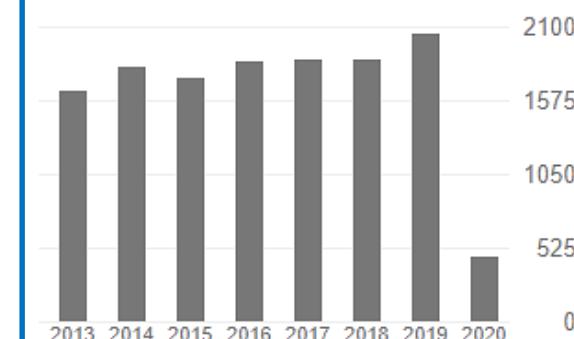
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| | | |
|-----------|-------|------|
| Citations | 33276 | 9862 |
| h-index | 70 | 26 |
| i10-index | 270 | 98 |



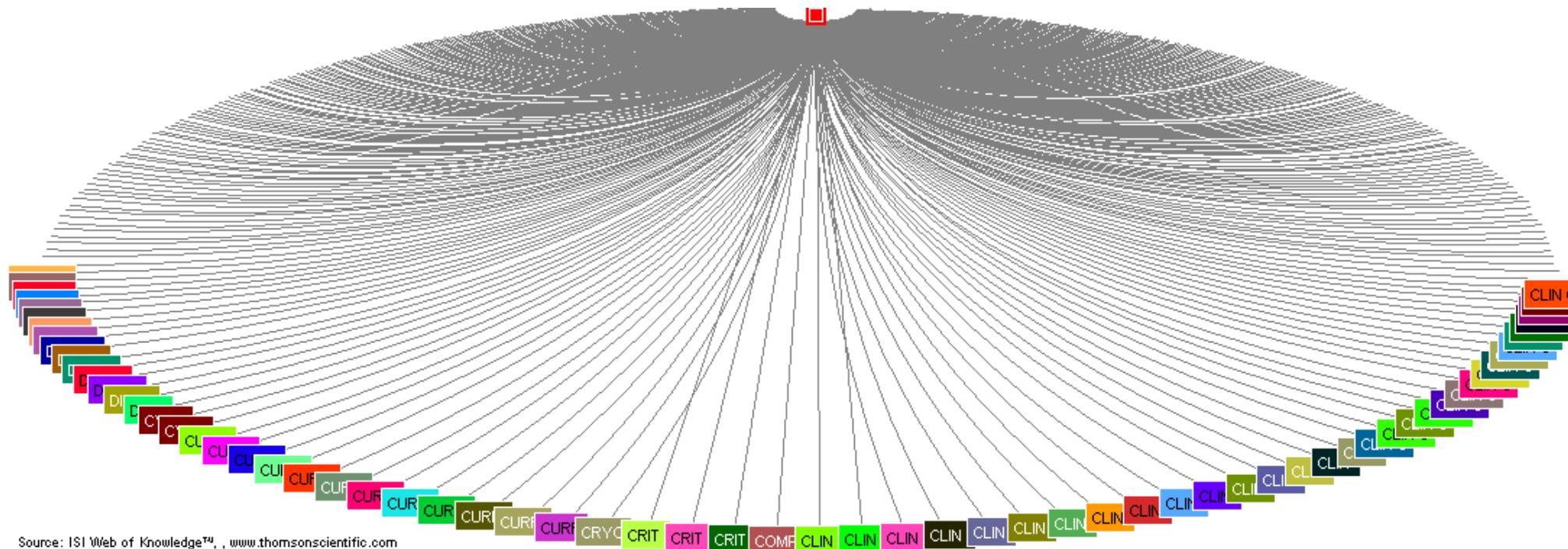
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- Mike Hayball
Managing Director, Cambridge C... >

“Quantitative-Analysis of Dose-Effect Relationships- The Combined Effects of Multiple-Drugs or Enzyme-Inhibitors”

ADVANCES IN ENZYME REGULATION, 22: 27-55, 1984*

[The Combination Index Theorem & Software for Synergy Quantification]



Source: ISI Web of Knowledge™, www.thomsonscientific.com

T.C. CHOU & P. TALALAY

Cited: 6,538 Times; (5,078 Citations *in* 1,287 Journals) [As of 3.13.2020]

*Elsevier News Release: “Chou & Talalay Article from 1984 Makes History” [3.16.2016]

Chou & Talalay Paper from 1984 Makes History

<https://www.journals.elsevier.com/advances-in-enzyme-regulation/news/-chou-talalay-paper-from-1984-makes-history>

One of the most cited papers

Published in 1984, the manuscript “Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors” by Ting-Chao Chou and Paul Talalay has become one of most cited articles in all fields. With **3,520 citations**, it is not only the most cited article in Advances in Biological Regulation, but also one of the most cited articles (being in the top 1% of most cited articles) in the field of Biochemistry, Cancer Research, Molecular Biology and Genetics (Scopus, 16thMarch 2016).

Here is what Ting-Chao Chou, first author of the manuscript tells us:

“Over 31 years ago, Prof. George Weber of Indiana University invited Prof. Paul Talalay (JHU) and me (MSKCC) to give a symposium talk sponsored by Eli Lilly, in conjunction with Advances in Enzyme Regulation. My talk was very much impressed by Professor Carl F. Cori of Harvard (Nobel Laureate of Medicine 1947). His vision has proven to be extremely insightful and accurate. The paper in Adv. Enz. Regul. 22:27-55, 1984 by Chou & Talalay has become among the most cited and the most broadly cited theoretical papers of all time in all fields.”

It is our pleasure to celebrate this milestone for our journal and for this occasion we have provided free promotional access to the article for 6 months on [ScienceDirect](#).

The Mass-Action Law PD/BD/BI Theory, Equations, and New Paradigm Revelations:

Chou TC. Pharmacol. Rev.
58: 621-681, 2006.
Eqs. 7-9; 16,19,20; and 21-23.

Median-Effect Equation [MEE], (Chou, 1976) [1st Law of MAL] {Doctrine of the Median}

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m} \right)^m \quad D = D_m \left(\frac{f_a}{1-f_a} \right)^{\frac{1}{m}} \quad f_a = \frac{1}{1 + \left(\frac{D_m}{D} \right)^m}$$

Combination Index Equation [CIE], (Chou-Talalay, 1984)

$$CI = \frac{(D_{\text{comb}})_1}{(D_{\text{alone}})_1} + \frac{(D_{\text{comb}})_2}{(D_{\text{alone}})_2} = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2}, \quad \text{Ratio: } \frac{(D)_1}{(D)_2} = \frac{P}{Q}$$

$$\frac{(D)_{1,2} [P/(P+Q)]}{(D_m)_1 [f_a/(1-f_a)]^{1/m_1}} + \frac{(D)_{1,2} [Q/(P+Q)]}{(D_m)_2 [f_a/(1-f_a)]^{1/m_2}}$$

CI = 1 indicates additive effect
 < 1 indicates synergism
 > 1 indicates antagonism

D & E Interchangeability
 D-E Curves Linearization
 Dm as Universal Reference Point
 and Dynamic Common Link.

Dynamic Interaction
 Dynamic Integration
 Synergy Quantification

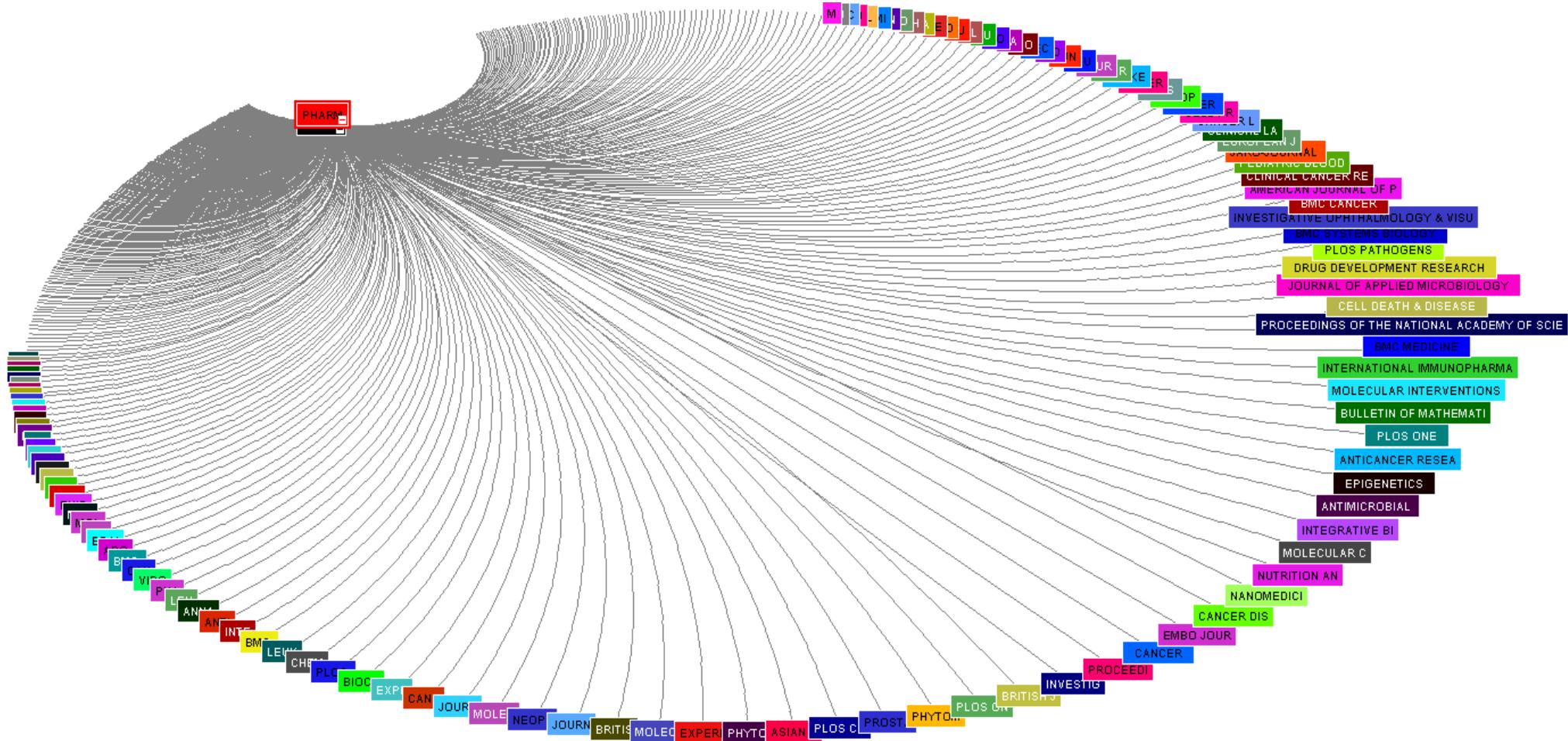
Dose-Reduction Index [DRIE], (Chou-Chou, 1988)

$$(DRI)_1 = \frac{(D_{\text{alone}})_1}{(D_{\text{comb}})_1} = \frac{(D_x)_1}{(D)_1} = \frac{(D_m)_1 [f_a/(1-f_a)]^{1/m_1}}{(D)_1}, \quad (DRI)_2 = \dots$$

DRI = 1 No dose reduction
 > 1 Favorable dose reduction
 < 1 Not favorable dose reduction⁶²⁰

Retaining Efficacy &
 Decreasing Toxicity
 Therapeutic Advantage

“Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies”



CHOU TC, Pharmacological Reviews 58: 621-681, 2006

Times Cited: 3,369 (2,443 Citations in 956 Journals) [3.132020 Citation Results]

The Mass-Action Law [MAL]

The Fundamental Physico-Chemical & Functional PD/BD/BI Principle

“Doctrine of the Median”

The Review of General Applications

[In Over 1,287 Biomedical Journals Worldwide, Encompasses Nearly *All* Disciplines of Biomedical Sciences]

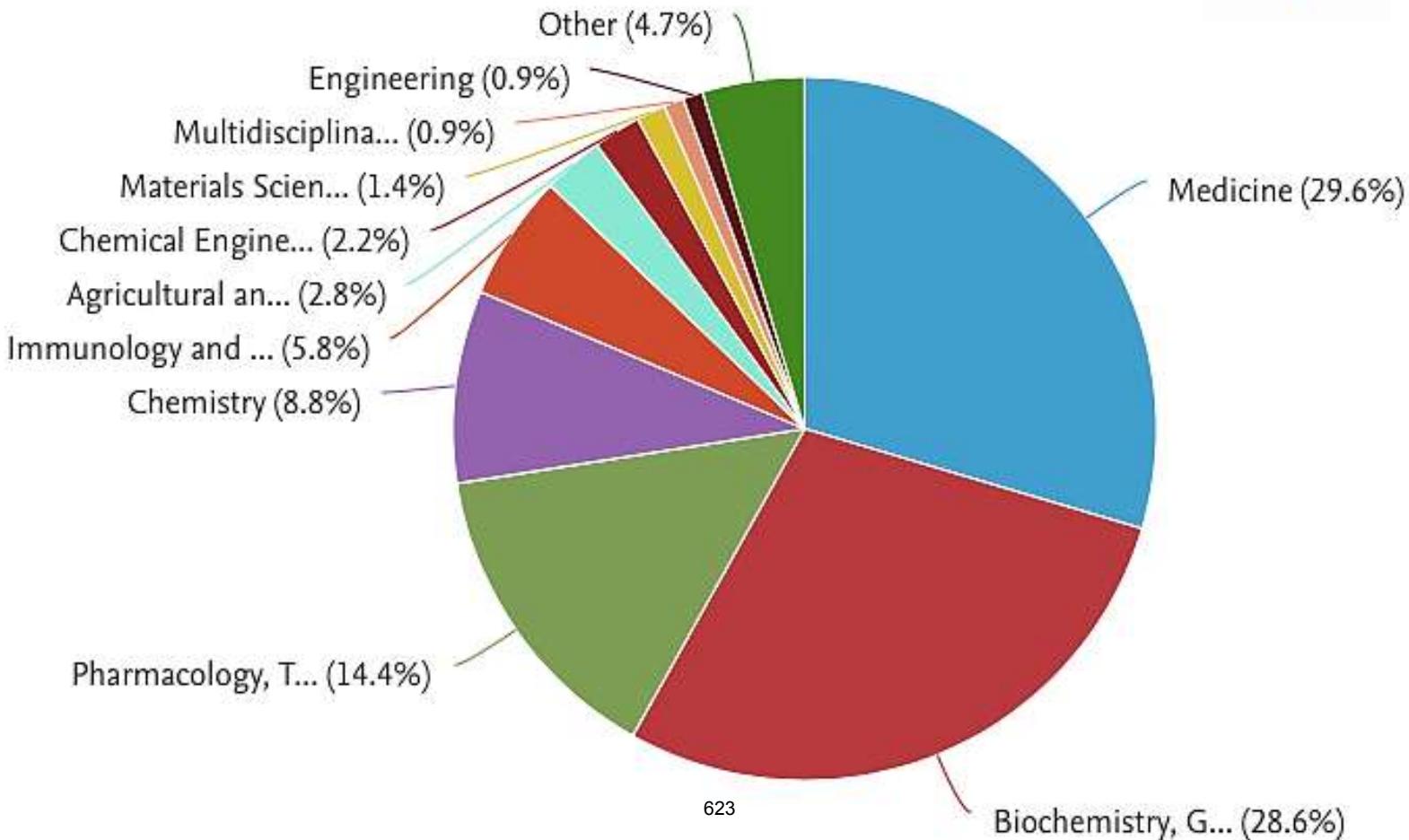
- Defines *Pharmaco-Dynamics* for Single Drug & Drug Combinations
- Provides *Algorithms* for Computerized Simulation & Diagnostics
- Allows Efficient-Designed Experiments, Using Fewer Data Points in Animal Studies and Clinical Trials
- Facilitate Bio-Medical ‘*Econo-Green*’ R&D with Small Size Data
- Reform, Modernize, Streamline ⁶²² Drug Regulatory Guidances

Scopus Analysis: Citations of TC Chou's Publications by papers in Subjects/Disciplines

05.03.2019 (In Over 1,215 Journals)

Documents by subject area

Scopus



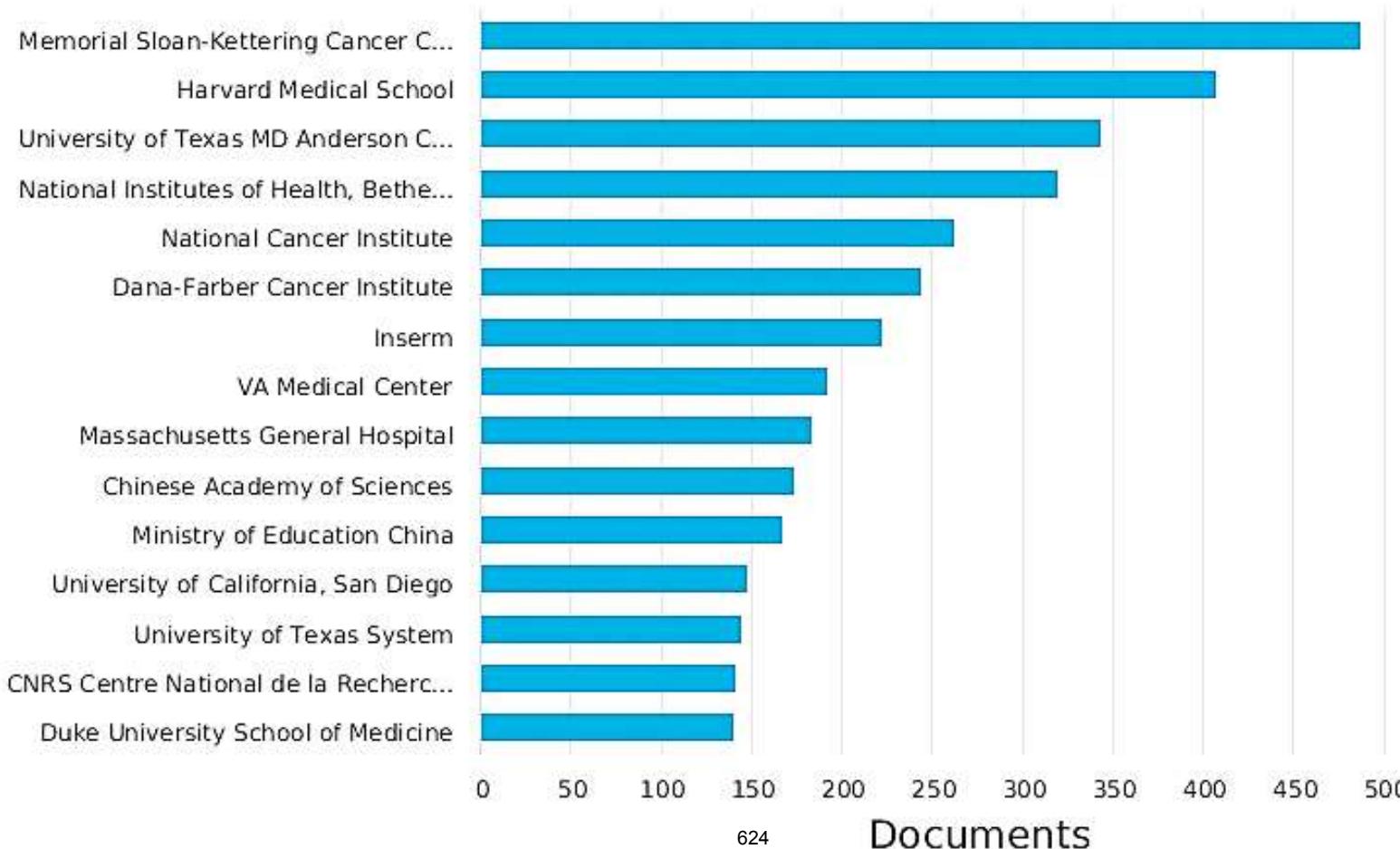
Scopus Analysis: Chou TC's Publications Cited by Papers from Institutional Affiliations

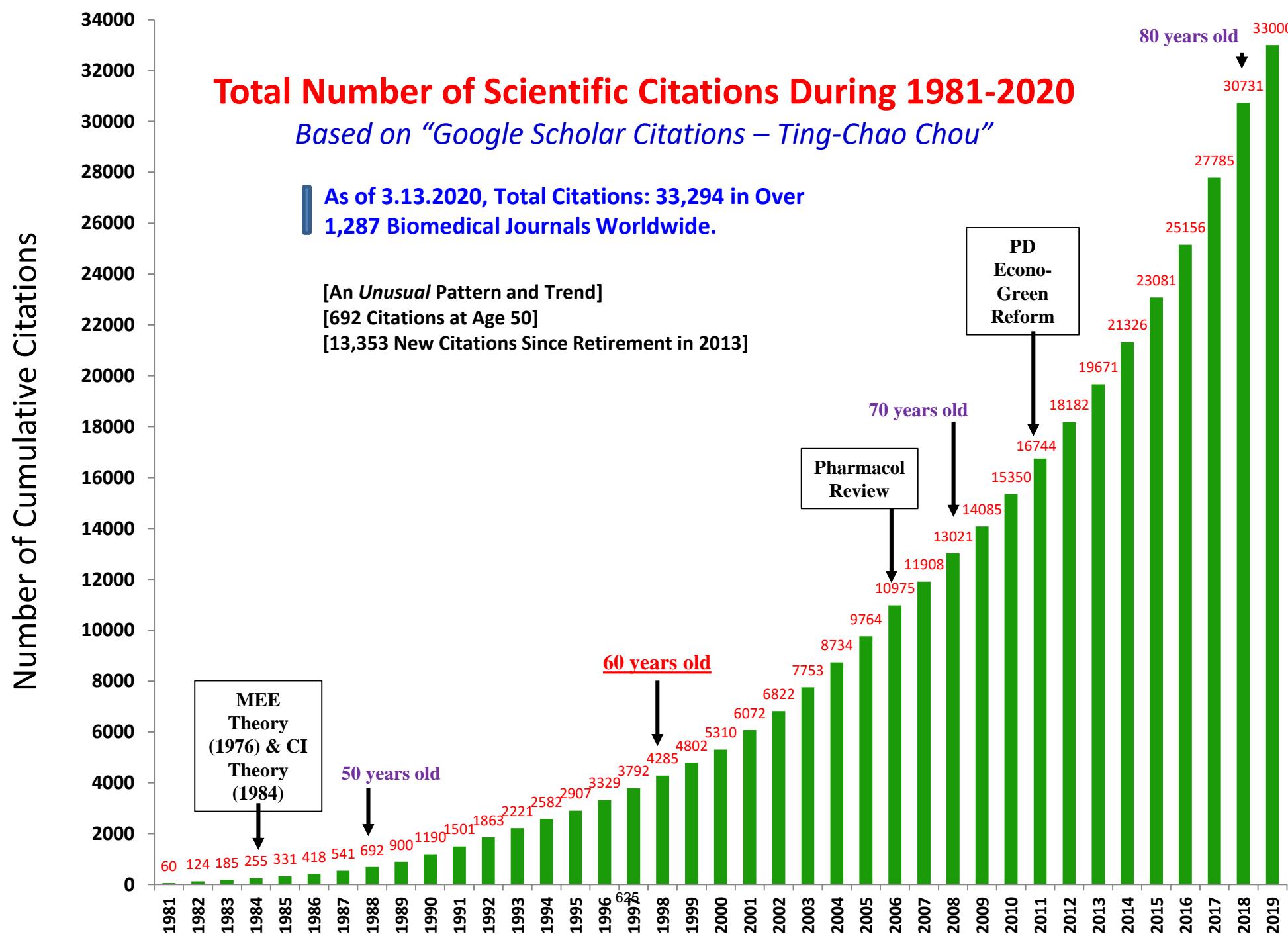
8.29.2018

Documents by affiliation

Scopus

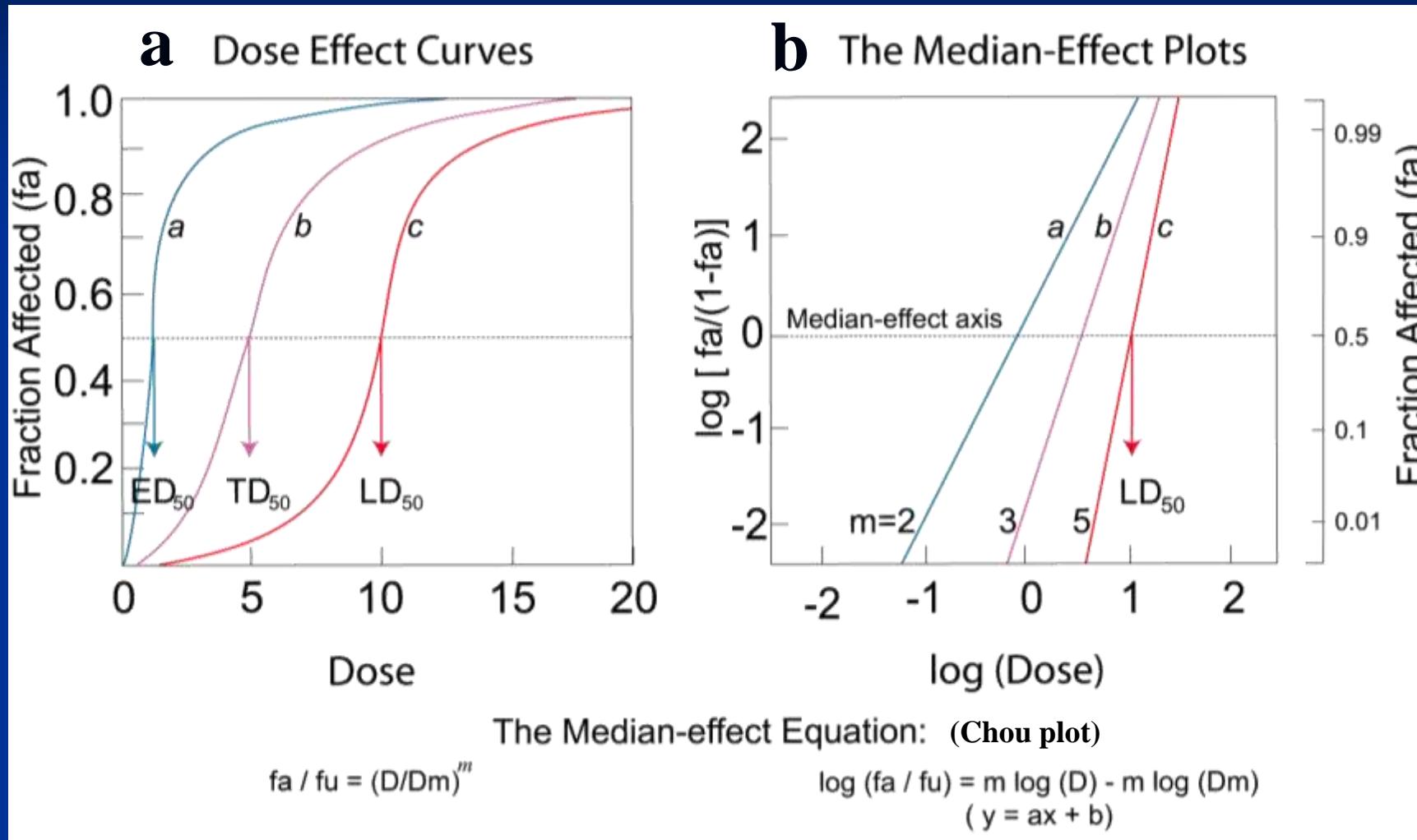
Compare the document counts for up to 15 affiliations





“Linearization” of Dose-Effect Curves

[X-Intercept for Potency; Slope for Dynamic Order (Sigmoidicity of Shape)]



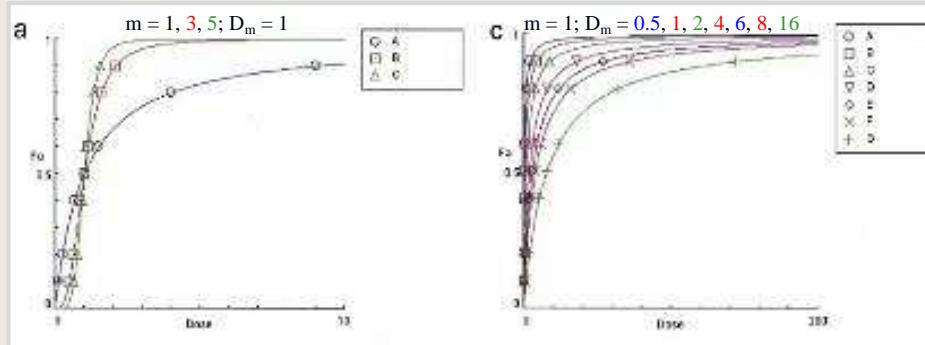
[Chou T.C. J. Theor. Biol. 59: 253-276, 1976; Figs. 1 and 4]

The Computer Simulation of the Median-Effect Equation

Linearize All Dose-Effect Curves of Different Shapes and Different Potencies with a Minimum of Only Two Data Points.

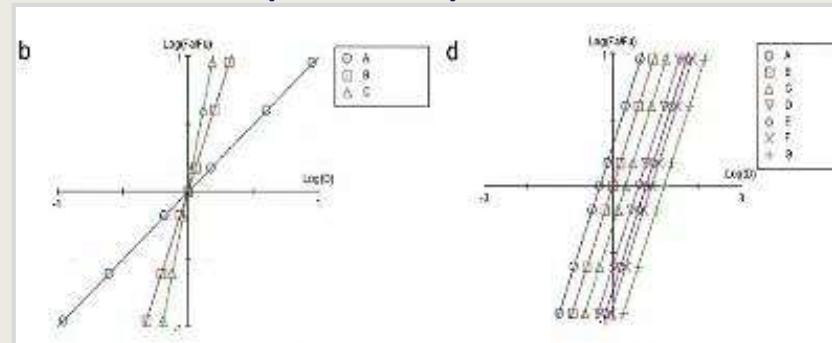
Source: Chou TC.
Pharmacol. Rev. 58:
621-681, 2006. **Fig. 11.**
Chou TC. Integr. Biol. 3:
548-559, 2011. **Fig. 1.**
Synergy 1: 3-21, 2014.
Fig.2

The Dose-Effect Curves: with different “shape” and “potency”



The Most Important Bio-Dynamic Findings of MAL-MEE ! Using the Reverse Logics.

The Median-Effect Plot: (Chou Plot): The “Linearization” Principle



“ The Two-Data Point Theory” : A New Paradigm that Defies The Centuries-Old Common Held Belief”

With MAL-PD, “Only Two Data Points” are required to simulate A Dose-Effect Curve !

- Dose-Effect Curves Follow the Median-Effect Principle of the Mass-Action Law: The “Median” Serves as “The Universal Reference Point and Link as The Largest Common Denominator for Simplifying the Complex Biological Systems”.
- “One can draw a specific dose-effect curve with a *theoretical minimum* of “only two data points” - [The 3rd Point is dose zero, and the 4th point the Median-Effect Dose (D_m). Any 2-data points on a line represent the same line or the same Dose-Effect Curve!] {The Two Data Points Minimum Theory}. This the Basis for the “Digital Bio-Dynamics” and for the Efficient, Effective “Econo-Green” Biomedical Research & Development and Drug-Evaluation Regulations in Animals and in Clinical Trials. [Chou TC. *Integr. Biol.* 3: 548-559, 2011, Fig. 1; *Pharmacol. Rev.* 58: 621-681, Table 7, Fig. 11; *Synergy 1: 3-21, 2014, Fig. 2; Synergy 9: (2019) 100049 (Drug Synergy Quantitation in Animals or Clinical Trials with Only 10 Data Points)*]

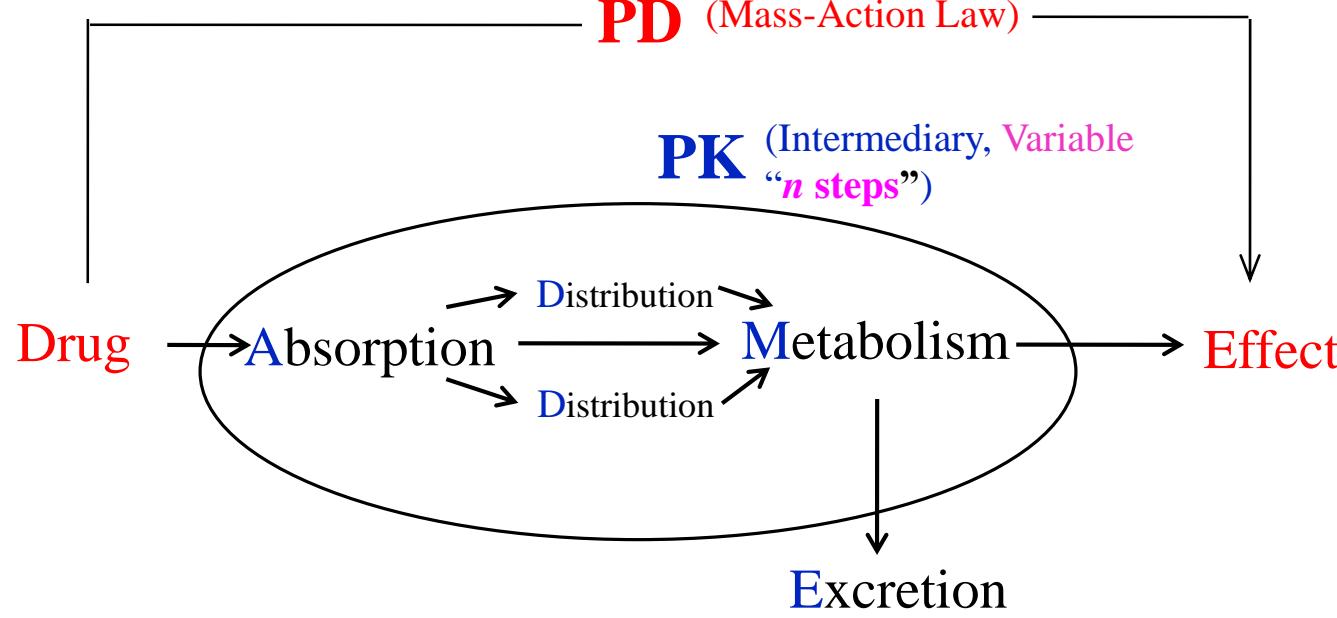
The Nature's Mass-Action Law Is The “Model” of “PD”

PD Is The Fundamental “Dose” and “Effect” Mathematical Relationship.

[PK (Pharmacokinetics) is Empirical Observational Science that Has No “Model”].

[PK is Just the Intermediary *n*-Steps (ADME) within the PD Domain].

[PK Is An Endless Sink of Research Resources]. **[PD Theory Determines of Drug Efficacy & Toxicity; But “PK” Does Not].**



Chou, TC. Comments to FDA
& NIH/ASPET/AACR, 2017 20
PD Science, LLC (USA)

Let's Work Together To
Change The Basic
Conceptual Priority !

Source: Chou TC.
Am J Cancer Res. 1:
925-954, 2011. Fig. 7

**“PD” Should Have Higher Priority than “PK” in
Drug Evaluations and Regulations !**

PD to Avoid Wasting Time, Effort, and Resources.

PD trims the R&D Attrition Rate by “Optimized PD Practice”
628

We, the Biomedical
Communities, FDA, NIH
and USPTO need to
Define “What Is PD”? &
“What is Synergy”? to
avoid confusion,
Inefficiency and waste
of resources.

Why Emphasis on Pharmacodynamics (PD) Over Pharmacokinetics (PK)

[Presented at *Drug Development Summit, Zurich, Switzerland*, by Chou TC 6.08.2011; *Am J Cancer Res* 1(7): 925-954, 2011, Table 2]

| Items | PD | PK |
|--|--|--|
| Mode of action | <i>What drug does to the body</i> | <i>What body does to the drug</i> |
| Characteristics | Mainly vary dose (fixed time) Single Unified Theory of Mass-Action Law | Mainly vary time (fixed dose) Observational Multi-Factorial Mix |
| Principle | The median-effect principle of the mass-action law | Empirical phenomenal /observations |
| Rigorosity | Explicitly derived equations | Empirically perceived formula |
| Applications | Physico/chemical quantitative parameters in Vitro & in Vivo | Probabilistic empiric parameters in Vivo Only |
| Parameters & Constants <i>[Defined PD And Empirical PK]</i> | D_m , m, r, CI, DRI, IC_{50} , K_m , K_i , K_a and K_d Competitiveness, Exclusivity, Synergism, Antagonism [Mass-action parameters for potency, shape, dynamic order, and interaction indices] | $t_{1/2}$, C_{max} , Cl, AUC, V_{dis} Absorption, Distribution, Metabolism, Excretion [Measurement of Parameters without direct physico-chemical bearing] |
| Determining Efficacy | Yes | No |
| Determining Toxicity | Yes | No |
| Determinant for | <i>What it takes to be a good drug</i> ⁶²⁹ | <i>Help proper use of a drug</i> |

5th International Conference and Exhibition on
Pharmaceutical Regulatory Affairs

August 03-05, 2015 Orlando, USA



Ting-Chao Chou

PD Science LLC, USA

Keynote Forum

Essential consensus and scientific definitions for advancement in pharmaceutical regulatory affairs

Disparity in basic scientific concept and theory lead to weakness in setting policy and regulatory affairs. Confusion and controversy in at least three major areas in biomedical-research and pharmaceutical development exists that compromise research efficiency, developmental cost-effectiveness and rigorous regulatory policy and affairs, namely: (1) Lack of consensus on "synergy definition and its quantification" in drug combination and treatment, especially in cancer and AIDS. (2) The terms PK/PD referred as Pharmacokinetics and Pharmacodynamics are used casually where PD is poorly defined and neglected. (3) The "care and use" legislatures for laboratory animals are good policy and regulation. However, the basic means for conservation of laboratory animals "use", for reducing waste and minimizing data points and experimental size is poorly developed. It is proposed that all the above three serious problems can be minimized by employing the unified theory of the 'median-effect equation' for single entity drugs, and the 'combination index theorem' of drug combinations, based on the physico-chemical principle of mass-action law. Its computer software, "CompuSyn", for automated simulation of pharmacodynamics for new drug evaluation and for synergy quantification, have already been adopted by >10,000 scientists worldwide and is growing at over 1,000 citation papers per year.

Biography

Ting-Chao Chou received MS in Pharmacology from National Taiwan University, and PhD from Yale University, and Postdoctoral Fellowship at Johns Hopkins University, School of Medicine. He joined the Memorial Sloan-Kettering Cancer Center (MSKCC) and became a member in 1988, and was a Professor of Pharmacology at Cornell University, Graduate School of Medical Sciences during 1988-2000. He was the Director of Preclinical Pharmacology Core at MSKCC, where he retired on January 06, 2013. He is the Founder of PD Science, LLC., USA. He published 273 articles that have been cited by 16,421 papers in 620 biomedical journals worldwide including Thomson Reuters Web of Science and Google Scholar Citations with 22,336 citations, h-index 65 and 38 U.S. Patents. He introduced the "Unified Theory of the Median-Effect Equation of the Mass-Action Law" in 1976 for single drug, and with Prof. Paul Talalay (JHU) in 1984, created the "Combination Index Theorem" for multiple drug dynamics. His dynamics equations and software have been utilized to advance Econo-Green Bio-Research.

630

dtchou99@gmail.com

Advocacy For *Defined Cost-Effective Bio-Medical R&D* and *Quantitative Drug-Evaluation Guidelines* for Reform and Modernization.

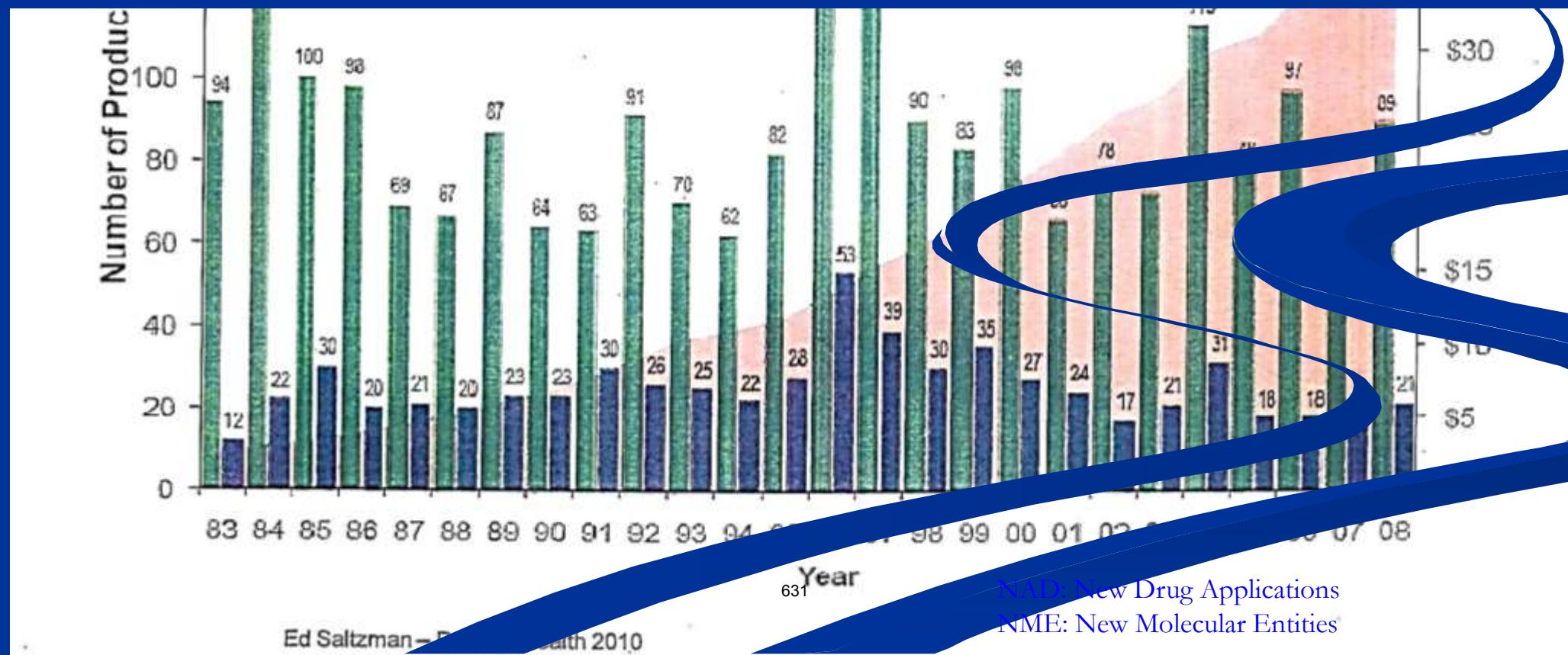
Mathematical Definitions For:

"PD", "Dose-Effect Curve", "Additive Effect of Two Drug (or more-drugs)", "Synergy", and "Valid Model" for Making Streamlined *General Regulatory Process & Claims*".

Biomedical Communities of the World, (and NIH/Academic Associations & Societies), And FDAs, Are to Share the Innovation of the Rigorous, Definitive and Cost-Effective Biomedical Science.

The Quantitative, Econo-Green Biomedical R&D and Basic Principle for Efficient Drug-Evaluation Regulatory Guidance, Are Overdue.

Is This Normal? Is This Sustainable?
Is This Cost-Effective? We Need A
More Reliable Defined Bio-Science.



MAL-PD/BD/BI is Rigorous Derived, Proven Equation/Algorithm, with Quantitative, Digital or Indexed Conclusions & with Computerized Auto-Simulation.

Exposure Response Analysis (ERA), Model- Informed Drug Development (MIDD), Bioanalytical Method Validation (BMV) and Drug-Drug Interaction (DDI) are observational science that have No Clear Theoretical Basis, No Algorithm, and Non-Quantitative. They are Out-of-Date that Need to be Updated.

“Synergy Definition” for Drug Combination

(Controversy for Over 100 Years)

- Drug Combination: Widely Used in Cancer , AIDS & Chinese Traditional Medicine...
- Synergism: About 20 Different Definitions for Synergy in literature. Very Confusing.
Only CI Method is Quantitative
- Combination Index (CI): Chou & Talalay, Adv. Enz. Regul. 22: 27 55, 1984 (Cited 6,538 times, in over 1,287 biomedical journals worldwide); [Computerized Quantitation & Simulation]
CI <1, Synergism CI=1, Additive Effect CI>1, Antagonism
- Challenge: *If No Clear Definition for Synergy: NIH, FDA, USPTO and Journal Editors & Peer Reviewers have No Basis to Judge or to Regulate the “Synergy Claims”*

Biomedical Communities Need A Definition & Consensus

A Quiz

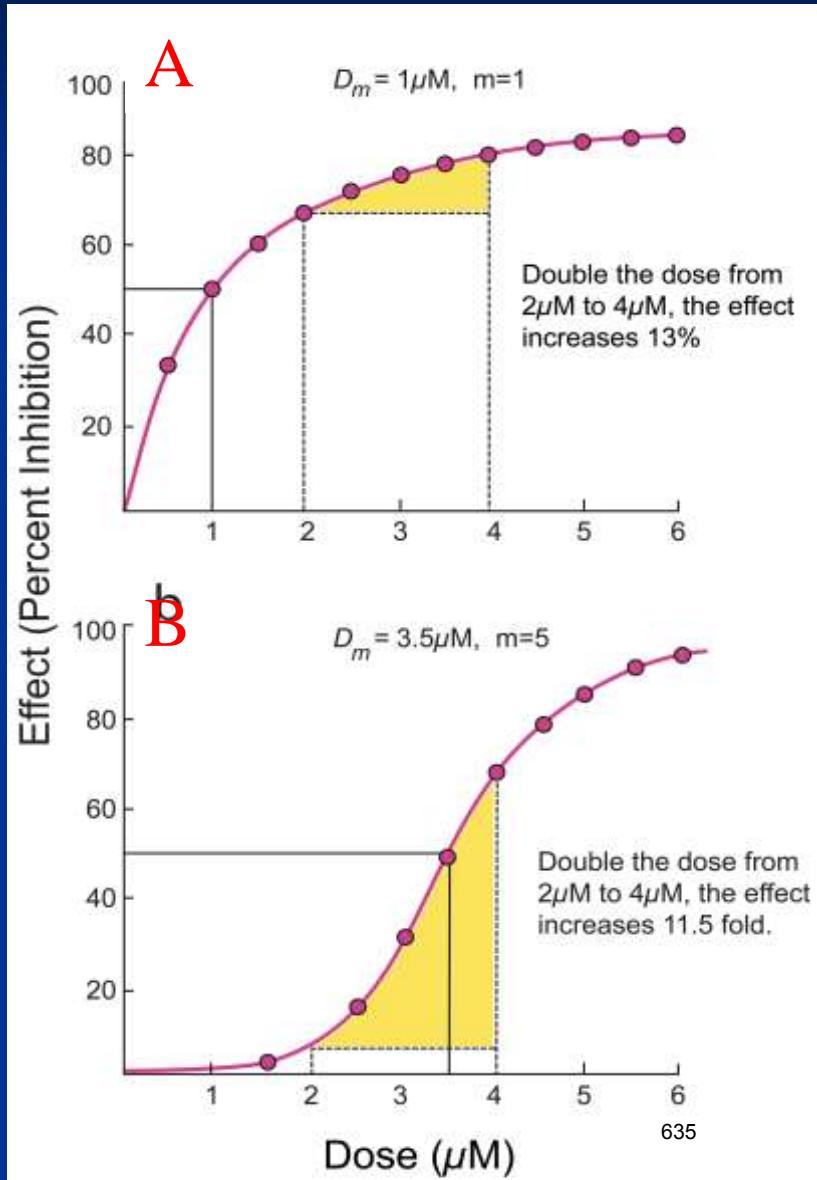
If I_1 and I_2 each inhibits 30% of a bio-system, then in combination, if additive (i.e., no synergism nor antagonism) should inhibit:

- A. 60% $[30+30 = 60]$
- B. <60%
- C. 51% $[1-0.3] \times [1-0.3]=0.49; [1-0.49] = 0.51$
- D. None of the above
- E. Don't know

Why Determination of Additive –Effect or Synergism is More Complicated than Expected: Pre-requirement: How To Draw A Dose-Effect Curve? What is Pharmacodynamics (PD)?

- Single Dose of Any Drug (or Drug Combo) Gives Only One-Data Point of Potency. One-Point has “No Shape”, Therefore, It is Not Possible to Study PD Interaction or Synergy-Quantification.
- PD Need Two or More Data Points.
- In Vitro, in Cells,
- In Tissues, in Animals and In Clinical Trials

From Chou TC.
Pharmacol. Rev. 58:
621-681, 2006. Fig. 1



An Example for Illustration :

What is Additive Effect of **A + B** ?

For “PD”, We need to know both **Potency** (D_m) and **Shape** (m)

[In the past, the Dynamic Order (Shape) has been ignored].

[Considering Only Potency without Dynamics Shape Is Insufficient].

The Mass-Action Law PD’s Median-Effect Equation (MEE) and the Combination-Index Equation (CIE) are the “**Quantitative Solutions**”.

Algorithm for Computerized Simulation of Synergism, Additivism and Antagonism of the Effect of Multiple Drugs

The Median Effect Equation

$$\begin{array}{l} (1) \frac{f_a}{f_u} = (\frac{D}{D_m})^m \\ (2) \log(\frac{f_a}{f_u}) = m \log(D) - m \log(D_m) \\ (3) f_a = 1/[1 + (\frac{D_m}{D})^m] \\ (4) D_x = D_m [f_a / (1 - f_a)]^{1/m} \end{array}$$

The Combination Index Equation

$$\begin{array}{l} (5) CI = \frac{(D)_1 + (D)_2}{(D_x)_1 + (D_x)_2} = \frac{1}{(DRI)_1} + \frac{1}{(DRI)_2} \\ (D_x)_{1,2} = (D)_1 + (D)_2 \\ \text{and } (D)_1 / (D)_2 = P/Q \\ (D)_1 = (D_x)_{1,2} \times P/(P+Q) \\ (D)_2 = (D_x)_{1,2} \times Q/(P+Q) \end{array}$$

General Theory for General Bio-Interactions Dynamics

[Chou. Pharmacol Rev 58: 621-681, 1984. Fig. 7]

D = Dose

f_a Fraction affected

f_u Fraction unaffected

D_m Median effect dose

m Slope, Hill type coefficient or kinetic/dynamic order

CI: Combination Index

$CI = 1$ (additive effect)

< 1 (synergism)

> 1 (antagonism)

DRI: Dose-Reduction Index

$$(DRI)_1 = \frac{(D)_1}{(D)_x}, \quad (DRI)_2 = \frac{(D)_2}{(D)_x}$$

For n Drug Combinations:

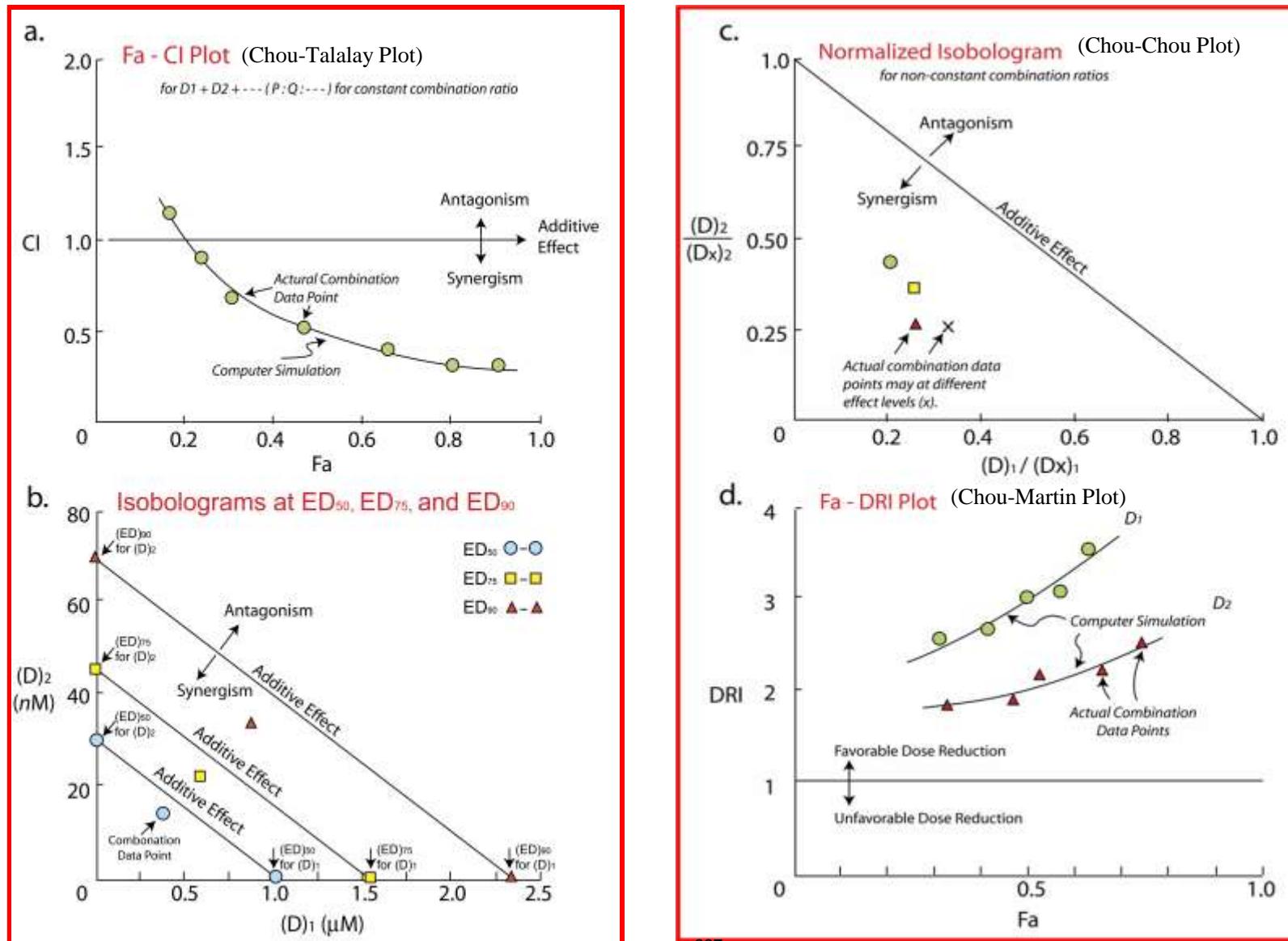
$$CI = \sum_{j=1}^n \frac{(D)_j}{(D)_x^j}$$

**The Mass-Action Law
Derived General Theory:
The Applications of this
Unified Algorithm is**

Independent to drug ratio, drug units, mode of actions, and “mechanism of actions”.

It is valid for 2 to n drugs, or Entities (Virus, Radiation, etc.) for Combination Interactions ***in vitro, in Cells, in Animals and in Clinical Trials.***

Auto-generated Diagnostic Plots for Drug Combination Dynamics by CompuSyn: Geometric Transformations and Algorithm Based Simulation with Digitalized, Indexed Conclusions in One Second.



**"The New Era of
Digital/Indexed
Pharmacodynamics
Biodynamics &
Bioinformatics"
Require only
"Doses" and
"Effects" Data
Entry.**

[All These Four
Types of Diagnostic
Plots can be
generated in about
one second,
following the
"Dose" & "Effect"
Data Entries].

Trends of Drug Combination Methods for Synergy Determination, 1900 to December 28, 2019*

The Combination Index (CI) equation is actually "mathematically derived" from system analysis of the mass-action law (MAL), and its algorithm is exactly for general "quantitative determination" of synergy.

This algorithm-based digital computerized CI method, distinguishes from all others methods available in field.

This Table Is updated from Zhang N. et al. Synergy 6: 97-104, 2016. [Table 2](#).

| Method, and Reference Source | Trend of Citation | | | | | | Total Citations Since Publication | Average Citations per year |
|---|-------------------|------|------|------|------------|--|-----------------------------------|----------------------------|
| | 2016 | 2017 | 2018 | 2019 | 2020 ** | | | |
| A. Chou, TC & Talalay, P Adv. Eng. Regul. 1984; 22:27-55 [MEE & CI Theory] | 315 | 333 | 333 | 329 | 4 | | 5,105 | 145.9 |
| B. Chou, TC Pharmacol. Rev. 2006;58: 621-681 [MEE, CI Review] | 309 | 325 | 311 | 342 | 2 | | 2,423 | 186.4 |
| C. Chou TC Cancer Res. 2010; 70: 440-446 [CI Perspectives] | 293 | 323 | 340 | 437 | 4 | | 2,079 | 231.0 |
| D. Bliss, CI Ann. Appl. Biol. 1939; 26: 585-615 | 108 | 94 | 100 | 89 | 4 | | 1,173 | 14.7 |
| E. Berenbaum, MC Pharmacol. Rev. 1989; 41: 93-141 | 51 | 40 | 43 | 38 | 0 | | 1,130 | 37.7 |
| F. Greco, WR et al Pharamacol. Rev. 1995; 47: 331-385 | 80 | 75 | 64 | 58 | 0 | | 966 | 40.3 |
| G. Steel GG & Peckham MJ Int. J. Radiat. Oncol. BioPhys. 1979; 5: 85-91 | 18 | 22 | 11 | 17 | 0 | | 772 | 19.3 |
| H. Tallarida, RJ J. Pharmacol. Exp. Ther. 2001; 298: 865-872 | 35 | 37 | 24 | 24 | 2 | | 511 | 7.9 |
| I. Elion GB, Singer S & Hitchings GH J. Biol. Chem. 1954; 208: 477-488 | 3 | 7 | 4 | 2 | 1 | | 474 | 26.3 |
| J. Prichard, MN & Shipman C Jr Antiviral Res. 1990; 14: 181-205 | 35 | 30 | 15 | 12 | 0 | | 453 | 15.6 |
| K. Webb J.L. Acad. Press. 1963; 1: 66-79, 488-512 | 7 | 12 | 11 | 6 | 0 | | 317 [#] | 5.7 |
| L. Loewe, S Pharmacol. Rev. 1957; 9: 237-242 | 0 | 2 | 2 | 6 | 0 | | 129 | 2.1 |

*Based on Thomson Reuters Web of Science ⁶³⁸ all database, as of December 28, 2019. (Citation numbers are higher in Google Scholar Citations).

[#]Based on Google Scholar Citations (for books), as of December 28, 2019. ** Citations assigned by Journals as of December 28, 2019, but not yet published.

CompuSyn

For PD/BD/BI of Single Drug or Drug Combinations

[An “One Second” Automated Data Analysis Based on The Mass-Action Law]

A Computer Program for Quantitation of
Synergism and Antagonism in Drug Combinations,
and the Determination of IC_{50} , ED_{50} and LD_{50} Values.

By Ting-Chao Chou (MSKCC)

and Nick Martin (MIT)

Published and Distributed by ComboSyn, Inc.

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[As of 3.13.2020: 36,944 Downloads by Bio-Medical Scientists from 129 Countries or Territories]

<http://www.combosyn.com> – PD Science, LLC (USA)

Synergy

International Journal for Synergy Research in Life Sciences

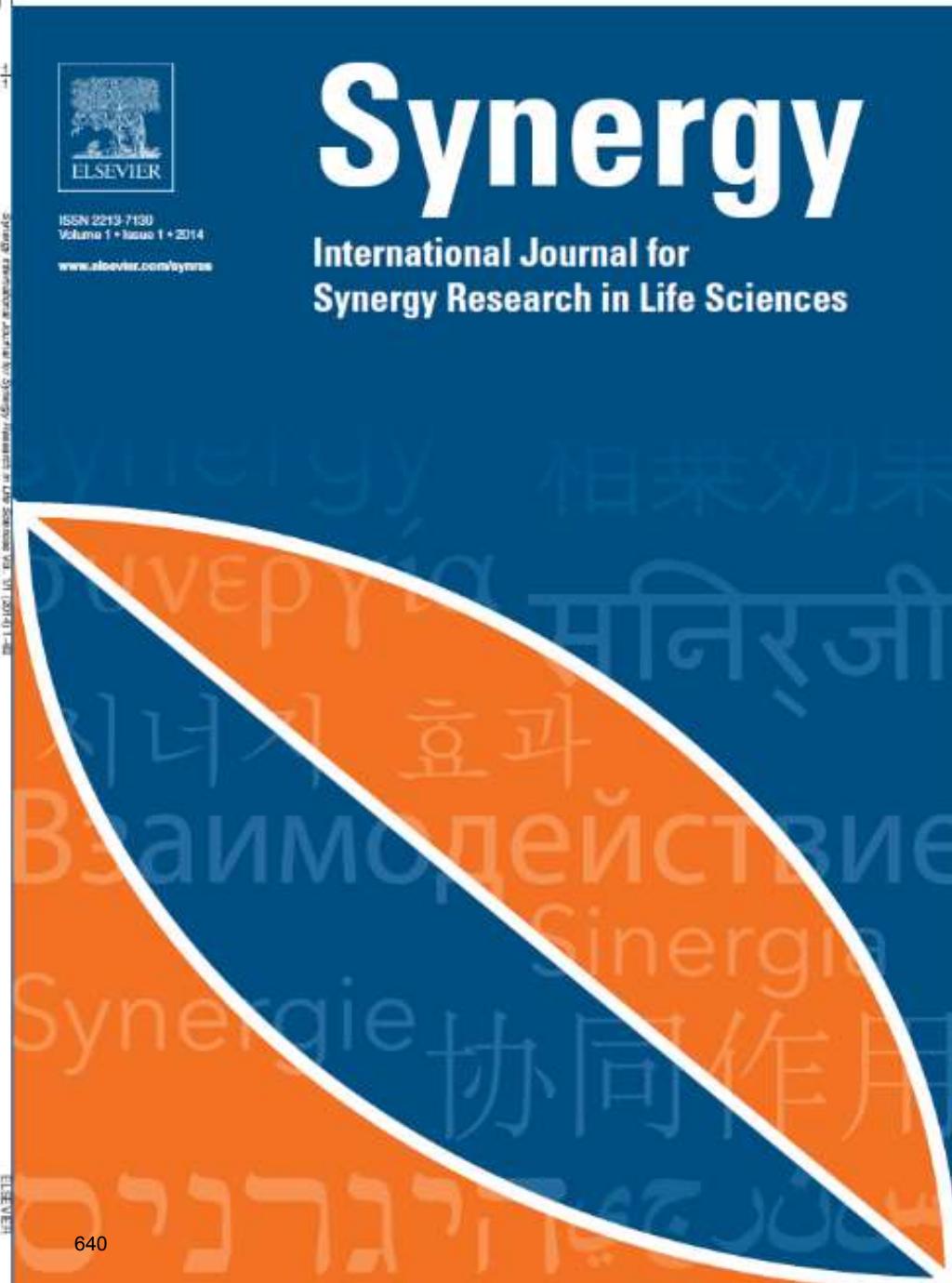
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Journal Inauguration First Article
September 23, 2014
Basel, Switzerland

Available online at www.sciencedirect.com

ScienceDirect



A “Constant-Ratio” Econo-Green Experimental Design Showing the Outlay of Two Drugs for Drug Combination Analysis in Vitro

[Using Only 16 Data Points, $(3 \times 5 + 1 = 16)$ in duplicates or triplicates]*

Simple and Efficient
Constant-Ratio
Diagonal Combo Design
(Recommended)

Chou TC.
Pharmacol. Rev. 56:
621-681, 2006. *Table 5.*

| | | Drug 1 | | | | |
|--------|---|---|---|--|--|--|
| | | 0 | 0.25X (ED ₅₀) ₁ | 0.5X (ED ₅₀) ₁ | 2X (ED ₅₀) ₁ | 4X (ED ₅₀) ₁ |
| Drug 2 | 0 | Control (f _a) ₀ | (f _a) ₁ | (f _a) ₁ | (f _a) ₁ | (f _a) ₁ |
| | 0.25X (ED ₅₀) ₂ | (f _a) ₂ | (f _a) _{1,2} | | | |
| | 0.5X (ED ₅₀) ₂ | (f _a) ₂ | | (f _a) _{1,2} | | |
| | (ED ₅₀) ₂ | (f _a) ₂ | ----- | | (f _a) _{1,2} | |
| | 2X (ED ₅₀) ₂ | (f _a) ₂ | | | (f _a) _{1,2} | |
| | 4X (ED ₅₀) ₂ | (f _a) ₂ | | | | (f _a) _{1,2} |

[The “Non-Constant Ratio Design” can also be used for quantitative Synergy determination. But No automatic computerized simulation can be done]

*For animal or clinical trials, the practical minimum is 10 data points ($3 \times 3 + 1 = 10$), by removing the lowest and highest doses in this scheme. Each Dose has 4-6 or more animals or patients, depending on the measurement need, *in vivo* with 1.3-1.5 fold serial dose dilutions instead of 2-fold dilutions *in vitro*.

[The Recommended Practical Minimum Number of Data Points for Two Drug Combinations *In Vitro, In Animals and In Clinical Trials* need: 16, 10, and 10 Dose-Points, respectively]

Quantitative (CI) and Qualitative Presentations of Synergy

[CI is the Key For All. Prefer to Use CI Value Directly]

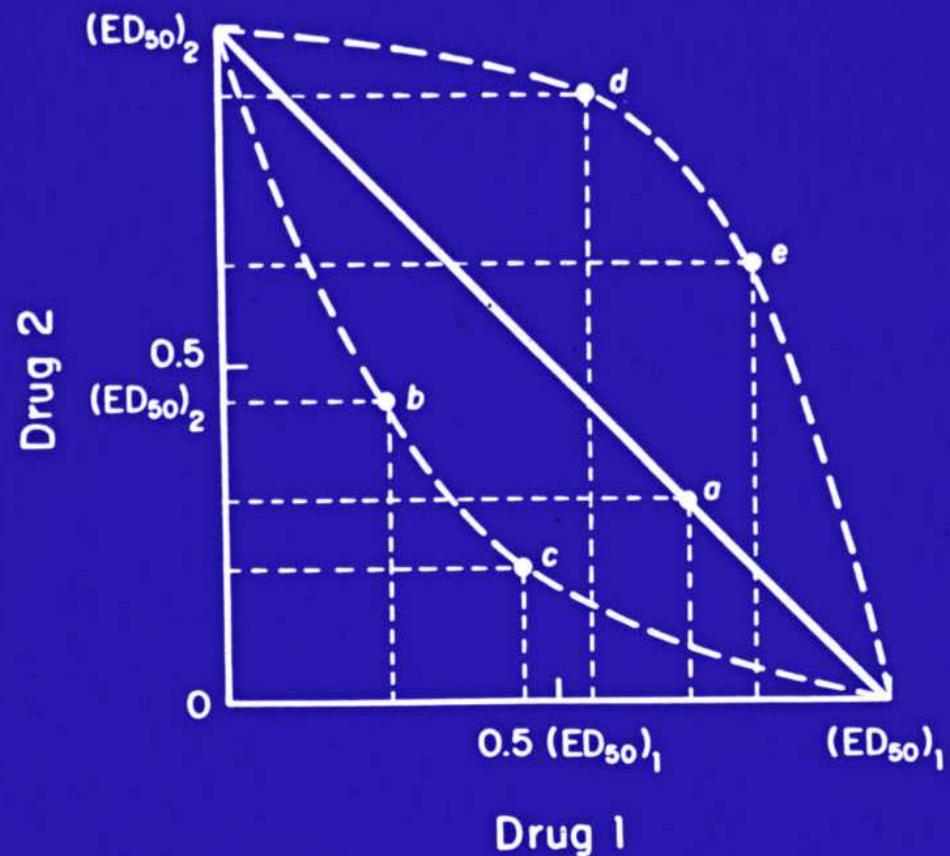
| Range of combination index | Description | Graded symbols | Graphic symbols |
|----------------------------|------------------------|----------------|-----------------|
| <0.1 | very strong synergism | +++++ | |
| 0.1-0.3 | strong synergism | ++++ | |
| 0.3-0.7 | synergism | +++ | |
| 0.7-0.85 | moderate synergism | ++ | |
| 0.85-0.90 | slight synergism | + | |
| 0.90-1.10 | nearly additive | ± | |
| 1.10-1.20 | slight antagonism | - | |
| 1.20-1.45 | moderate antagonism | -- | |
| 1.45-3.3 | antagonism | --- | |
| 3.3-10 | strong antagonism | ---- | |
| >10 | very strong antagonism | ----- | |

^a Combination index method is based on those described by Chou and Talalay (1984) and the computer software of Chou and Martin (2005). The ranges of CI and the symbols are refined from those described earlier by Chou (1991). CI<1, =1, and >1 indicates synergism, additive effect and antagonism, respectively. (Modified from Chou and Martin, 2005)

Fa-CI Plot Is More Practical than Isobol, Since Isobol has limited Dose-Levels or Effect-levels. Both can be generated by CompuSyn automatically, and instantly.

Chou TC,
Pharmacol. Rev.
58: 621-681,
2006; Fig. 6

ISOBOLOGRAM (Equi-Effective Curve)



CI < 1 Synergism

CI = 1 Additive Effect

CI > 1 Antagonism

$$CI = \frac{D_1}{(D_x)_1} + \frac{D_2}{(D_x)_2}$$

(Chou & Talalay, Adv. Enz. Regul. 22:27-55, 1984)

Combination Data Points:
On Diagonal Line (point *a*) indicates Additive Effect.
On Lower-Left (points *b.c.*) indicate Synergism,
On Upper-Right (points *d.e.*) indicate Antagonism.

This Graph is for *Visual Diagnosis*.

Isobol Equation is formally a special case of the Chou-Talalay's CI Equation (i.e., when CI=1).

Now the Isobogram can be generated in less than one second by using PD algorithm Based CompuSyn software.

Anti-Cancer 2 & 3 Drug Combinations In Vitro:

Experimental “*Design*”,
Data “*Analysis*”
& Digital Parameters
Results/Conclusions
“Summary Reporting”
Computer Analysis: About
2 seconds.
Report Printout: About 1
min. (about 15 pages).

Data from: Chou TC et al.
JNCI 86: 1517-1524, 1994.
(Table 3).

[Cited 537 Times in 255 Journals]

Dose-Effect Relationships and Parameters of Taxol, Cis-Pt and Topotecan in 844K Cells

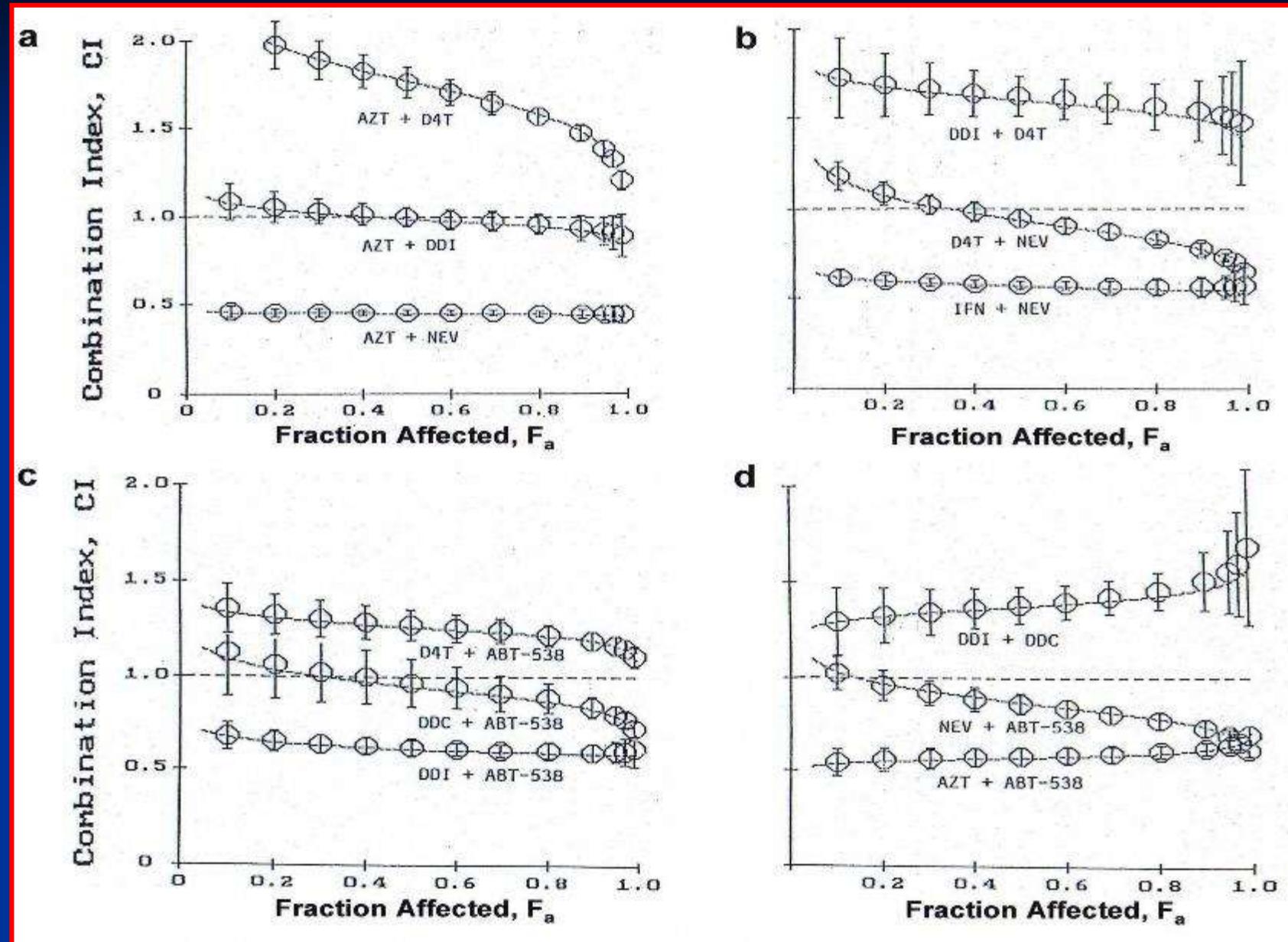
| Drug (μM) Taxol | Parameters ^a | | | | | |
|---------------------------------|-------------------------|-----------|--|---------|--------------------------------------|-------|
| | Cis-Pt | Topotecan | Fractional inhibition (f _i) | m | D ₅₀ (μM) | r |
| 0.002 | | | 0.429 | | | |
| 0.004 | | | 0.708 | | | |
| 0.005 | | | 0.761 | | | |
| 0.01 | | | 0.882 | | | |
| 0.02 | | | 0.932 | 1.248 | 0.0022 | 0.990 |
| | | | | | | |
| 0.05 | | | 0.055 | | | |
| 0.1 | | | 0.233 | | | |
| 0.2 | | | 0.301 | | | |
| 0.5 | | | 0.559 | | | |
| 1 | | | 0.821 | | | |
| 2 | | | 0.953 | 1.458 | 0.320 | 0.986 |
| | | | | | | |
| 0.01 | | | 0.069 | | | |
| 0.02 | | | 0.213 | | | |
| 0.05 | | | 0.373 | | | |
| 0.1 | | | 0.785 | | | |
| 0.2 | | | 0.940 | | | |
| 0.5 | | | 0.991 | 1.847 | 0.046 | 0.991 |
| | | | | | | |
| 0.01 0.1 | | | 0.450 | | | |
| 0.02 0.2 | | | 0.671 | | | |
| 0.05 0.5 | | | 0.921 | 0.00115 | | |
| 0.1 1.0 | | | 0.958 | 1.510 | +0.115 | 0.994 |
| | | | | | | |
| 0.05 0.005 | | | 0.314 | | | |
| 0.1 0.01 | | | 0.382 | | | |
| 0.2 0.02 | | | 0.675 | | | |
| 0.5 0.05 | | | 0.903 | 0.0108 | | |
| 1 0.1 | | | 0.987 | 1.706 | +0.108 | 0.974 |
| | | | | | | |
| 0.01 0.1 | | | 0.173 | | | |
| 0.02 0.2 | | | 0.579 | | | |
| 0.05 0.5 | | | 0.901 | 0.0019 | | |
| 0.01 0.1 | | | 0.946 | 1.937 | +0.0193 | 0.984 |
| | | | | | | |
| 0.001 0.1 | | 0.01 | 0.356 | | | |
| 0.002 0.2 | | 0.02 | 0.806 | 0.00126 | | |
| 0.003 0.3 | | 0.03 | 0.947 | +0.1256 | | |
| 0.005 0.5 | | 0.05 | 0.995 | 3.619 | +0.0126 | 0.992 |

m : Shape of dose-effect curve. (m=1, >1 and <1 indicate hyperbolic, sigmoidal and negative sigmoidal)

D₅₀: Potency (IC₅₀)

r : Conformity (Linear correlation coefficient)

Typical ‘Diagnostic Fa-CI Plots’ for Anti-HIV Agents Combinations in Vitro



[Cancer & AIDS
Chemotherapy
**Combination-
Cocktail Design**]

Chou TC.
Pharmacol. Rev.
58: 621-681, 2006.
Fig. 9

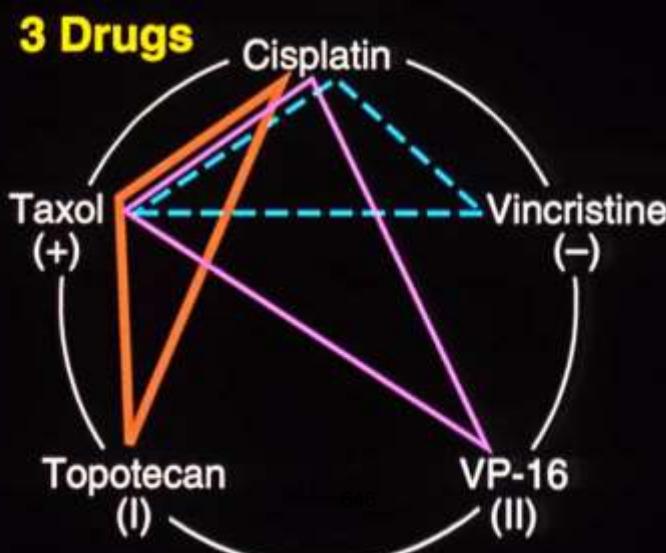
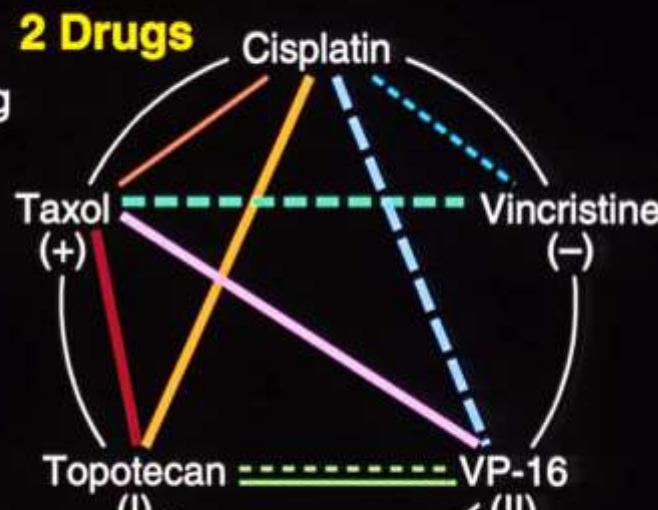
Featured on the front
cover in Integrative.
Biology. 3: 548-559,
2011 (May)]

Mechanism **Drug Interactions**

Alkylation
DNA cross-linking

Microtubule
Polymerization

DNA
Topoisomerase
Inhibition



5-Drug
“Polygonogram”
With 5 Different
Anti-Cancer
Mechanisms

*Mechanisms Can Not
Predict Synergy
Quantitatively!*

Polygonogram
“Projects the
Outcomes”
Visually and
Semi-quantitatively.

**Efficient,
Cost-Effective.
Fewer
Doses/Data
Point.**

**Computer-Simulated
Quantitative/ Indexed
Conclusions.**

**No Reason to Waste
Time, Efforts and
Resources in Animal
Studies and in Clinical
Trials When Simple,
Quantitative, Efficient,
Effective Method Is
Available.**

Comparison of Two-Drug Combinations for Anti-Cancer Agents Using “Econo-Green” Small Size Experimental Design

[Chou TC, Am J Cancer Res 1(7): 925-954, 2011, Table 6]

[Chou TC, Integrative Biol. 3: 548-559, 2011, Table 1]

| | In Vitro | In Animal | In Clinic (Phase I) |
|--|---|---|--|
| Time & Effort | 2 weeks | 2 months | >1 year |
| Non-wage Cost | \$200 [cells and chemicals] | \$3,000 [nude mice] | Expensive Trials [\$ Multi-millions, Vary] |
| Sample Size | $> 2 \times 10^6$ [cells] | > 65 [nude mice] [Chou-Talalay method] | > 36 [vary based on accuracy of end-point determination] [Chou-Talalay method] |
| “Practical” Minimum of Data Points (Econo-Green Approach) | 16* (5+5+5+1) | 10 (3+3+3+1) | 10 (3+3+3+1) |
| Quantitative “Synergy” Determination | Very Easy [But frequently not done properly in the past] | Not Difficult [Rarely properly done in the past] | Difficult Use Surrogate Markers, Fractional Doses and Scanning |

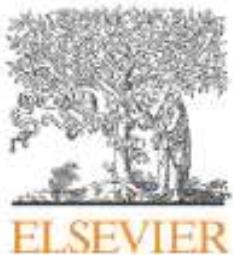
*Practical increase of data points in vitro due to simplicity, low cost, and no ethical, legal restrictions.

“Design”
Dictates Analytic Method and *Precludes* Possible Conclusions.

If use only single dose of any drug in drug combination, it is not possible to determine “Synergy”, no matter how accurate is the assay, or how long time spent for the research project.

Specific Drug Combo Example in Animals for Illustration:

A “Model” for Clinical Trial Protocol Design & Data Analysis with *Only 10 Data Points*



Drug combination *in vivo* using combination index method: Taxotere and T607 against colon carcinoma HCT-116 xenograft tumor in nude mice

Jianing Fu^{a,1}, Ning Zhang^{b,1}, Joseph H. Chou^c, Hua-Jin Dong^d, Shu-Fu Lin^e, Gudrun S. Ulrich-Merzenich^f, Ting-Chao Chou^{g,*}

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^b Department of Obstetrics & Gynecology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200126, PR China

^c Department of Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

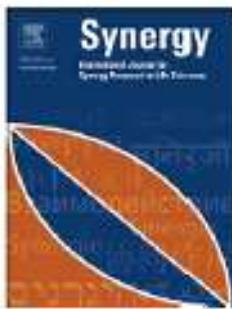
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For a Review,
see Chou et al.
Synergy 9:
100049 Dec.
2019, and Supp.
Slides)



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Taxotere

ABSTRACT

The median-effect equation (MEE) of the mass-action law and the combination index (CI) theorem have been used for quantitative determination of synergism (CI <1), antagonism (CI >1) and additive effect (CI=1) in animals *in vivo*. Experimental design, the theoretical algorithm and the CompuSyn software simulation have been used to illustrate step-by-step for the combination of two anti-cancer agents, Taxotere and T607 compound, with similar mode of actions of targeting microtubule polymerization, but with distinct chemical structures. These two compounds acted synergistically against human colon carcinoma HCT-116 xenograft tumor in athymic nude mice. In all, only 78 nude mice have been used. The synergy is especially significant ($p < 0.01\text{--}0.05$) following Q3Dx4, x3 i.v. treatments, at higher doses and at later stages of treatment. The MEE and the CI theorem of Chou-Talalay quantitatively determined synergism or antagonism at different doses and different effect levels as indicated by the Fa-CI plot and by isobolograms in CompuSyn simulation and automated graphics. The practical logistics on pre-experimental planning, scheme/design/layout, and precautions in terms of dose number, dose range, dose density, drug combination ratio, conservation of laboratory animals as well as regulatory and cost-effective considerations have been presented. The mass-action law based CI algorithm has been proven to be simple to use, economy to practice, even for *in vivo* experimentations. Most significantly, the mass-action law based algorithm provides quantitative indexed conclusions.

Synergy 3: 15-30, 2016

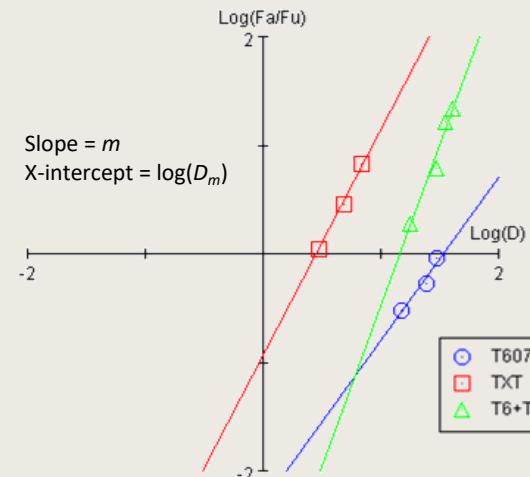
Graphic Dynamic Transformations of Mass-Action Law Algorithms

"Drug Combination Study *In Animals* Using Only 10 Data Points"

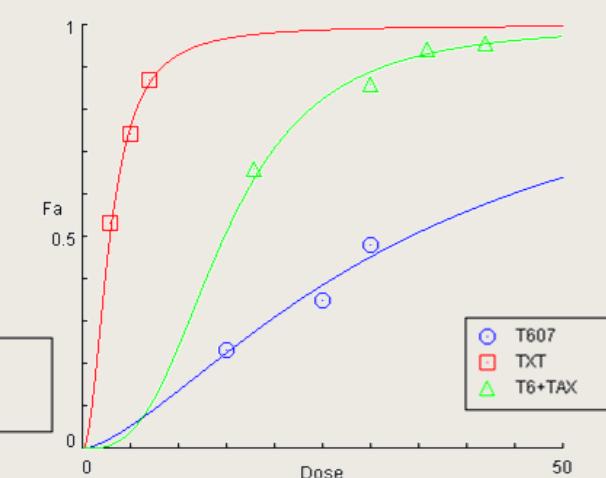
Anti-HCT-116 Tumor Xenograft in Nude Mice: T-607:Taxotere & Combinations (5:1), Day 35 Data. (Each dose point, n=6 mice/dose).

Fu J, Zhang N, Chou JH, Dong H, Lin SF, Ulrich-Merzenich G, & Chou TC. Synergy 3: 15-30, 2016. (Figs.4 & 5)

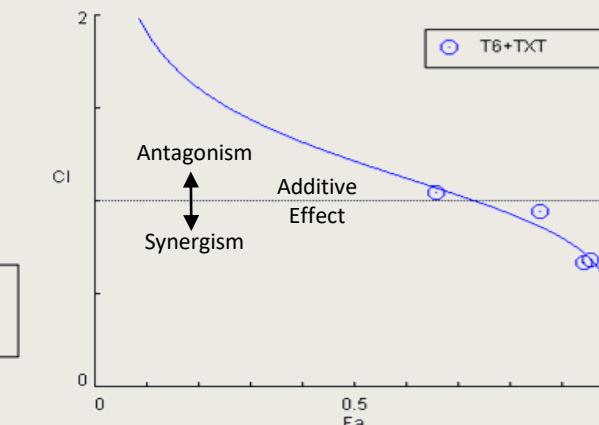
A. Median-Effect Plot (Chou Plot)



B. Dose-Effect Curve (Simulated)



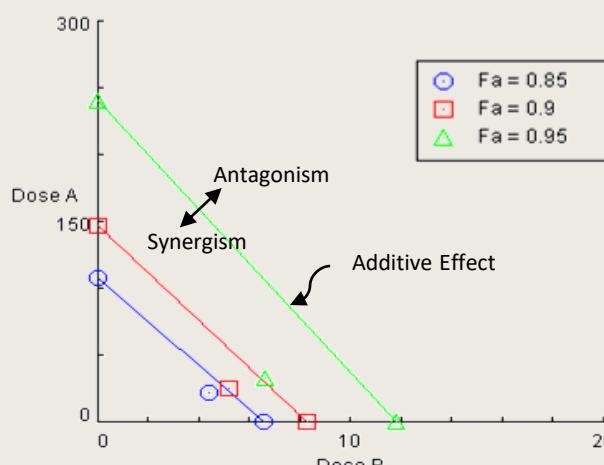
C. Fa-CI Plot (Chou-Talalay Plot)



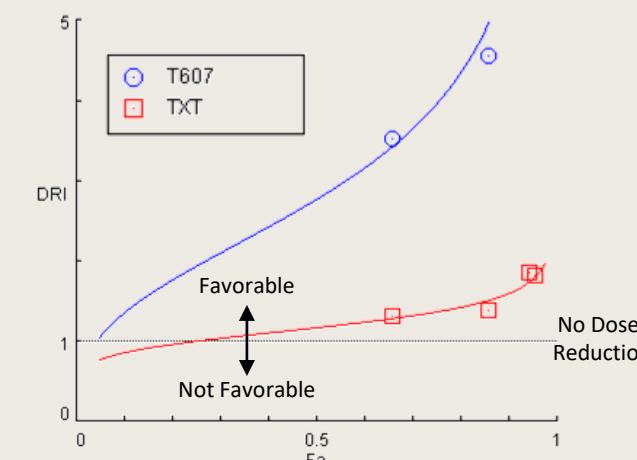
MAL New Informatics:

We Cannot Use Over 3 or 4 Data Points in Animals or in Humans! It Would be *too Toxic or too Ineffective*. This Problem is Now Solved with the *Minimum 2-Data Points Theory of MAL-PD/BD*.

D. Isobolograms (Classic Isobol)



E. Fa-DRI Plot (Chou-Martin Plot)



All five Diagnostic Graphs are based on the "Same" 10 Dose-Data Points in Graph "A" or "B" (3+3+4) by automated computerized simulation of 10 data points with 5 graphs, in one second.

Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies[§]

TING-CHAO CHOU

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Bio-Dynamic Principle

Theory

Equations

Algorithms

Experimental Design

Very Few Data Points

Small Size Experiments

2-D Combo Protocol

Constant Ratio Scheme

Computer Simulation & Automation

Graphics/Diagnostic Plots

Quantitation

Digitalized/Indexed &

Definitive Conclusions &

Silico-Bio-Informatics.

[A Case of Theory First, Applications Later]

Chou TC. *Pharmacol. Rev.*
58: 621-681, 2006.

(61-pages, 23 Tables, 14 Figures, 45 Equations, plus five Appendices).

Received 3,364 citations in 956 bio-medical journals worldwide, as of 3.11.2020.

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The author is a principal in and holds the copyright to CompuSyn, the software used for the analyses performed in this article. His son, who contributed to the software's development, is in a position to receive royalties for its publication.

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>.
doi:10.1134/pr.58.3.10.

[§] The online version of this article (available at <http://pharmrev.aspetjournals.org>) contains supplemental material.

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A Unique Approach

“Basic Principle & Theory First, and Experiments & Interpretations Later”.

Instead of

“Empirical/Arbitrary Experiments First”, and Hypothesis and Speculations Later.

“Experimental Design Is of Critical Importance”
It Should Not be Arbitrary, Random or Casual. Never conduct drug Synergy studies with Single Dose! Never Use p-Value to determine Synergy ! Use the CI Value.

“How We Design” may Dictate What Type of Data We Get, and What Kind of Analysis, Interpretations and Conclusions Can be Obtained.
[e.g., Impossible to determine “Synergy” if you use single dose of any drug.

No mater how accurate is your assay or measurement, how many times you repeat your experiment, or how many years you spent on your project]

Other Applications of MAL

MEE/CIE for PD/BE/BI:

1. Low Dose Risk Assessment of Carcinogens, Toxic Substances and Radiation (p.658-660, Tables 12-13, Fig.14; Table 14, Hiroshima A-Bomb & Leukemia)
2. Topological Receptor Analysis (p.657-658, Fig.13)
3. Therapeutic Index and Safety Margin (p.660-663, Table 15)
4. Age-Specific Cancer Incidence Rate Analysis & Epidemiological Analysis (p.663-664, Table 16)
5. Calculation of Ki from IC50 (p.664, Table 17). Ki can never greater than IC50.
6. Five Drug Combinations against HIV (p.665-668, Table 20-23, Supplement. 90 pages)
7. Insecticides Combination against House Flies (p.664-665, Table 18, Appendix V)
8. Approaches for Conservation of Laboratory Animals & Regulations (p.668-669)
9. Econo-Green R&D & Basic Drug Evaluation Regulation Guidance (see Slides #2,5,7,15-20, 31-33)
10. Animal Studies,or Clinical Trial Protocol Design with Fewer Data Points (see Slides #18-21, 31-33, 39-41.45)
11. Applications from Molecular, to Cells to Animals & Clinical Trials (see Slides #2,7,12,19, 36-46)

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Abstract—The median-effect equation derived from the mass-action law principle at equilibrium-steady state via mathematical induction and deduction for different reaction sequences and mechanisms and different types of inhibition has been shown to be the unified theory for the Michaelis-Menten equation, Hill equation, Henderson-Hasselbalch equation, and Scatchard equation. It is shown that dose and effect are interchangeable via defined parameters. This general equation for the single drug effect has been extended to the multiple drug effect equation for n drugs. These equations provide the theoretical basis for the combination index (CI)-isobogram equation that allows quantitative determination of drug interactions, where $CI < 1, = 1$, and > 1 indicate synergism, additive effect, and antagonism, respectively. Based on these algorithms, computer software has been developed to allow automated simulation of synergism and antagonism at all dose or effect levels. It displays the dose-effect curve, median-effect plot, combination index plot, isobogram, dose-reduction index plot, and polygonogram for in vitro or in vivo studies. This theoretical development, experimental design, and computerized data analysis have facilitated dose-effect analysis for single drug evaluation or carcinogen and radiation risk assessment, as well as for drug or other entity combinations in a vast field of disciplines of biomedical sciences. In this review, selected examples of applications are given, and step-by-step examples of experimental designs and real data analysis are also illustrated. The merging of the mass-action law principle with mathematical induction-deduction has been proven to be a unique and effective scientific method for general theory development. The median-effect principle and its mass-action law based computer software are gaining increased applications in biomedical sciences, from how to effectively evaluate a single compound or entity to how to beneficially use multiple drugs or modalities in combination therapies.

I. Introduction

Ever since the earliest days of recorded history, drug combinations have been used for treating diseases and reducing suffering. The traditional Chinese medicines, especially herbal medicines, are vivid examples. As the science of isolation technology and chemical synthetic capability advance, drug combinations have been more defined and sophisticated and their scope continues to broaden. Attempts have been made during the past century to quantitatively measure the dose-effect relationships of each drug alone and its combinations and to determine whether or not a given drug combination would gain a synergistic effect. Because biological sys-

This Article in PDF format is Available for Download via Publisher's Internet/Website at:

[doi:10.1124/pr.58.3.10](https://doi.org/10.1124/pr.58.3.10)
or
pharmrev.aspetjournals.org/cgi/reprint/58/3/621

Tales of Two Anti-HIV Clinical Trials

| | AZT + 3TC | AZT + INF _a |
|------------------------------|---|--|
| Authors | J.J. Eron et al. (9 authors + Northern Am. HIV Working Party) | D. Mildvan et al. (21 authors) |
| Publication | <u>N. Engl. J. Med.</u> 333: 1662-1669, 1995 | <u>Antiviral Therapy</u> 1(2): 77-88, 1996 |
| Journal Impact Factor | 28.5 | 3.1 |
| Number of Patients | 366 [Problems with Design & Analysis] | 36 |
| Surrogate Marker | CD ₄ ⁺ , HIV RNA | P24 Antigen, CD ₄ ⁺ |
| Treatment Design | Fractionated Repeated Doses AZT <u>Single Dose</u> , 3TC 2 Doses | Fractionated Repeated Doses Both Drugs have 3 Doses. <u>Used Only 10 Data Points</u> |
| What They Have Proved | <u>“Combination Effect is Greater than Each Drug Alone”</u> <u>Statistics Not Possible to Claim Synergism</u> A+B > A, A+B > B (p<0.001). Axiom Does Not Need A Proof ! | <u>“Quantitative Determination of Synergism”</u> Using Combination Index Method Simulation (CI < 1 determined synergism) Used Chou-Talalay CI Method. Adv. Enz. Regul. 22: 27-55, 1984 |

It Is *Not Possible* to Quantify Synergy with a Single Dose of Any Drug !

AZT+IFN Is A Life Example for Econo Green, Efficient, Computerized Clinical Protocol Design, Using the Chou Talalay CI Method.

PD Needs Two (or More) Doses, for both “Potency” and “Shape”. Single Dose Generates A Potency “Point”, But No “Shape”.

The PD-Doctrine indicates that “*All Clinical Trials*” for Protocol-Designs Using “*Only Single Dose*” is *Not a PD Study*. Should Use 2 (or More) Doses, & Analyzed with PD Automated Simulation.

Conclusion: Synergy is Not determined by *p* values but rather by the CI values
Synergy is Not a Statistical Issue but rather a Mass-Action Law Issue
[Chou T.C. Integrative Biol. 3: 548-559, 2011. p.557 and Chou TC. Synergy 1: 3-21, 2014. Table 4]

MAL-PD Based Computerized CI Simulation

of Synergism/Antagonism by CompuSyn

[The Practical , Efficient, Econo-Green & Quantitative Bio-Informatics]

Refs. Chou TC.

Pharmacol. Rev. 58: 621-681, 2006. pp.638-643.

Cancer Res. 70:440-446, 2010. p.444

Integr. Biol. 3: 548-559, 2011, p. 558.

Synergy 1: 3-21, 2014. (Q&A).

Fu J. et.al. Synergy 3: 15-30, 2016. (CompuSyn Report : pp.21-26).

Answers Primary Questions:

- Is there any synergism?
- How much synergism?
- Synergism at what dose levels?
- Synergism at what effect levels?
- What the exhibited isobologram looks like?
- How many folds dose reduction for each drug as results of synergism?

These Questions Are Answered by MAL-PD Combination Index Equation, and CompuSyn software with Proper Experimental Designs.

"CI Method is the *Only* Method in Literature that Quantitatively Determines Synergism, Additive Effect, and Antagonism" by Computer Simulation, with Proven Algorithm".

Answers Other Questions:

- Optimal combination ratio (1:1; 3:1; 1:3 which better?)
- Schedule dependency (Simultaneous, A follows B, B follows A)
- Selectivity of synergism (Target vs Host)
- Condition directed synergism (Temperature, Pressure, pH, Oxygen Tension ..)

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Combination Therapy Is the Mostly Widely Used Treatment for the Most Dreadful Diseases Such As Cancer and AIDS. It is Important to Define and "Quantify Synergy".

[Chou TC. Pharmacol. Rev. 58:621-681, 2006. Eq. 20]

Source: Chou TC.
Pharmacol. Rev. 58: 621-
681, 2016, Eqs. 19-20.
The Theoretical Basis for
the Future Drug
Combination in *High*
Throughput Robotic Data
Analysis. e.g., for cocktails
or for the Traditional
Chinese Medicine.

$n(Cl)_x$ Combination index for n drugs at x% inhibition

$(D_x)_{1 \sim n}$ The sum of n drugs that exerts x% inhibition in combination

$\left\{ [D]_i / \sum_1^n [D] \right\}$ The proportionality of each of n drugs that exerts x% inhibition in combination

$(D_m)_i \left\{ (fa_x)_i / [1 - (fa_x)_i] \right\}^{1/m_i}$ The dose of each drug alone that exerts x% inhibition.
Where D_m : The median-effect dose (Antilog of the x-intercept of the
median-effect plot)
 fa_x : Fractional inhibition at x% inhibition
 m : The slope of the median-effect plot which denotes the type of
the dose-response curve. $m=1, >1, <1$ for sigmoidal, hyperbolic,
sigmoidal, and negative linear curves, respectively.
655

New Reality for Drug Combinations

- “Mechanisms” and “Statistics” Can Not Predict Synergy Quantitatively
- Even if it Sometimes Predictions Happen to Be Correct,
They are Still Qualitative, Not Quantitative
- Synergy is Not To Be Predicted But To Be Determined Quantitatively.
- Not Possible to Quantify “Synergy”, Using “Single Dose” of Any Drug.
- Synergy Is “Mutual” (A&B or B&A); Not “One-Sided” (A to B, or B to A) Such as Enhancement or Potentiation, e.g., 30% Enhancement, No Need of the Calculation of CI.
- Synergy is Determined by the Combination Index (CI < 1)
Not by the Statistical *p* values

[Synergy is A Mass-Action Law Issue, Not A Statistical Issue]

[Chou TC, Pharmacol. Rev. 58: 621-681, 2008; Synergy 1: 3-21, 2014]

The Combination Index (CI<1) As the Definition of Synergism and Synergy Claims

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International Synergy Forum – 2018

Bonn, Germany. March 9-10, 2018

A Keynote Presentation
[Synergy 7: 49-50, 2018]

New Pharmacodynamics (PD) For Digitalized Biomedical R&D and the New Drug Evaluation Regulations

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Uniformed Services University of Health Sciences, Bethesda, MD
October 1, 2018

Philosophy Theory Equation Algorithm Digitalized-Computer-Simulation
Small-Size-Experiment Cost-Effectiveness Guidelines

Pharmacodynamics (PD) Algorithm Based General Drug-Evaluation Guidance, Clinical Protocol Design, Computerized Data Simulation, and Digitalized/Indexed Conclusions

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April 9, 2019

Johns Hopkins University School of Medicine, Baltimore MD

Mass-Action Law Based Pharmacodynamics (PD) Theory/Algorithms For Digital Biomedical R&D and For Basic Drug-Evaluation General Guidance

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May 7, 2019

FDA *Public Hearing Presentation* at 2019- Pharmaceutical Science and Clinical
Pharmacology (PSCP) Advisory Committee Meeting

Food and Drug Administration

White Oak Campus, 10903 New Hampshire Avenue, Silver Spring MD 20993
660

FDA PUBLIC MEETING PROMOTING EFFECTIVE DRUG DEVELOPMENT PROGRAMS: OPPORTUNITIES AND PRIORITIES FOR FDA'S OFFICE OF NEW DRUGS

Speaker: **Ting-Chao Chou**, PD Science LLC, Paramus, New Jersey 07652-1754
E-Mail: dtchou99@gmail.com

Mass-Action Law Pharmacodynamics (MAL-PD) for Quantitative Biomedical R&D, and Efficient Drug-Evaluation Guidance: Computerized Data Analysis of Single Drug and Drug Combinations in Vitro, in Animals and in Clinical Trials

Place: **Food and Drug Administration**
White Oak Campus, 10903 New Hampshire Ave. Silver Spring, MD 20993

Date: **November 7, 2019**

T.C. Chou's Web Site

References

- Thomson-Reuters (Publons) Web of Science:
<http://www.researcherid.com/rid/B-4111-2009>
- Google Search: Ting-Chao Chou
- Ting-Chao Chou - Google Scholar Citations
- Wikipedia: Ting-Chao Chou
- www.Combosyn.com [Donated “CompuSyn” for Free Download upon Registration beginning 8.1.2012, by PD Science LLC (USA)]

Submission No.: 234

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

Attachment: ClinicalTrials.gov%20Modernization%20RFI%20(final).docx

ClinicalTrials.gov Modernization RFI

I. Information Submission

- a. **(Response to RFI 2a & 2c) Suggestion to (i) adequately identify study records categorized as non-applicable clinical trials (non-ACT); and (ii) change or remove the following default messages displayed on clinicaltrials.gov's public website for clinical trial for which results are not required as per 42 CFR Part 11:**
 1. “No Results Posted”; and
 2. “No study results posted on clinicaltrials.gov for this study”.

Currently, and corresponding to suggestion a.(ii) above, the internal Protocol Registration and Results System (PRS) classifies study records as an Applicable Clinical Trial (ACT), non-ACT or possible ACT. However, the study record information on the clinicaltrials.gov public website does not convey the ACT, non-ACT and possible-ACT distinction, nor does it mention or define these terms for the public.

The lack of clarity on this classification of clinical trials is misleading and confusing to the public and research community on the obligation sponsors have on meeting regulatory clinical trial registration and results requirements. This confusion leads to the public assumption that clinical trial sponsors are not meeting their regulatory obligations. This assumption perpetuates the public misperception that the reason for a sponsor’s non-compliance is to conceal underhanded clinical practices by the sponsor. We suggest the National Library of Medicine (NLM) rectify this inaccuracy as part of the Clinicaltrials.gov Modernization Project.

With regards to suggestion a.(ii) above, it is important to note, clinical studies assessed by PRS to be a non-ACT (such as Phase I and withdrawn trials), as defined by FDAAA 801 “Final Rule”, are not required to report clinical study results. We would like to bring to NLM’s attention, for all clinical studies not reporting results, there are two default messages displayed on the results tab on clinicaltrials.gov public website for each study record irrespective of whether the study is required to report results as per FDAAA 801 “Final Rule” (42 CFR Part 11). We feel these default messages also creates the misperception that clinical trial sponsors are not meeting their regulatory obligations. The first default message we find to be problematic is the label of the results tab for each clinical study record not required to report results is “No Results Posted”. The second default message we also find problematic is located on the results page itself for each clinical study record not required to report results, which states “No Results Posted on ClinicalTrials.gov for this Study.” We feel these messages on the clinicaltrials.gov public website in association with clinical study records that legitimately do not have a regulatory obligation to disclose clinical study results is misleading the public.

It is our suggestion, for the purposes of clarity and accurate communication of regulatory compliance for these clinical study records not required to report results, that NLM adopt a method similar to that currently in use in the internal PRS system, wherein studies are assessed per FDAAA guidelines for reportability of results and a status of “Non-ACT” or “possible ACT” is assigned for those studies deemed to be as such.

- b. **(Response to RFI 2d) Request and suggestion for NLM to provide further guidance defining “good cause” explanations on requests for extension to a certification of delayed submission of results for clinical trials on an unapproved, unlicensed, or uncleared product (“certify initial approval”) submitted under 42 CFR 11.44(c), or a certification of delay for an approved, licensed, or cleared product (“certify new use”) submitted under 42 CFR 11.44(b).**

The currently available guidance from 42 CFR Part 11 indicates two cases under which the NIH would consider good cause to grant an extension of a delayed results submission deadline:

“(1) The need to preserve the scientific integrity of an applicable clinical trial for which data collection is ongoing, including situations in which the submission of results information for the primary outcome(s) of an applicable clinical trial would impair or otherwise bias the ongoing collection, analysis, and/or interpretation of data for secondary outcome(s). We indicated our belief that an extension should be granted only in those situations in which the following could be demonstrated: Data collection for the secondary outcome(s) of interest extends more than 1 year beyond the completion date, the secondary outcome(s) is pre-specified in the protocol or SAP, and the planned analysis of the outcome measure is also described in the protocol or SAP. We noted that the responsible party could provide this information either by voluntarily submitting copies of the protocol or statistical analysis plan with the extension request or describing them in the extension request itself.

(2) Emergencies that would prevent timely submission of clinical trial results information, including situations in which one or more data collection sites were affected by natural disasters or other catastrophes outside the responsible party’s or sponsor’s control. In such cases, we indicated that we would generally expect to grant the responsible party an initial extension of up to 6 months, after which time additional extensions could be granted, as necessary. We generally would not consider events that might reasonably have been avoided or anticipated through standard contingency planning (e.g., transition planning for key staff members who leave an organization) to constitute good cause for an extension... ”

The regulation makes note that the list of examples presented as “good cause” to grant an extension of delayed publication of results is not exhaustive. It is further iterated in the Final Rule (42 CFR Part 11) Information document issued in December 2019 information on cases that constitute “good cause” for an extension of delayed publication of results is forthcoming.

In recognizing the need to protect the scientific integrity of data collected for studies, and considering that premature disclosure of results information for such studies could potentially bias the collection, analysis, and interpretation of ongoing and future trials, it is requested the Agency provide further guidance and clarification on cases under which the Agency would consider the extension of delayed results submission deadlines.

c. (Response to RFI 2a and 2c) Suggestion is to communicate to the public clinical trial information in Plain Language Summary (PLS) format as a novel or emerging method that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

The suggestion to communicate clinical trial information to the public in PLS format would require NLM to restructure how the clinical trial information of a study record on clinicaltrials.gov is displayed. In order to successfully restructure the display of clinical trial information, it would require NLM to align clinicaltrials.gov with current industry best practices for communicating aggregated results information on clinical trials in an easily digestible form for trial participants and the public who are unfamiliar with scientific terms and clinical research practices associated with the development of drugs, biologics and medical devices for use in humans. This would require clinicaltrials.gov to display clinical trial information using lay language in a lay summary format where the information is written, organized and displayed in a manner understandable to someone with a health literacy level of a twelve year-old. To elaborate on what a PLS format would look like, it would employ the use of infographics, pie charts, and tables to provide visuals in conveying complex information. There are many ways NLM can accomplish this goal and stay compliant with the intricacies and nuances of the “Final Rule”. However, NLM’s budget, resources and timelines would impact NLM’s project management and implementation approach. We feel this suggestion to display clinical trial information on clinicaltrials.gov in PLS format, despite its unconventional method, is necessary and important to enhance information quality and content available to the public on clinicaltrials.gov.

Submission No.: 235

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

I would like to see increased number of links from MedlinePlus to clinicaltrials.gov -- there are built-in links from major illnesses like Non-Hodgkins Lymphoma on MedlinePlus, but not for less common disease entities like Mantle Cell Lymphoma. Likewise, it would be helpful to have links from disease entities in clinicaltrials.gov to the appropriate section of MedlinePlus. Lastly, it would be very helpful to link from these resources to online support communities for those disease entities. Neither MedlinePlus or clinicaltrials.gov link to a definitive list of online communities. Helping new patients to navigate among these resources (online communities, MedlinePlus, and clinicaltrials.gov) will increase patient's familiarity and use of these resources. Thank you!

Submission No.: 236

Date: 3/13/2020

Name: Andrew Pleasant

Name of Organization: Health Literacy Media/C3T

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**
 - Desperate need for easy-to-read summaries and plain language summaries—currently don't exist on ClinicalTrials.gov. EU efforts are leading the way on this.
 - No capacity for feedback or question asking
 - Access to complete reports that are published from a clinical trial, not just the current data requirements for reporting on a clinical trial, e.g. CSR and CTRD and any published articles
 - Whistle blowing capability missing
 - Video summaries would be very helpful, short videos of the researchers explaining their key findings and what they mean for people.
 - Graphic representations of data, not just numbers on a screen
 - Educational information about clinical trials and the clinical trial process—build capacity in society to better understand science
 - An accurate and complete list of adverse events with an explanation if the intervention is suspected as the cause or not
 - Contact information of lead researchers and study sponsors beyond only names.
 - The home page should allow the user to select who they are, so the site can be tailored to their purpose and language, such as “patients/public” and “researchers”
 - Healthy literacy and plain language need to be applied to all content - I think health literacy can be considered within the emerging methods section
 - The search functions need to give clear instructions on the same page (could use video to give an example) and could be reformatted to a Q&A format to use words that people are familiar with
 - Consider a more visually appealing format for each study record, too. For example, use of icons to visually indicate the sections or color to break up the sections.
 - Consider questions a headings in the study record to align with how readers think, such as who can join this study for eligibility criteria

- There are 2 main audiences for ClinicalTrials.gov: public/patients and researchers. The home page should start by having the user select who they are. Then, the website would take them to pages only relevant for them. For example, the patient page would not have a dropdown for 'submit studies' because public aren't doing that. This will also help ensure the language is appropriate for each audience.
- Give specific, step by step instructions on how to use the search within the search page so users don't have to go back and forth with the instructions and search pages. A video showing an example would be ideal here.
- Use words that are familiar to a general audience, not scientific audience. In the advanced search, there are too many unfamiliar words that require glossary definitions. Other jargon words, like eligibility criteria, are even linked to a glossary word.
- Consider changing "find a study" and "searchs" to a question format to help gather information from people and then generate the relevant studies. This would hopefully produce a shorter list of studies based on inclusion criteria. The questions should be written using words that are familiar to a general audience.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

Lots of government information written online - but at a very high readability level and assumed understanding of science and research.

Two non-profit organizations in the space - Health Literacy Media/C3T effort and CISCRP. See www.healthliteracy.media; www.c3t.media; www.ciscrp.org for active U.S.-based organizations.

Fairly active advocacy organizations, but we would not recommend linking from ClinicalTrials.gov

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

- If– and only if– a person is familiar with science and very user savvy on the internet the current site works. Otherwise it is largely inaccessible and unusable and, in fact, could lead people to make a poor health decision based on a minority of evidence.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- Greater enforcement of the requirement to submit– we all know all trials aren't reporting ... funding is an issue here. NIH and other agencies as well as universities need to step up.

- Lower burden in the submission process. The burden of all this is especially difficult for non-profit/non-governmental/non-academic organizations in the U.S. context

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

- Dominated by a biomedical research paradigm; hard for social sciences to fit. Needs to expand to incorporate clinical trials in the social science paradigm.
- Standardization of basic data only -- allow flexibility to reflect the diverse range of clinical trials and methodologies and not impose a methodology on all trials that costs more and may just not be a good fit.
- People— at all levels of education and experience— desperately need help learning how to incorporate evidence into decision-making processes. That should be the goal of these standards, yet there is no compiling of data across studies on the clinicaltrials.gov site. If you impose standards, as you are, you should actually do something with that information to help people make decisions. This can be done without crossing a line into advocacy for anything other than informed decision making ... that is the outcome of the application of health literacy

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

- Largely adopt and adapt the EU guidelines - but those are continuing to evolve and organizations are leading the way in making Plain Language summaries even more effective and useful for people. Involve people who are really doing this work in your ongoing efforts.
- Require people who submit study information to take an online plain language training so they can provide study info in easy to understand language - see Health Literacy Media about building this training capacity.

Submission No.: 237

Date: 3/13/2020

Name: Amar Patel

Name of Organization: Wellstar Health System

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

We use a mobile app called “Loop” from Clinical Softworks to help with patient awareness and trial recruitment. It is excellent. It is a HIPAA compliant app to help with our workflows in clinic. Our understanding is that this portion of the app is “free” to users. This app allows for broad visibility of the app through sponsors providing awareness opportunities of trials to providers to us here and nationwide.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Clinical Softworks -Loop (clinicalsoftworks.com) uses clinicaltrials.gov's data output to populate data elements within the app. This app has been exclusively designed around clinicaltrials.gov. Most the current data elements for this app are used.

Potential improvements

1. Focus around data quality. The data that is currently entered is not consistent. It seems that much of the time the data is inadequate to understand how a patient can be sent to a center for evaluation. It may be that sponsors do not know what type of information to enter. This does not allow the app to work well for us
2. Have the option to include all trials going on in the country. Not every trial is included in CT.gov. Having a singular source for data access is key to improving trial visibility.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Option 1 is best. Utilizing certain keyword or search elements helps identify the appropriate trial and nearest trial sites to evaluate patients further.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

There needs to be better quality assurance regarding the information that is entered. We are using the data coming out of this application to populate one part of the app we use (Clinical Softworks Loop) to help providers find the closest, most appropriate trial site location for their patients. Not having the correct information entered does not allow for easy referral of their patients into their center of choice.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The following are useful aside from Trial name and specifics

1. Location information of ALL the addresses of where a patient can be evaluated. (would want to make sure that addresses are in Google Places so that all sites can be found to ensure that distance to a trial center is not necessarily a factor)
2. Site contact information that contains an email address, phone number, and the name of the site contact

This would make the app work better overall and for others who are coming to your website.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

That is tough...and I don't know if this can be done, but what about providing sponsors "Loop credit" that can be used towards helping to provide awareness of their trials in the geographies their trials are active for those that excel? I am not sure of how can be budgeted for. Of course, this would also be something to discuss with the folks at Loop.

Submission No.: 238

Date: 3/13/2020

Name: [Not provided]

Name of Organization: Association of American Medical Colleges

Attachment: AAMC Comments on Modernizing ClinicalTrials.gov.pdf

March 14, 2020

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Re: Request for Information- ClinicalTrials.gov Modernization (NOT-LM-20-003)

The Association of American Medical Colleges (AAMC) appreciates the opportunity to comment to the National Library of Medicine (NLM) on modernizing ClinicalTrials.gov. The AAMC is a not-for-profit association representing all 155 accredited U.S. medical schools, nearly 400 major teaching hospitals and health systems, and more than 80 academic and scientific societies. Through these institutions and organizations, the AAMC represents nearly 173,000 faculty members, 89,000 medical students, 129,000 resident physicians, and more than 60,000 graduate students and postdoctoral researchers in the biomedical sciences.

The AAMC supports the goal of ClinicalTrials.gov to provide greater transparency around the clinical research enterprise by functioning as a platform to store and make available clinical study trial data. As an association that represents medical schools and hospitals that conduct the majority of clinical trials funded by NIH, we want to ensure that there are continued efforts to assess the unique needs of all the audiences who use the site, including researchers, patients, and the public, and appreciate the NLM's intention to modernize both the technical infrastructure and outward-facing components of the site. We also recognize that NLM has already made substantial updates to ClinicalTrials.gov in response to feedback from the community and appreciate the commitment to continue making improvements to the site to better serve its users.

We note that many of AAMC's member institutions have responded to this request for information with specific challenges, use-cases, and suggestions for improvement based on feedback from a broad spectrum of users, including clinicians, scientists, administrators, and individuals who participate in and search for clinical trial data and urge the careful consideration of these comments from the platform's regular users. We especially recommend that the NLM

consider comments of the Clinical Trials Registration and Results Reporting Taskforce (“Clinical Trials Taskforce”), a national consortium of academic medical centers, universities, and hospitals. This Taskforce frequently engages with NLM on best practices for ClinicalTrials.gov, especially concerning the site’s technical infrastructure. We hope that this feedback from a diverse range of site users will be used to inform the strategy and actions to modernize and improve ClinicalTrials.gov, and that NLM will continue to engage experts in the field during the course of this initiative.

The AAMC is pleased to offer the following comments based on our own expertise and experience as well as input received from our member institutions in response to the RFI.

Website Functionality

There are many aspects of the public-facing site at ClinicalTrials.gov that could be updated to enable the site to more effectively fulfill the goal of increasing transparency as well as providing “easy access to information” on clinical trials for a wide range of stakeholders. The current public site presents significant challenges both from a navigation perspective as well as in the comprehensibility of the content for those less familiar with research and clinical trials.

A starting point would be to implement best practices in web design to improve the appearance, accessibility, and search function, organizing and ordering information and queries so the site can be effectively used by an individual with limited specialized knowledge. As a potential model, we refer you to Trials Today,¹ developed by Vanderbilt University, both for its user-friendly interface and as a site which effectively links to data on ClinicalTrials.gov to function as a recruitment tool.

With regard to the content itself, NLM should look for opportunities to display information in a more understandable way while still maintaining the scientific integrity of the site. For example, the Brief Summary section contained in each study record should, according to ClinicalTrial.gov element definitions, be written in language “intended for the lay public.” Yet this section is often complex and full of technical jargon. We recommend that NLM work with experts in health literacy to create guidelines for researchers to ensure that this part of the study record fulfills its stated purpose.

¹ Trials Today. <https://trialstoday.org/>

Additionally, as highlighted by recent criticism, many individuals erroneously believe that all studies listed on ClinicalTrials.gov are funded, overseen, and “endorsed” by the federal government. Despite efforts by the NLM to provide information to the contrary, there are still issues regarding public understanding of what it means to have a trial listed on the site. While ClinicalTrials.gov includes a text disclaimer that “listing a study on the site does not mean it has been evaluated by the U.S. Federal Government,” and that “the safety and scientific validity of a study... is the responsibility of the study sponsors and investigators” it is clear that these constraints are not fully understood, particularly when listed on a “.gov” site. We encourage NLM to study mechanisms and additional language that would make this aspect of ClinicalTrials.gov more readily understood. For example, including an explicit “yes or no” on a listing to indicate if a study is federally funded, clearly defining the meaning of the term “sponsor” and making this an available search field, and creating a layperson primer to understanding the different types of trials which might be encountered on ClinicalTrials.gov.

In envisioning changes to ClinicalTrials.gov that would make it more accessible and usable by the public, it is important to specifically acknowledge the particular histories and resulting mistrust among many communities of color with regard to clinical research. Anything the site can do to increase transparency and communicate the value of research and its outcomes will serve to make the research enterprise more trustworthy and hopefully will yield more diverse research participation. ClinicalTrials.gov can assist in this process not only by listing information on trials but also by more actively connecting users to further resources for recruitment or engagement. We encourage meaningful partnerships with diverse communities before initiating changes to the website to ensure the relevance and utility of any revisions.

Finally, it is important to examine how the site interface can better serve all potential audiences, including but not limited to patients and the general public. For example, a physician might want to access the site with the intent of searching for specific scientific or technological terms and be connected directly to recruitment materials for a patient. Scientists may be looking for studies to generate ideas or look at outcomes and variables of previous trials, or perhaps to perform a search of more specialized fields such as investigational drugs and devices. The ideal site for these different stakeholder groups may well include separate search functions so that individuals can easily filter by the information most important to them.

Information Submission

Researchers and administrators have noted that the NLM provides helpful guidance on certain aspects of the site, such as the Example Studies for Results Data Entry. We encourage NLM to work with the Clinical Trials Taskforce to develop additional materials to aid with the registration and results submission process, and for these to be as illustrative as possible, including specific cases, screenshots or video tutorials. To reach the maximum number of users of the site, we also encourage NLM to make resources and trainings available virtually, whenever possible, including the information offered at in-person “Train the Trainer” workshops.

The ability of the ClinicalTrials.gov Protocol Registration and Results System (PRS) to align with other technical infrastructure used during the clinical research process is an essential element for many institutions. Greater interoperability would allow administrators to streamline processes and reduces duplicative data entry for researchers. We recommend that NLM query users on the most used systems or databases that would benefit from increased interoperability (such as Clinical Trials Management Systems, IRB submission systems, and electronic health record systems), as well as how NLM could achieve this goal, perhaps through a more flexible application programming interface.

We recommend that NLM look closely at the capability and adaptability of other databases which institutions currently use to manage clinical trial data and associated tasks, such as REDCap, which allows for user-specific adjustments, alerts, and customized reports. Many institutions requested that ClinicalTrials.gov create an internal dashboard to help institutions keep track of studies as well as maintain a higher-level view of metrics and compliance, that could be shared with institutional leaders if needed. It would also be beneficial to develop auto-notifications to responsible parties and record owners to alert them when their record appears on the institutional problem list and action is required.

We additionally encourage ClinicalTrials.gov to standardize requirements and/or processes as much as possible. For example, the site should use drop-down menus or provide lists of standardized fields wherever applicable, not only for data points but also administrative information such as the name of an institution. The need for clear guidelines was also mentioned in relation to the Quality Control (QC) review process, with the suggestion that NLM make available sufficient guidance up front so that data can be entered correctly as often as possible

prior to the QC process, and also provide examples of common QC comment scenarios to elucidate what particular feedback means and how to best navigate this process. These changes will hopefully simplify the workflow at the institutional level and reduce the length of time of QC review.

Finally, the AAMC strongly encourages the use of identifiers to tie individuals to the data they submit on ClinicalTrials.gov and track related outputs to a clinical trial. We appreciate the ability to link the ClinicalTrials.gov identifier (NCT number) with a PubMed ID (PMID), to link results on the site to a publication, as well as the ability to search PubMed specifically for publications linked to this NCT number. In order to link all of these products to an investigator, ClinicalTrials.gov can add the option for researchers to provide their ORCID iD, and in time possibly expand to other types of identifiers currently under development, such as grant and organizational identifiers, to create a comprehensive map of research impact.² The AAMC has appreciated the NLM's involvement in the multi-stakeholder Credit for Data Sharing³ initiative and remains eager to partner with the NLM to assist in implementing the recommendations of that project.

The AAMC appreciates NLM's efforts in the ClinicalTrials.gov modernization initiative, which presents a significant opportunity to make the site more usable and useful for patients, researchers, the public, and all other stakeholders. Please feel free to contact me or my colleagues Anurupa Dev, PhD, Lead Specialist for Science Policy (adev@aamc.org) and Heather Pierce, JD, MPH, Senior Director for Science Policy and Regulatory Counsel (hpierce@aamc.org) with any questions about these comments.

Sincerely,

A handwritten signature in blue ink, appearing to read "Ross McKinney, Jr., MD".

Ross McKinney, Jr., MD
Chief Scientific Officer

² Pierce, et al. Credit Data Generators for Data Reuse. *Nature* 570, 30-32 (2019).
<https://www.nature.com/articles/d41586-019-01715-4>

³ See more at: www.aamc.org/datasharing.

Submission No.: 239

Date: 3/13/2020

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

No comment.

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

No comment.

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

No comment.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

No comment.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

When inputting information into the record there is a fair amount of toggling between screens to input and update information. It would be beneficial to have all information in one place or put it under easily accessible tabs as opposed to having to go back to a previous screen.

Please send an emailed PDF receipt when the record is submitted so there isn't an extra step to create a receipt.

Suggestion for users to choose between a "basic" form with only the bare minimum required information and an "advanced" form with the additional, optional information when registering the study or entering results.

Suggestion to make the “submit” button more obvious.

The system is set up to report 1 discrete measurement/result for each endpoint. In some of our products, we have multi-factorial results characterizing the performance parameters of the device to answer the primary outcome. It is difficult to figure out how to put all of the results parameters into the system when reporting results. Basically, our outcomes are often around device performance so it is not always intuitive how to fit the results.

The errors in the planning report are not always useful or actionable by the PRS admin. It is helpful to know what studies are coming due for results submission. It would also be helpful to update the flag of Late Results per FDAAA so it no longer remains on the record after results have been submitted. Currently, this fires when results are not public by the due date, and doesn't recognize when studies have posted results on time, but are currently still under review by PRS.

Also, in the PRS user guide, there is a comment under this flag that needs to be updated to reflect the new review and release process.

Note: This problem will continue to be listed for the record until results information is posted without Major Comments.

This will need to be updated since records can now be released with Major comments.

The “Not Recently Updated” flag remains on the record even after the study was submitted to PRS. Please include only error comments that are actionable or need attention from the admins.

Include an option to dismiss spelling errors within the system.

I use the Record list and Planning report several times a week. On the Record list it would be nice to have column options for FDAAA type (ACT/pACT/Non-ACT) and study type (Observational/Interventional) and a column option for All Results Expected date. It would also be nice to be able to have the option to move the columns into the order that makes the most sense to each user (this option also on the Planning report).

In the review process, the feedback and comments can vary from reviewer to reviewer making it difficult for study teams. Please assess the review process to ensure that it is less subjective from reviewer to reviewer.

The system is intuitively set up for comparative studies with 2 arms (or more). Since our products are minimal risk, non-implantable and (mostly) non-therapeutic, we rarely have multi arm studies and randomization would be extremely rare. Often, we have studies where all subjects receive the device and it is compared to standard of care so it is difficult to navigate how to set up our study design in the system. It takes some effort to figure out how to characterize the 2 procedures to compare when there are not 2 ‘arms’.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

We would like to have the ability to integrate the admin PRS view with Siebel Clinical Trial Management System (CTMS), including fields for:

- NCT number
- Study Name
- ACT/pACT/Voluntary Submission
- Primary Completion Date
- Record last updated date
- results public date
- days since submission
- +/- days from required submission date
- Results Status (including on time/late)
- Record Status and Date
- Secondary Outcome Measure reporting dates.

The option for real time information pushed from the system would be ideal, rather than a manual process.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

No comment.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Our organization submits a wide range of studies, not only ACTs. We have found it difficult to fit a study that is not a traditional study— e.g. a non-randomized clinical study into the system currently. Some guidance for posting studies that are not ACTs and how to utilize the currently available fields to submit those studies would help avoid longer review cycles and extra work on the sponsor side updating record information.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

No comment.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

No comment.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Does ClinicalTrials.gov leverage CDISC standards?

The benefits of implementing CDISC Standards include:

- Fostered efficiency
- Complete traceability
- Enhanced innovation
- Improved data quality
- Facilitated data sharing
- Reduced costs
- Increased predictability
- Streamlined processes

Submission No.: 240

Date: 3/13/2020

Name: Jamie Webb

Name of Organization: Working Group on Pediatric Gene Therapy and Medical Ethics, Division of Medical Ethics, New York University, Grossman School of Medicine

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Although the Food and Drug Administration Modernization Act of 1997 mandated the establishment of a registry of clinical trial information, it was not initially intended as a search tool for patient use. Indeed, it was only made available to the public in February 2000. However, it is now often used as such, a fact recognized and even endorsed by the Food and Drug Administration (FDA) and the National Institute of Health (NIH), which actively promote ClinicalTrials.gov as a resource for patients to find suitable clinical trials. [See: 1) <https://www.fda.gov/patients/clinical-trials-what-patients-need-know>, 2) <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/websites-information-about-clinical-trials>, and 3) <https://www.nih.gov/health-information/nih-clinical-research-trials-you/finding-clinical-trial>.]

Given this real world usage, there are a number of adjustments that could be made to ClinicalTrials.gov's user interface to make it a more suitable tool for patients searching for trials. Specifically, the initial search could be preceded by a query about the user's role, e.g., patient/caregiver, clinician/researcher, or other. While the same search terms in a query for patients and clinicians may result in the same results, the data that are presented for each of these results could be different, shaped by what would be of most use to the respective audience. For example, the patient search results could be written for laypeople and in a more accessible style than what is currently available on the website. This change would likely mean more effort on the part of trial sponsors, such as the work to customize the language they submit to ClinicalTrials.gov, but it would enhance usability for the end users. Focus groups of patients/caregivers, clinicians/researchers, and other users could be conducted to determine what information would be most relevant to each type of user.

With regard to patient users, they are likely more interested in trials that are enrolling or planning to enroll than those that have closed to accrual or completely ended. Thus, at the initial search, patients should be able to indicate whether they want all trials, past and present, that meet their search criteria or they want to restrict the search by status. Other filters that might be more useful in the initial search, as opposed to after that search has been conducted, would be location and trial type (for example, interventional versus observational).

Based on the focus group findings, there may be other filter types that would be of use to patients looking for possible trial opportunities, including whether there is any cost to participate in the trial (direct costs, as in a pay-to-play trial); whether the sponsor offers compensation for participation; and the duration of the trial.

Here are some features of various trial finder websites that could be adopted by ClinicalTrials.gov to make the site more useful for patients:

- Centerwatch (<https://www.centerwatch.com/>) provides patients with notifications of new relevant clinical trials if they sign up for alerts. In listening sessions with patient/patient advocates, participants voiced support for the ability to sign up to be notified for new trials that meet one's search query. It might also be of interest to be notified when trials on their watchlist post results.
- Centerwatch allows patients to sort trials by location and learn how close they are to an enrollment site; it also includes information about multi-site studies.
- Both Centerwatch and Smart Patients (<https://www.smartpatients.com/home>) provide forms that patients can complete to make contact with trial teams. Smart Patients also has an "Ask about the trial" section, where patients can "Ask my doctor," which takes patients to an online form they can fill in to contact their doctor; in some cases the site also provides a form for contacting a relevant patient group, e.g. "Ask the Colon Cancer Alliance."
- Trials Today (<https://www.trialstoday.org/guide>) takes users through a series of questions that filter search results so the trials shown are relevant to the searcher's situation, e.g. 'I have/had a disease or condition and...' with the options of 'I have already tried the currently approved treatment options, and they are not working/are no longer working for me' and 'I am interested in finding studies that test new treatments.'
- Trials Today centers the trial's inclusion/exclusion, whereas on ClinicalTrials.gov, the user must scroll past a lot of information to see this information.

Finally, FDAAA 801 and the Final Rule, which became effective in 2017, requires the reporting of certain trial results to ClinicalTrials.gov. We are unaware of any instances where this regulation has been enforced. Is it possible to use automation within ClinicalTrials.gov to enable and encourage the expedient reporting of results and/or draw attention to sponsors who don't comply? For example, based on the dates it tracks on trial progress (completion dates), could the system remind research sponsors to post results in the time frame mandated by law? ClinicalTrials.gov allows reporting of results in an agnostic/objective, non-promotional way on its site, even if this is not a link to a peer reviewed publication. Would it be appropriate for ClinicalTrials.gov to indicate which trials/sponsors are not in compliance with the reporting of results? Could ClinicalTrials.gov report out-of-compliance sponsors? Moreover, with the goal of being more inclusive, could ClinicalTrials.gov make a greater effort to use technology and automation to "scrape" other sites for trial registration in search of trials that may be appropriate to post on its registry?

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- 1) ClinicalTrials.gov could link to publicly available decision support tools. One such example, the Ottawa Personal Decision Guide, is available here: <https://decisionaid.ohri.ca/docs/das/OPDG.pdf>.
- 2) Trials Today offers a service that allows users interested in a particular trial to create an account (https://www.researchmatch.org/volunteers/trials/inquire/NCT02483468?rm=TT_RM). The site then

shares the user's contact details with the trial team at the closest trial site. As Trials Today is an NIH-funded endeavor, the ClinicalTrials.gov website could link to it.

3) For certain diseases, advocacy groups manage excellent, user-friendly trial finders. ClinicalTrials.gov could link to them. For example, Parent Project Muscular Dystrophy (PPMD) runs its own trial registry, which allows PPMD to match patients with trials that may be suitable for them, if they register and complete a medical survey: <https://www.duchenneregistry.org/>)

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

ClinicalTrials.gov could take steps to encourage the standardization of terminology: different companies use different terms to describe similar therapies/diseases/populations, and while the search function does a good job of intelligently expanding searches, our testing found that one of the 4 FDA approved gene therapies (Kymriah) did not appear when we searched "gene therapy," even though it is commonly described as a "cell-based gene therapy." Although sponsors are responsible for inputting their own trial information, ClinicalTrials.gov could do more to encourage consistency in terminology.

Attachment: PGTME clinicaltrials.gov letter_final.docx



March 14, 2020

Dear ClinicalTrials.gov Information Team:

We applaud the National Library of Medicine for seeking to better support the users of ClinicalTrials.gov and for requesting the public's input on how to enhance the user experience of this essential resource. We are pleased to have this opportunity to submit comments.

The mission of the Working Group on Pediatric Gene Therapy and Medical Ethics (<https://med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/medical-ethics/research/working-group-pediatric-gene-therapy-medical-ethics>) is to advance research, policy, and education regarding ethical issues surrounding gene therapy trials. We seek to promote improved understanding of challenges and nascent best practices for ethical research across the evolving landscape of genetic technologies. One of the questions that we identified early on in our work was “How do prospective research subjects and/or their caregivers identify possible options for clinical trial participation, both of gene therapy and other therapeutic modalities?” To find out, we have been studying both ClinicalTrials.gov and other trial finder websites. Based on this, we would like to offer the following comments:

1. **Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its *application programming interface (API)*.
 - a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Although the Food and Drug Administration Modernization Act of 1997 mandated the establishment of a registry of clinical trial information, it was not initially intended as a search tool for patient use. Indeed, it was only made available to the public in February 2000. However, it is now often used as such, a fact recognized and even endorsed by the Food and Drug Administration (FDA) and the National Institute of Health (NIH), which actively promote [ClinicalTrials.gov](https://www.fda.gov/patients/clinical-trials-what-patients-need-know) as a resource for patients to find suitable clinical trials. [See: 1) <https://www.fda.gov/patients/clinical-trials-what-patients-need-know>, 2) <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/websites-information-about-clinical-trials>, and 3) <https://www.nih.gov/health-information/nih-clinical-research-trials-you/finding-clinical-trial>.]

Given this real world usage, there are a number of adjustments that could be made to ClinicalTrials.gov's user interface to make it a more suitable tool for patients searching for trials. Specifically, the initial search could be preceded by a query about the user's role, e.g., patient/caregiver, clinician/researcher, or other. While the same search terms in a query for patients and clinicians may result in the same results, the data that are presented for each of these results could be different, shaped by what would be of most use to the respective audience. For example, the patient search results could be written for laypeople and in a more accessible style than what is currently available on the website. This change would likely mean more effort on the part of trial sponsors, such as the work to customize the language they submit to ClinicalTrials.gov, but it would enhance usability for the end users. Focus groups of patients/caregivers, clinicians/researchers, and other users could be conducted to determine what information would be most relevant to each type of user.

With regard to patient users, they are likely more interested in trials that are enrolling or planning to enroll than those that have closed to accrual or completely ended. Thus, at the initial search, patients should be able to indicate whether they want all trials, past and present, that meet their search criteria or they want to restrict the search by status. Other filters that might be more useful in the initial search, as opposed to after that search has been conducted, would be location and trial type (for example, interventional versus observational).

Based on the focus group findings, there may be other filter types that would be of use to patients looking for possible trial opportunities, including whether there is any cost to participate in the trial (direct costs, as in a pay-to-play trial); whether the sponsor offers compensation for participation; and the duration of the trial.

Here are some features of various trial finder websites that could be adopted by [ClinicalTrials.gov](#) to make the site more useful for patients:

- Centerwatch (<https://www.centerwatch.com/>) provides patients with notifications of new relevant clinical trials if they sign up for alerts. In listening sessions with patient/patient advocates, participants voiced support for the ability to sign up to be notified for new trials that meet one's search query. It might also be of interest to be notified when trials on their watchlist post results.
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- Both Centerwatch and Smart Patients (<https://www.smartpatients.com/home>) provide forms that patients can complete to make contact with trial teams. Smart Patients also has an "Ask about the trial" section, where patients can "Ask my doctor," which takes patients to an online form they can fill in to contact their doctor; in some cases the site also provides a form for contacting a relevant patient group, e.g. "Ask the Colon Cancer Alliance."
- Trials Today (<https://www.trialstoday.org/guide>) takes users through a series of questions that filter search results so the trials shown are relevant to the searcher's situation, e.g. 'I have/had a disease or condition and...' with the options of 'I have already tried the currently approved treatment options, and they are not working/are no longer working for me' and 'I am interested in finding studies that test new treatments.'
- Trials Today centers the trial's inclusion/exclusion, whereas on [ClinicalTrials.gov](#), the user must scroll past a lot of information to see this information.

Finally, FDAAA 801 and the Final Rule, which became effective in 2017, requires the reporting of certain trial results to ClinicalTrials.gov. We are unaware of any instances where this regulation has been enforced. Is it possible to use automation within ClinicalTrials.gov to enable and encourage the expedient reporting of results and/or draw attention to sponsors who don't comply? For example, based on the dates it tracks on trial progress (completion dates), could the system remind research sponsors to post results in the time frame mandated by law? ClinicalTrials.gov allows reporting of results in an agnostic/objective, non-promotional way on its site, even if this is not a link to a peer reviewed publication. Would it be appropriate for ClinicalTrials.gov to indicate which trials/sponsors are not in compliance with the reporting of results? Could ClinicalTrials.gov report out-of-compliance sponsors? Moreover, with the goal of being more inclusive, could ClinicalTrials.gov make a greater effort to use technology and automation to "scrape" other sites for trial registration in search of trials that may be appropriate to post on its registry?

- b. *Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.*

- 1) [ClinicalTrials.gov](#) could link to publicly available decision support tools. One such example, the Ottawa Personal Decision Guide, is available here: <https://decisionaid.ohri.ca/docs/das/OPDG.pdf>.
- 2) Trials Today offers a service that allows users interested in a particular trial to create an account (https://www.researchmatch.org/volunteers/trials/inquire/NCT02483468?rm=TT_RM). The site then shares the user's contact details with the trial team at the closest trial site. As Trials Today is an NIH-funded endeavor, the [ClinicalTrials.gov](#) website could link to it.
- 3) For certain diseases, advocacy groups manage excellent, user-friendly trial finders. [ClinicalTrials.gov](#) could link to them. For example, Parent Project Muscular Dystrophy (PPMD) runs its own trial registry, which allows PPMD to match patients with trials that may be suitable for them, if they register and complete a medical survey : <https://www.duchenneregistry.org/>

2. ***Information submission.*** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

[ClinicalTrials.gov](#) could take steps to encourage the standardization of terminology: different companies use different terms to describe similar therapies/diseases/populations, and while the search function does a good job of intelligently expanding searches, our testing found that one of the 4 FDA approved gene therapies (Kymriah) did not appear when we searched “gene therapy,” even though it is commonly described as a “cell-based gene therapy.” Although sponsors are responsible for inputting their own trial information, ClinicalTrials.gov could do more to encourage consistency in terminology.

Thank you for the opportunity to contribute these comments. We look forward to seeing how ClinicalTrials.gov will be transformed as a result of this initiative.

Sincerely,

Members of the Working Group on Pediatric Gene Therapy and Medical Ethics

Alison Bateman-House, PhD, MPH, MA (co-chair)

Lesha Shah, MD (co-chair)

Katherine Beaverson, MS

Arthur L. Caplan, PhD

Moshe M. Cohn, MD.

Timothy Cripe, MD, PhD

Jennifer E. deSante-Bertkau, MD, MBE

Rafael Escandon, DrPH, MS, MPH

Pat Furlong, MS, RN, BSN

Lisa Kearns, MS, MA

Aisha Langford, PhD, MPH

Ron-Li Liaw, MD.

Andrew McFadyen

Patrick Moeschen

Timothy Miller, MD

Brendan Parent, JD

Holly Tabor, PhD

Submission No.: 241

Date: 3/13/2020

Name: Laura Iliescu

Name of Organization: PRA Health Sciences

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Search for trials/trial sites within X/Y/Z distance from you home address

A user friendly interface like FindMeCure's for patients/potential participants to run searches from, they search very differently than clinicians or data experts

See FindMeCure's search platform at:

https://www.findmecure.com/clinicaltrials/search?gclid=EA1alQobChMIqP2HrJuZ6AIVC2KGCh0SSACvEAAYASABEgL7KfD_BwE

Provide Sponsors with a way to include a patient-friendly description of a study in simple language and to address some of the questions patients might have - like... how many days in total will I have to be in clinic, will I have to change my medications... etc..

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

For both the patient and the clinician interface, listing a link to patient advocacy groups that are involved in supporting a condition that a trial is focused on could be of good value to people who may not know that a group exists, thinking especially about rare diseases and oncology. The value of having this is that people who may not know that an advocacy group exists, would become aware and able to connect for resources and support to help them understand a study and clinical research in general.

For the patient/public facing site, the “about studies” section could be made more attractive, prominent, user-friendly, and maybe include videos.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Having to either specify a country or all countries when I run a search is really frustrating. I'd like to be able to have a listing that puts the studies closest to me first and then ones that are farther away, international, etc... down the list. See FindMeCure's...

It would be great to have a function that lets me signal my interest in a study by submitting my phone number or email address and then being contacted by the sponsor or trial site. That would save me the trouble of being the one to reach out and not being sure if I'm calling someone who is expecting my call, etc...

Also in some cases the phone number or contact details don't appear for trial sites so it would be great to be able to say 'hey i'm interested, call me!'

Notifications! I'd love to be notified when new studies are listed for the condition in my family... I'd love to be able to set alerts. It's perhaps a long shot... but maybe even an app?

It would also be great to have a "compare trials" feature! that would highlight key differences between two or more studies that are available.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I've used the site both personally and professionally. Personally in order to look for studies in the conditions that affect my family members. I keep an eye out for anything new that might come up. Professionally as well because I've worked in pharma for a long time and recently started working in clinical research. So I used it to double check study information I might need or look for which studies are active in a specific therapy area.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

I'm not sure because I have never tried to register a study or results.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

I'm not sure.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I'm not sure about content submission. For display, a dedicated interface should absolutely be created with human factors expertise and usability experts, based on deep understanding of public/patients needs through qualitative research or reaching out to companies like Clara Health or FindMeCure who've done it really well. Usability is a discipline all its own and really needed to make this interface respond to patient/public needs.

Patient-friendly results summaries for trials that have ended would be really valuable.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

I'm not sure.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Create a short list of criteria (like 10) that determines “information quality” about a study. Give each study a rank out of 10. So for example if ‘patient-friendly language synopsis/schedule of assessments’ is one of them if a company doesn't have it they would not get that point. Display that rating prominently to the public!

Have a “compare trials” feature that a user can use to compare key elements about two trials and include the ‘info quality’ score each one gets!

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Have a dedicated user interface for patient/public searches. That would allow the flexibility to display data to clinical/science stakeholders in ways that make sense to them and to patients/public in ways that make sense to them. Put the onus for providing content for both on the Sponsor!!

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

ISO9241-11:2018 Ergonomics of human-system interaction — Part 11: Usability

<https://www.iso.org/obp/ui/#iso:std:iso:9241:-11:ed-2:v1:en> - this will be relevant to changes you make for any and all stakeholders

For patient/public facing interface, observe guidelines for reading age of 12-16.

Submission No.: 242

Date: 3/14/2020

Name: Guy Becker

Name of Organization: Microsoft

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

ClinicalTrials.gov currently offer a basic search mechanism over the trial metadata, as well as free text search. While this is useful for initial query, for many conditions, there are hundreds of potentially relevant trials recruiting participants at any given time. Clinical trials descriptions can be long and hard to read and understand, with complicated inclusion and exclusion criteria caged in medical language mostly unfamiliar and often meaningless to the patient and his/her caregivers.

ClinicalTrials.gov has represented a valuable pipeline of available information since it was launched in 2000, “but this data is not presented in a way that is easy for either physicians or patients to access, interact with, and apply to their specific cases. It is thus much less helpful today than it has the potential to be.”

The Microsoft Clinical Trials Matching technology uses the clinical trials protocols, and offers a solution that would be easy to access and use for doctors, care teams, and patients, while quickly and effectively narrowing down available and relevant clinical trials “within minutes, instead of days or weeks as is the case today.”

“The technology helps match patients with clinical trials according to the condition, location, mobility options, priorities, eligibility criteria and other criteria that the patient may choose to prioritize. The system helps narrow down and prioritize the set of relevant clinical trials to a smaller set of trials to start with, that the patient appears to be qualified for.” “The system does not promise that the patient will be fully qualified to the trials or that the patient will be accepted as participant, but it will help patients and doctors to know where to start from, rather than flooding them with all possible results. The system is updated on a regular basis and has the most up to date set of clinical trials from the governmental repository with their updated status.”

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Microsoft Clinical Trials Matching technology currently use the ClinicalTrials.gov API to retrieve all recruiting trials.

It would be beneficial to have the data available in a downloadable SQL db, for a more sophisticated and faster querying.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of**

studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Microsoft Clinical Trials Matching technology relies on all recruiting studies to provide its service. Customers can select which subset of studies to use.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

The Microsoft Clinical Trials Matching technology restructures the studies into FHIR ResearchStudy resources.

The trials' eligibility criteria are analyzed through various machine reading and NLP tools. The clinical entities are recognized and classified, linked to relevant medical ontologies, and the relations between them are extracted—all used to enrich the data within the researchStudy FHIR resource and to allow the sophisticated querying performed by the technology.

Submission No.: 243

Date: 3/14/2020

Name: Rebecca Li

Name of Organization: Vivli

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

We suggest considering additional linkages between clinicaltrials.gov and data sharing repositories (Vivli, YODA, Clinicalstudydatarequest, Project Datasphere and others). Clinicaltrials.gov would not be necessarily endorsing any one repository but since it is typically the initiation point for searches it is an important hub for linkages.

Adding in other linkages would have the beneficial effect we believe of potentially spurring greater data sharing especially among academic trialists whose institutions do not always have the capability nor capacity to support data sharing of de-identified participant data.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**

We would like to recommend that the data sharing statement module on clinicaltrials.gov synchronize language with that of ICMJE. We hear from our users that the lack of fidelity between the two data sharing statements causes confusion and likely inconsistency in responses at times.

- 2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**

We commend clinicaltrial.gov for recognizing that it plays a valuable role in the clinical trials ecosystem. Vivli and its members would suggest to NLM consider how it handles any user updates to the data sharing field. This field is not an update to the clinical trial information itself; rather a reflection of the evolving landscape of how data is being shared and where the underlying dataset may be currently accessed (which could change over time). An update of this field should not necessarily open up a re-review of the entire entry (which actually is a deterrent to updating this field), and would promote more open science.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

ClinicalTrials.gov can require ORCID for all PIs, and can then generate for each investigator a report of their submission performance. Similarly, institutions can be uniquely identified using ROR and performance reports generated. Once ClinicalTrials.gov makes such reports available, it will spur the conversation and the design of credit, incentive, and recognition mechanisms.

To further facilitate tracking of data sharing, the IPD Sharing Access Criteria field should have a specific field for the name of the IPD repository. Ideally the value set for this field would be a unique ID (e.g., a ROR).

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

ClinicalTrials.gov is the center of the information ecosystem for clinical trial data. ClinicalTrials.gov's underlying data model and approaches to annotations has extensive impact on multiple other members of the information ecosystem, including data repositories like Vivli. The current model is ambiguous or under-specified in several areas (e.g., representation of arms, representation of interventional regimens (e.g., chemotherapy cycles)) that require a large effort of manual curation to prepare ClinicalTrials.gov records for machine processing for Findability, Accessibility, Interoperability, Reusability (FAIR(1)) activities. We strongly recommend that ClinicalTrials.gov identify and convene relevant stakeholders to define a common data model for representing interventional and observational human studies that will be able to support FAIR data sharing worldwide for clinical trial summary and participant-level data. Relevant stakeholders include but are not limited to data repositories (e.g., Vivli), CTTI's AACT project, Cochrane Informatics, UC Trial Finder, WHO's ICTRP, and others.

1. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship [Internet]. Scientific Data. 2016 [cited 2018 Jun 28]. Available from: <https://www.nature.com/articles/sdata201618>

Submission No.: 244

Date: 3/14/2020

Name: Alissa Gentile

Name of Organization: The Leukemia & Lymphoma Society

Attachment: RFI ClinicalTrials.gov Modernization_LLS Response 3.14.2020.pdf



March 13, 2020

Patricia Flatley Brennan, RN, PhD
Director
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

RE: Request for Information (RFI): ClinicalTrials.gov Modernization

Dear Director Brennan:

The Leukemia & Lymphoma Society (LLS) appreciates the opportunity to submit comments on the National Cancer Institute's (NCI) request for information on ClinicalTrials.gov Modernization. As the world's largest voluntary organization dedicated to the needs of blood cancer patients, LLS recognizes the critical role that clinical trials play in identifying new approaches for treating blood cancers and managing disease-related side effects. Accordingly, we fully support the NCI's commitment in planning infrastructure enhancements aimed at both the users of and submitters to ClinicalTrials.gov as part of a multi-year modernization initiative. By updating the technological infrastructure underlying ClinicalTrials.gov, the interface will be more efficient and better able to accommodate the increasing number of sponsors, investigators and patients that use the database to maintain or search for clinical trials.

Because patients and caregivers are often overwhelmed by the complex clinical trial search process, LLS launched the Clinical Trial Support Center (CTSC) in 2016. Our Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers who work one-on-one with patients throughout the process of finding and enrolling into clinical trials. They help patients determine if a trial might be an option for them, explain the trial process, identify potential trials, connect patients with sites, and follow the patient throughout the entire clinical course. In LLS's FY2019, which ended June 30, 2019, nurse navigators in the CTSC provided more than 600 patients with in-depth assistance, identifying appropriate trials and helping patients overcome obstacles to enrollment. Because of our high-touch, individualized approach, the accrual rate for patients through the CTSC is approximately 21 percent, a significant difference from the 5-8 percent accrual nationwide. On average, it takes 20 interactions with patients, caregivers and trial sites to help a patient enroll in a trial and ensure that the patient has the resources he or she needs. Nurse navigators had nearly 8,000 interactions with patients, caregivers and medical professionals in FY2019 and has been expanding its capacity to serve more patients.



Despite recent improvements to NCI's clinical trials searching capabilities, searching and finding appropriate cancer clinical trials remains challenging. We applaud NCI's efforts to update the technological infrastructure underlying ClinicalTrials.gov by enhancing its functionality and improving its data standards. Based on our extensive work in this area, LLS submits the following suggestions in response to NCI's request for information.

Website Functionality

LLS uses ClinicalTrials.gov to find specific blood cancer trials for patients based on their cancer type, cancer subtype, disease status, age, biomarker status, and geographic preferences. In order to do this with the greatest accuracy, the CTSC nurses use the function of "advanced search" to input as much pertinent information as possible to narrow the search results. LLS has put considerable time and effort into developing search criteria in the "other terms" search box to narrow down the trials results based on modality or disease status. These terms are helpful in cultivating a list of trials that are more applicable to the individual patient; however, the general public does not have these terms available to use when searching on their own. It would be beneficial for ClinicalTrials.gov to have structural data that would allow patients to have the ability to select a disease status or modality when filling out the search information to help better narrow the results.

We rely on ClinicalTrials.gov to produce results of differing study and intervention types in a variety of geographical situations, while doing so in a highly filtered manner based on a patient's individual needs. We often need to consider many different modalities for the same patient, different geographic locations, or even disease status. Having structured information within the website that would further filter the results would be beneficial. This could include diagnosis/condition, subtype of disease, status of disease (relapse, refractory, maintenance, treatment naïve), performance status, central nervous system criteria, trials locations and contact, prior treatment history, mutations and markers, and history of other malignancies. In particular, we have found that the ability to filter results based on CNS disease presence would be extremely helpful to be in a structural data field. This would include currently present, not present but on treatment for CNS disease, no CNS disease or history of CNS disease.

It is also important within the search functionality to be able to search by the categories and names of prior treatments that a patient has received. In the blood cancer space, many clinical trials exclude patients who have already received a certain treatment modality, for instance, prior stem cell transplant or CAR T therapy. This would help



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both healthcare professionals searching on behalf of their patients or patients themselves who use clinicaltrials.gov to find clinical trials for which they may be eligible.

Further, it would be ideal for clinicaltrials.gov to have a patient interface and a healthcare provider interface. Ideally, a patient interface would include simple terminology in structural fields with patient friendly information. A healthcare provider interface would allow for additional data to be entered, such as, but not limited to, CNS disease, specific types of treatment, stem cell transplant history or candidate for stem cell transplant, as well as ECOG or performance status.

Given our frequent contact with patients who are interested in clinical trials, we are regularly asked about available results/early data from specific clinical trials. Although we recognize that this information is not always available, it would be beneficial for the NCI to have the ability to share early pre-clinical data, articles/results, early-phase data/abstracts, and publicized articles with respect to the clinical trials listed on the site. In addition, any information regarding trial accrual, enrollment status, and most current trial phase would also be beneficial information for the patient. Our CTSC has developed relationships with various organizations and pharmaceutical partners that support up-to-date communication around new clinical trials, changes to trials, results from trials, and new therapies. This allows for accurate and first-hand dissemination of information regarding new treatments and allows for patients to make more informed decisions regarding clinical trial enrollment.

With respect to trial sites and contacts for a clinical trial, there is no consistency within each trial on clinicaltrials.gov record. Within our organizational CTSC database, we document trial or clinical updates that we have received directly from site or sponsor regarding contact and trial specific information. CTSC staff then must manually add this trial information before sending the list of available trials to patients and physicians. Having structured data field requirements for each trial, such as specific sites, principle investigator, and specific contact information for a site, would enable patients and healthcare providers to more easily access these clinical trials for their patients or would help the patient themselves to know where the particular trial is located.

Many disease-focused patient advocacy groups have resources for clinical trial patient education, matching, navigation and disease-focused education. They also provide educational materials and personal assistance to patients navigating their cancer care. It would be beneficial if clinicaltrials.gov could link particular cancer clinical trials to specific organizations that may be beneficial to the patient.



Information Submission

While our CTSC does not have experience inputting data into the NCI Clinical Trials Reporting Program (CTRP), LLS believes that a user-friendly system/database that provides reliable, consistent and accurate search results would likely result in higher rates of clinical trial participation. It can be confusing to patients if the data listed is outdated or inaccurate, such as a trial site listed as recruiting when it is not or an erroneous contact. It would be beneficial for the CTRP to provide an incentive to submitting parties to keep information up to date and for NCI personnel to make appropriate updates in a timely manner to decrease confusion. In addition, the use of a standardized protocol format would further enhance readability and consistency of information provided.

Data Standards

A point of difficulty with respect to selecting clinical trials that might be appropriate for a given patient is the content of the inclusion and exclusion criteria. The LLS supports efforts to use controlled terminologies to narrow clinical trial search/match criteria retrievals to those for which the patient is most likely eligible. We encourage the use of electronic health records (EHR) for pulling specific data elements from the medical records, as opposed to human input, which relies on the patient's comprehensive knowledge of their medical and treatment history and understanding of medical terminology. An EHR report that captures all the data elements included in a trial description would greatly enhance trial searches.

LLS strongly supports the standardization of medical language and terminology in all clinical trials. This would greatly improve readability and consistency of interpretation of clinical trial information and improve accuracy of search results. As mentioned above, LLS encourages the development of a report within the EHR that captures data elements included in a trial description.

In addition to the key data elements discussed above, patients and providers need access to information relevant to the financial, socioeconomic, travel, and support factors effecting clinical trial participation. As such, protocols should include information about requirements related to frequency of visits to trial site, tests, biopsies, and treatments.

Additional information

LLS is eager to help advance the NCI goal of better understanding what information about clinical trials and the existing ClinicalTrials.gov interface is most consequential for modernization of ClinicalTrials.gov. We agree that by planning and implementing



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infrastructure enhancements aimed at both users of and submitters to ClinicalTrials.gov, both groups will benefit by making it easier for patients and physicians to find clinical trials, and trials will likely reach target accrual faster, resulting in more rapid completion of trials and improvements in cancer care. LLS will continue to support NCI's work in the modernization of ClinicalTrials.gov, and welcomes the opportunity for further collaboration. Please feel free to contact us with any questions.

Sincerely,

Alissa Gentile

Alissa Gentile, MSN, RN,
Director, Clinical Trial Support Center
The Leukemia & Lymphoma Society
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Leah Szumita

Leah Szumita, MS, RN, CCRN
Associate Director of Nursing, Clinical
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Submission No.: 245

Date: 3/14/2020

Name: Maia Walker

Name of Organization: Fight Colorectal Cancer

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

1. In the interface of Advanced Search, add search for Recruiting Status at each particular location for a clinical trial.

At the present, an Advanced Search with the parameters “Recruiting” set to a specific location (“Country”, “State”) can result (too often is the case) in a list with studies that are not actually available at the location suitable for the patients and physicians performing the search, but recruiting somewhere else.

Explanations/ examples (retrieved 2/22/2020):

1.1 When looking for a trial for a KRAS mutant colorectal patient in Kansas (US), a regular user would be likely using the following parameters in the Advanced Search:

<https://clinicaltrials.gov/ct2/results/refine?term=KRAS+NRAS+Mutant&recrs=a&cond=Colorectal+Cancer&cntry=US&state=US%3AKS>

which results in 1 Study found for: KRAS NRAS Mutant | Recruiting Studies | Colorectal Cancer | Kansas, United States: Binimetinib and Palbociclib or TAS-102 in Treating Patients With KRAS and NRAS Mutant Metastatic or Unresectable Colorectal Cancer

However, when accessing the trial record page, the location in Kansas shows as “Not yet recruiting” (<https://clinicaltrials.gov/ct2/show/NCT03981614?term=KRAS+NRAS+Mutant&recrs=a&cond=Colorectal+Cancer&cntry=US&state=US%3AKS&draw=2&rank=1>).

In that case, the trial is not really an option for that patient in Kansas. If a patient and/or physician finds a similar false positive in the next element of the results list, or needs to perform the search several times, it is likely they will abandon the search.

That happens because the search string uses the API field name OverallStatus (that corresponds to the Registration Data Element “Overall Recruitment Status”, as per <https://clinicaltrials.gov/api/gui/ref/crosswalks>)

In the Search engine (at least, in the Advanced Search), regular users need to be able to look up if the particular location that is suitable for them is recruiting: that would mean providing a function that uses the API field name LocationStatus (that corresponds to the Registration Data Element “Individual Site Status”, under Facility Information), instead of only using OverallStatus.

1.2. A regular user, a physician in Missouri, looking for a treatment for a colorectal cancer patient with liver metastasis, performs a search using the following parameters in the Advanced Search

<https://clinicaltrials.gov/ct2/results/refine?term=liver+metastasis&recrs=a&cond=Neoplasm+Metastasis&cntry=US&state=US%3AMO>

which results in 1 Study found for: liver metastasis | Recruiting Studies | Neoplasm Metastasis | Missouri, United States: Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Liver Tumors Alone and in Combination With Systemic Pembrolizumab (MASTERKEY-318)

However, when accessing the trial record page, the location in Missouri shows as “Completed” (<https://clinicaltrials.gov/ct2/show/NCT02509507?term=liver+metastasis&recrs=a&cond=Neoplasm+Metastasis&cntry=US&state=US%3AMO&draw=2&rank=1>), despite the user being careful about setting up a very specific search on Advanced search, for Recruiting trials only, at his/her location. But that immunotherapy trial is not really an option for that patient in Missouri. Again, this type of disappointing results increases the probabilities of users giving up on the use of the search engine, making for them more difficult to find treatments potentially life extending/saving.

The Advanced Search at clinicaltrials.gov proposes other good, precise parameters under the subtitle “Location”: not only “Country” and “State”, but also “City”, “Distance” (that even allows to set a radius in miles) and “Location Terms” (that could be used to search for particular facilities). However, all of them will be underused or even useless if LocationStatus is not searchable, and only OverallStatus is offered.

An example of good model for this use (i.e., search for particular Recruiting Locations/ Individual Site Status, not whole trial): CRI Clinical Trial Finder (provided by EmergingMed):
<https://app.emergingmed.com/cri/trials/>

The clinical trial considered as an example in point 1.2 above (trial for liver mets from CRC in Missouri) would not show up if looking for trials in Missouri, since the results are only for the actually recruiting locations, and Missouri has been completed (See “Study Locations” in the trial page
<https://app.emergingmed.com/cri/trial/101984/>: it only shows the 6 locations currently recruiting in USA. On a side note, the CRI Clinical Trial Finder is USA centered, hence not helpful for patients in the rest of the world).

2. In Advanced Search, it should be possible for patients to input driver/main mutations for CRC, and obtain univocal results (trials aimed to that mutation).

Also, searching for MSS or MSI-H status and obtaining univocal results is an urgent need.

Explanation: Certain mutations are key in the treatment/development of CRC: KRAS, BRAF, HER2 At the moment, patients and physicians looking for such trials need to input the mutation in the field “Other terms”.

For example, performing the search with the keyword “BRAF”:

[https://clinicaltrials.gov/ct2/results?cond=Colorectal+Neoplasms&term=BRAF&type=&rslt=&recrs=a&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort="](https://clinicaltrials.gov/ct2/results?cond=Colorectal+Neoplasms&term=BRAF&type=&rslt=&recrs=a&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=)

This results in a list of trials that simply include the word “BRAF” in the title or as keywords. That means that trials for BRAF wildtype (the opposite of mutated) are also on that list. This renders the search pointless.

This happens for all the other mutations, and even for the Microsatellite Status (Stable/Low OR Instable/High).

A simple search for trials for Colorectal Cancer with MSI-H, recruiting, gives at the present (March 11 2020) just 5 results, when we know there are many trials that admit MSI-H CRC patients:

https://clinicaltrials.gov/ct2/results?cond=Colorectal+Neoplasms&term=MSI-High&type=&rslt=&recrs=a&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

To make these unambiguous results possible, a systematic input in the Keywords field, in each trial record, from the researchers, is needed. It should be a requirement at the time of registering a clinical trial.

3. In a similar line, patients and physicians need to be able to search for trials that require only one, only two, or more prior lines of SOC (standard of care) treatment. Univocal results will be possible only by establishing controlled terminologies for inclusion and exclusion criteria, and making the current field EligibilityCriteria (just a “block of text” at the moment) a series of sub-fields.

At the moment, EligibilityCriteria is an unsearchable field.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

The presence of links to the publications of the preclinical studies, or results from prior, pertinent trials, supporting the rationale of each trial should be mandatory in the trial record at clinicaltrials.gov. This way, physicians and patients can evaluate if a certain trial is right for a particular case.

Submission No.: 246

Date: 3/14/2020

Name: Katherine Regan

Name of Organization: Pfizer, Inc.

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a.** List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

See attachment.

- 1b.** Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

See attachment.

- 1c.** Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

See attachment.

- 1d.** Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

See attachment.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

- 2a.** Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

See attachment.

- 2b.** Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

See attachment.

- 2c.** Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

See attachment.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

See attachment.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

See attachment.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

See attachment.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

See attachment.

Attachment: RFI_ClinicalTrials.gov Modernization_Pfizer_14Mar2020.pdf



Pfizer Inc.
235 East 42nd Street
New York, NY 10017

March 13, 2020

By Electronic Submission

Patricia Flatley Brennan, RN, PhD
U.S. National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

**Response to “Request for Information (RFI): ClinicalTrials.gov Modernization”
[Notice Number: NOT-LM-20-00]**

Dear Director Brennan:

Pfizer Inc. is submitting these comments in response to the Request for Information (RFI): ClinicalTrials.gov Modernization Effort.

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us.

Pfizer is equally committed to transparency by publicly disclosing study information and results data for patients, healthcare providers, and the scientific community. Over the past 20 years, we have seen many improvements made by the NIH, U.S. National Library of Medicine within ClinicalTrial.gov for the benefit of the public and the backend users of the system. We thank you for your continued dedication to public disclosure of studies and their results as your platform has been critical in facilitating Pfizer's commitment to disclosure. The following are our suggestions for improvements in each category:

1. Website Functionality

- Enhancements to the overall Search and Advanced Search capabilities as follows:
 - Adding functions to allow for narrowed search capabilities, i.e. ‘exact match’ option.

- For the Conditions and Sponsor fields, we think a standardized syntax in place of the free-text option would help to avoid search issues. We also think a concordance table would assist with standardization.
 - Instead of a concatenated list of Conditions, adding an independent assignment of primary, secondary, tertiary, and then all other buckets. We think this would help healthcare professionals and prospective clinical trial participants in identifying the indications corresponding to the trial. We also think separating out a primary with a single indication would decrease significantly the number of unique values; currently the free text and unique values for all concatenated records are over 96,000+.
 - Adding search tools that incorporate plain language, health literacy best practices, icons and symbology to enhance the experience and comprehension for participants. We support search tools for participants that are user friendly, with features such as simple language and synonym matching for simple medical terms.
 - Adding detailed instructions for referring physicians on how to search and learn about potential trials.
- Developing separate sections for physicians and patients for each study, i.e. plain language for participants and more technical for physicians.
- Enhancing the existing educational content around clinical trial participation and links to authoritative sources.
- Aside from RSS feeds, adding a opt-in or registration process that website users can avail themselves of to receive additional information about upcoming clinical trials, i.e. changes in eligibility criteria.

2. Information Submission

- Redesigning the “Other” option to add a section called “Plain Language Summary” with a link or pdf to the plain language summary.
- Increased alignment between US and EU Basic Results formatting. For example, we think it would be helpful if ClinicalTrials.gov permitted sponsors to create or delete different arms in different periods for multi-period studies where there is no requirement to include the arms which are not applicable for a period.
- In instances where measure type is “Median” but there is no method of dispersion, we think it would be helpful if ClinicalTrials.gov permitted sponsors to [select the option?] “Not Applicable.” Similarly, it would be helpful to have a “Not Applicable” option for when safety is not included in the study design rather than the current option which requires sponsors to report number affected as “0” and number at risk as “0.”
- We think it would be helpful to have an option to apply changes in all sections in lieu of updating the reporting arm title and description at each section of the study.
- Increasing character limits for certain fields, i.e. Analysis Population field, Termination Statement field.
- Adding an option to create a single primary endpoint with different time points.
- Adding an option to select multiple studies on the administration page to change the Record Owner or Collaborator without opening each individual record.

- For studies that have PRS Review Comments requiring attention, we think it would be helpful to link directly to the comments including the date QA Review Comments are expected to be addressed on the main PRS page.
- Adding a feature to permit sponsors access to retrievable XML archive of their results submissions in PRS.
- Adding a dropdown listing of outcome measures and timeframes that the sponsor has used in previously accepted submissions.

3. Data Standards

- We suggest here the development of additional guidance on the meaning of the following terms used on ClinicalTrials.gov for observational studies: Actual Enrollment, Study State Date, Primary Completion Date, Study Completion Date, Recruitment Status, Groups and Cohorts, Outcome Measures, and Eligibility. These terms do not have standard definitions across clinical research, and we believe there could be differences between how a healthcare professional and a patient would interpret some of the fields. An enhanced glossary for observational studies would assist in streamlining interpretations for a better user experience.

4. Other Suggestions

- Standardizing site contact information such that potential participants can connect and identify with peer to peer and/or potential participant to site.
- Adding a capability for physicians to refer patients to a specific study directly, with permissions.
- Developing a universal, customizable, IRB approved screening tool including inclusion/exclusion criteria for potential trial participants.
- Adding features for translations into multiple languages and location sensitivity, i.e. user selectable and automatic domain translation.
- Adding fields that permit sponsors to post IRB approved participant facing materials such as recruitment materials disclosing other details of the clinical trial.

We appreciate the opportunity to comment and your consideration for improving the ClinicalTrials.gov experience. Of note, Pfizer is a member of TransCelerate BioPharma Inc. who will be submitting a response on behalf of its member companies. If you have questions about these comments, please contact Katherine Regan at Katherine.Regan@pfizer.com.

Sincerely,

Katherine Regan
Team Lead, Clinical Trial Disclosure Group
Pfizer, Inc.

Submission No.: 247

Date: 3/14/2020

Name: Kristen Santiago

Name of Organization: LUNGevity Foundation

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

n/a

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Based on our interaction with the lung cancer patient community and studies conducted about ClinicalTRials.gov usability, we have identified the following areas for linking:

- It would be beneficial for patients to add links to drugs.com for patients to check interactions, etc., as well as medlineplus.gov, and to also include a glossary of terms in low health literacy language. In addition, we feel that it would be useful to “star” or italicize trials that are to be reported on the FDA Clinical Trial Drug Snapshots (<https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots>) as well as which studies will be reporting out demographics of the population involved in the specific trial. For patients and providers it would be helpful to include link outs (“you are leaving this website”) to patient advocacy organization websites based on disease-based searches as these websites may have trusted information that could serve as important resources for many providers and patients. Also, these websites may have information on resources that may be beneficial to patients.
- Patient advocacy organizations should put the clinicaltrials.gov link on their websites as many patients have co-morbid conditions and may be looking for other trials. This will contribute greatly to optimizing trusted information for healthcare professionals and patients.

In summary, it is very important to provide as much transparency as possible and to provide consumers with as much information as possible.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Currently, LUNGevity Foundation uses ClinicalTrials.gov for two purposes:

- Research endeavors: Such as analyzing different types of open, enrolling, interventional trials available at zip codes.
- Matching patients to trials: Our clinical trial search engine (LUNGevity Clinical Trial Finder available at <https://clinicaltrials.lungevity.org/>) on the Foundation website uses clinicaltrials.gov on the back end and we have a patient facing page. The Trial Finder is customized to provide information on

trials to specific histologies and zip code because these were two criteria cited by the patient community as important attributes for searchability of trials.

We recommend that it may be worth exploring having one provider/ investigator site and a separate patient site where the text is written in easy to understand, health literate language. This is because not all patient advocacy groups will have the capabilities of hosting a disease-specific clinical trial finder. Furthermore, the likelihood of primary care physicians (PCPs) using a patient-facing site to initiate discussions with their patients will be much higher. Research has shown that PCPs may be able to change patient perception on clinical trial participation [Baquet CR, Commiskey P, et al. Cancer Detect Prev. 2011;30(1):24–33] but in fact do not engage in discussions thinking that it's the role of the oncologist [Baer AR, Michael M, Good MJ, Schapira L, et al. J Oncol Pract. 2012 Jan;8(1):e8–e10.]. For those patient advocacy groups who have their own interfaces, we would recommend having a separate health literate version of clinicaltrials.gov for patients and primary care physicians.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

LUNGevity currently uses clinicaltrials.gov to help lung cancer patients search for clinical trials. Limiting criteria will help across cross trial comparison and also help usability and searchability on the patient side.

Allowing searches to be limited to a mile radius (10 miles, 25 miles, 50 miles, state, region and country) would be helpful to patients and providers. This should be enabled by putting in a zip code finder especially for US-based searches.

Multiple search criteria capability is needed for each search to ensure an efficient and customized return of results for action. e.g. Disease, eligibility criteria, requirement for biomarker testing, phase of trial, type of trial, remote trial, length of trial for full participation, total average time required of participant, whether logistical financial support is available and whether routine costs of clinical trials are covered for each major insurance type.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

n/a

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

n/a

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

We recommend having a patient-friendly, patient-facing health literate site for all PRS data elements, so patients can easily understand what different terms mean.

The PRS page needs to be particularly transparent with respect to privacy and what pieces of information from patients can be used, and for what reasons. It might also be beneficial to patients if they could register to save their searches.

The website should provide definitions of diseases as patients may not know what type of cancer they have. The website should start with broad definitions of disease and then drill down into more specific sub-types. Trials should be tagged consistent with this type of hierarchy. The clinical trial finder that LUNGevity has on our website uses this type of patient-friendly hierarchy.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

n/a

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

- We recommend that you gather feedback from primary care physicians, physician assistants, nurse practitioners, as well as professional societies and other stakeholders who typically “recommend” trials to patients.
- Getting feedback from patients on specific types of trials, especially on specific search functions as they have finished their trial search, will not only provide a platform to receive feedback but also remind the patient community that their opinions matter. In addition, acknowledging their participation by sending them a thank-you letter will build patient trust and establish clinicaltrials.gov as a valued resource for the patient community.
- Many sponsors of observational and clinical research enable their own websites which include their own studies for searching by providers and patients. Many Patient organizations enable clinical trial sites for the disease(s) for which they are expert. Across clinical trial sites regardless of owner, there is a broad enterprise wide need for plain language or health literate versions of study summaries to optimize patient and provider understanding of the indication, eligibility requirements and methods etc. Having consistent plain language or health literate versions of study summaries would result in patients, providers and caregivers more likely understanding and acting on research program offerings that might be right for them, regardless of the site that they went to.
- Providing a “health literate” (not just patient friendly) summary with clear site contact information of each research trial for review and download for patients and providers will be incredibly helpful for recruitment as well. This communication should be in Spanish in addition to English for trials having US-based sites.

- Currently, multiple stakeholders are trying to or would like to create a health literate or plain language or “patient friendly” summaries for a given trial. We recommend the NLM develop and own a process similar to the following to generate health literate/plain language study summaries for all stakeholders: NLM would create an expert input process and generate a plain language summary for a given study at the request of sponsors. Sponsors would pay for this centralized service. The study summary would be posted on clinicaltrials.gov and the use can be downloaded by all clinical study site owners. This would result in consistency and efficiency for users across government, sponsors and public sector sites.

[Resources: Michael Wolfe, MD from Northwestern and Ruth Parker, MD from Emory University are health literate experts and are part of a known process that creates health literate Patient/Consumer plans for pharmaceutical companies]

- In addition, individual trial Sponsors host their own websites. Sponsors should be charged for this service by NLM for each summary and then given the summary template back to place on their own sites. This would be appreciated and create an efficient process for consistency across the government, sponsors, and public sector stakeholders such as patient advocacy organizations.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

We commend the NLM on their willingness to address the need to have consistent language for describing trial protocols. As recognized by the NLM, inclusion and exclusion criteria are not consistently listed on the clinicaltrials.gov website. We have had extensive discussions with patients as well as other stakeholders of the clinical trial ecosystem, such as investigators, regulators, and sponsors. Based on our discussion, we recommend, at a minimum, the following specific data elements for input in a patient-friendly form with adequate explanations of different terms:

1. Type of cancer—Lung cancer, per se, is any malignancy arising in the lungs or associated structures. The search engine should include mesothelioma and other rare types of lung cancer such as neuroendocrine tumors. This is of vital importance as patients typically use terms included in their report to search for clinical trials.
2. Histology—Along with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), we recommend populating sub-options for NSCLC, such as adenocarcinoma, squamous cell lung cancer, and large cell lung cancer.
3. Current Stage of Disease—This data field should be included, as staging is different for the two main histologies of lung cancer. Though the 8th edition of the AJCC for both NSCLC and SCLC both use roman numerals (Stages I to IV), SCLC continues to be classified as Limited Stage-SCLC (LS-SCLC) and Extensive Stage-SCLC (ES-SCLC)

4. Line of therapy— This data field is relevant as first-line trials require chemotherapy-naïve patients. This should be included as a search criterion (rather than just an eligibility criterion).
5. Mutation (or biomarker)— This data field is becoming increasingly common in adenocarcinoma where a driver mutation (or any biomarker) will allow patients/physicians to select a targeted therapy/immunotherapy trial.
6. Geography - A patient should be able to search trials based on geographical location (in addition to other search attributes). While current search engines allow for the entry of a zip code, a Google map type of interface with a clear picture of distance would help patients and caregivers. They should be able to put in several zip codes, states, region, nationally. Several levels of geography that could be searched on.

The final output of a search should include top 10 or top 20 best trials, based on the six data elements described, and only RECRUITING trials should populate the search option.

We also recommend that in addition to the above, clinical trial search output should provide information on the schedule of study site visits (number of clinician/NP visits, number of drug dosing/infusion visits, number of monitoring visits). This information would help patients or their caregivers plan trial participation, especially if frequent study visits are required.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

n/a

Submission No.: 248

Date: 3/14/2020

Name: [Not provided]

Name of Organization: American Cancer Society Cancer Action Network (ACS CAN)

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The outcome of a January 2019 clinical trial matching summit sponsored by American Cancer Society Cancer Action Network (ACS CAN), was a consensus of 9 recommendations created to improve trial matching, many of which are relevant to ClinicalTrials.gov [3]. One proposed solution is to provide basic trial screening capabilities using currently required functionality of electronic health records (EHRs), which exist already in nearly all care settings. This “blue button” functionality would enable one-button clinical trial matching within EHRs by providers or by patients themselves through patient portal access to their medical record. Today most cancer clinical trial participants are identified and screened by their provider or treating institution, but the screens that occur are typically only conducted for clinical trials open at that particular institution. Small institutions may not screen patients at all if they do not offer trials, and larger institutions rarely bother to look for offsite trials if a patient does not match to an onsite trial. This means that often many interested patients are never made aware of available trials that may be located at neighboring institutions. This narrow confinement of screening to onsite trials also means that over half of patients will not have any clinical trial opportunities presented to them by their provider [4].

Enabling easy site-agnostic trial screening is critical to changing this paradigm, and ClinicalTrials.gov can play a critical role in this change.

The matching would be realized through the export of a select number of standardized deidentified patient clinical data points to external matching services as well as the receipt back into the EHR of the resulting trials. ACS CAN is leading a workgroup that has identified six high-value clinical criteria and are working on the data standards and protocol for export, with a proof-of-principle pilot expected by late summer of 2020. ClinicalTrials.gov could serve as one of the external matching services that receives data from EHRs and returns matching trials, paving the way for others.

The ability to search by cancer type, cancer subtype and cancer stage/grade via separate fields would be ideal. Currently, these three fields are grouped together in the condition field. Examples of trial finders that match based on separate fields for cancer type, cancer subtype and cancer stage/grade include the Pancreatic Cancer Action Network (<https://clinicaltrials.pancan.org>), BreastCancerTrials.org, and LUNGevity Foundation (<https://clinicaltrials.lungevity.org/>).

In the attached supporting document are screenshots (Figures 1 through 5) from the Pancreatic Cancer Action Network’s (PanCAN’s) trial database and trial finder that illustrate suggested functionality.

The ability to search by biomarker status, which may be a subtype for some cancers, is increasingly important for clinical trial matching. It is necessary to be able to search by biomarkers that would exclude patients from clinical trials and biomarkers that are required to be identified for a patient to enroll.

Other important search functions are the ability to search by the categories and names of prior treatments that a patient has received and the number of lines of previous treatment. This would serve as helpful for both healthcare professionals searching on behalf of their patients and patients themselves who come to ClinicalTrials.gov to find clinical trials. Examples of trial finders that match based on prior treatment history include clinicaltrials.pancan.org, BreastCancerTrials.org, and the JasonCarterClinicalTrialsProgram.org.

In the attached supporting document are examples (Figures 6 through 10) of PanCAN's structured and searchable fields for number and type of prior treatments.

Additional examples of this functionality can be found on
[“https://www.breastcancertrials.org/BCTIncludes/FindATrial/GetStarted.htm”](https://www.breastcancertrials.org/BCTIncludes/FindATrial/GetStarted.htm).

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

We recommend linking to websites of disease-focused patient advocacy groups that provide resources for clinical trial patient education, matching, and navigation. Many of these organizations provide educational materials and personal assistance to patients navigating their cancer care, including encouraging enrollment in clinical trials. As NLM understands, ClinicalTrials.gov cannot directly serve each disease community with pertinent information and this linkage provides an opportunity to navigate patients to respective expert communities. From the cancer perspective, some potential advocacy groups include:

- American Cancer Society (cancer.org)
- American Society for Clinical Oncology (<https://www.cancer.net/>)
- BreastCancerTrials.Org
- The Jason Carter Clinical Trials Program, offered by Be The Match® (<https://www.jasoncarterclinicaltrialsprogram.org/>)
- Leukemia & Lymphoma Society (LLS) (<https://www.lls.org/>)
- LUNGevity Foundation (<https://lungevity.org/>)
- PanCAN (pancan.org and clinicaltrials.pancan.org)
- Susan G. Komen (<https://ww5.komen.org/>)

Similar examples of such links to external groups from NIH websites include:

<https://supportorgs.cancer.gov/home.aspx?js=1> and <https://www.ninds.nih.gov/Disorders/All-Disorders/Sleep-Apnea-Information-Page/2794/organizations/1256>.

In addition to advocacy groups, government-funded education materials related to clinical trials, such as the resources on cancer.gov, would also be helpful links to educate patients on clinical trials.

Linking to publications of the published and presented results from completed clinical trials, including both positive and negative results, would be beneficial resources for not only researchers and clinicians, but also for patients considering clinical trial enrollment. Transparency in clinical trial results will continue to move research forward. Additionally, it would be helpful to explore the linking of publications and meeting abstracts automatically on the results tab by referencing the national clinical trial (NCT) numbers often included in these publications.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Use of the Application Programming Interface (API)

For patient advocacy groups who utilize the ClinicalTrials.gov API to access and download posted data on ClinicalTrials.gov studies, there is limited structured information provided. This requires that each of the advocacy groups download the data into their databases and manually curate it in order to make it structured and to make the data useable for clinical trial matching. This serves as very redundant work done by multiple advocacy groups. In addition to structuring the data, the advocacy groups also write patient-friendly summaries for each of the clinical trials and reach out to sponsors to ask clarifying questions of the vague eligibility criteria as well as gather important details on the trials for patients, such as the frequency of visits to the site to participate in the trial. For example, both BreastCancerTrials.org and PanCAN estimate that it takes 3-5 people hours per clinical trial to structure the data for matching, to write patient-friendly summaries, and to correspond with the sponsors to verify and gather additional information that is needed for patient matching and decision-making.

Given the labor and resources involved in this curation, our primary request is to increase the number of structured fields in the database. Increased structure assists not only third-party search services that utilize ClinicalTrials.gov data, but it can also increase the site's own native search functions. For example, the ability to search on non-patient clinical characteristics, such as patient preference fields like study type, study location, study phase, funder type, and access to study protocols is a very useful feature. These filter options are possible because of the structure of the underlying data. A multi-stakeholder group has identified high-priority data fields that would be most useful to have structured for oncology trials. These specific fields that would be helpful to have sponsors enter data in a structured way and include: 1) cancer type, 2) cancer subtype, 3) biomarker status, 4) stage/grade of cancer/presence of metastases, 5) number of prior therapies allowed/excluded, and 6) categories of or names of excluded or required prior treatments.

The lack of consistency in trial sites and names when trials are offered at the same institution also creates extra work for patient advocacy groups utilizing the API. For example, because of the lack of consistency in the sites within the ClinicalTrials.gov record, PanCAN does not utilize the site information through the API and instead maintains a consistent list of sites within their clinical trial database. From there, PanCAN staff must manually add these sites and the site contacts to each trial that is added to the database. Sites must also be manually removed from trial records in the PanCAN database as sites close. For the National Cancer Institute (NCI) National Clinical Trial Network (NCTN) group trials, which can include hundreds to a thousand sites, this can take up to 20 people hours for a single NCTN trial. Having

consistency in site records on ClinicalTrials.gov will allow advocacy group resources to be better spent in patient education and navigation of clinical trial matching and ultimately, lead to more enrollments. See the images (Figures 11a and b) in the attached supporting document for inconsistencies in both site name and contact information.

For both the API utilization and when viewing trial records when searching on ClinicalTrials.gov, we recommend adding the ability to easily identify the clinical trials that have had impactful modifications to the eligibility criteria and the arms without combing through the history of changes. Many times, records indicate that there has been a change, but when looking at the history of changes, there have simply been minor formatting changes and not changes to the actual criteria. This serves as unnecessary wasted time by users of ClinicalTrials.gov, including the advocacy groups utilizing the API that would be better spent in patient education and navigation.

Using the website

ClinicalTrials.gov serves as the most used search engine by oncology professionals when looking beyond their own facility for clinical trials for their patients. In the preliminary analysis of a recent survey conducted by several of the undersigned organizations, it overwhelmingly was cited as the go-to resource for providers, regardless of practice size or setting. When speaking with advocacy groups, patients also report the use of ClinicalTrials.gov to locate clinical trials for which they may be eligible. Advocacy groups also rely on ClinicalTrials.gov to find clinical trial information for patients to whom they are providing personalized assistance.

The ability to download search results of trials of interest is a helpful feature for healthcare professionals, patients and advocacy groups. This allows users to be able to have a list of matched trials when discussing clinical trial options during patient and healthcare professional communications. It also makes it relatively easy for advocacy groups to share a curated list of clinical trials for which a patient may qualify to that individual patient.

The world map feature is a valuable tool for patients to understand the location of trials beyond just those close to a given zip code. Patients may have extended networks of friends and family that could serve as host locations for a patient to stay during a trial, or the trial may be located close to an available hospitality house like the Hope Lodge network. Limiting trials to proximity of one single zip code, therefore, restricts the ability for mobile patients to explore alternate sites. The map provides a useful interface for that exploration.

As previously mentioned, the ability to search on non-patient clinical characteristics, such as patient preference fields like study type, study location, study phase, funder type, and access to study protocols is a very useful feature. To augment, we suggest including more of these features, including the ability to search by frequency and number of study visits, access to consent forms, and pre-enrollment requirements. As just-in-time sites become more common for clinical trials, it would also be helpful to be able to search for clinical trials that are designed to open a study site at the patient's treating facility.

Listed in Appendix A of the attached supporting document is a sampling of cancer type choices available from the ClinicalTrials.gov drop-down menu. These choices combine the cancer type, subtype and stage into one category. As prior mentioned, it would be more useful for website users and API users, to separate these into separate selection criteria. Also, the descriptions listed have some overlap in terms

of disease descriptions, and while the search engine utilizes a synonym function to search against multiple terms, not all synonyms are recognized. For example, a recent search for Phase III trials actively recruiting for metastatic pancreas cancer returned 10 results. A search for Phase III trials actively recruiting for pancreas cancer stage IV resulted in no trials. Stage IV cancer, by definition, is metastatic so these searches should have yielded the same results but did not. We recommend more work to improve mapping synonyms.

Other disease relationship functions need to be similarly improved. For example, searching for clinical trials for pancreas cancer does not yield trials open to any solid tumor even though pancreas cancer is a type of solid tumor. Increasingly cancer trials are open to multiple tumor types, so this lack of sophistication in understanding the mapping of cancer types to broader categories means patients are not being exposed to potential matching trials. At the same time, it would also be very helpful to have functionality for users to be able to filter out solid tumor trials if they would specifically like to find trials that are only studying their specific cancer diagnosis, as this is a desire for some patients.

Currently, the synonym mapping that is done is viewable in the search details tab which is not intuitive to users. Meaning, users may not know that they can view which search terms and synonyms were searched based on their own search terms. It would be helpful to have that information more visible to users, such as in the scenario in Figure 12 of the attached supporting document, stating “Also searched for Pancreatic Neoplasm, Neoplasm and 24 other terms – See Search Details.”

In addition to improved synonym mapping, the functionality to search by multiple terms in a single field could also mitigate the current shortcomings of the mapping of cancer types. For example, this could allow users to search by breast cancer and breast carcinoma at the same time, potentially yielding more accurate results.

Better functionality is needed to be able to search for keywords in the “other terms” search box. For example, in searching for pancreatic cancer trials in the second-line setting that are actively recruiting in the United States, the search results yielded only four clinical trials. However, when using PanCAN’s clinical trial finder (clinicaltrials.pancan.org), where trial information about the line of treatment being studied is structured, the search yields 119 clinical trials. This is an example of where structured data on the line(s) of therapy being studied would assist users in finding applicable trials.

There is a lack of patient-friendly descriptions of the clinical trials, especially when describing the purpose of the clinical trial, the arms being studied in the clinical trial and eligibility criteria. One option is to add a new field labeled lay summary for clinical trial sponsors to submit lay-level descriptions and eligibility criteria for their trials. Another option would be to explore collaborations with disease advocacy groups who already create patient-friendly versions of the clinical trial listings to explain the design and purpose of the trial and the eligibility criteria and include links in the clinical trial posting that will direct to these clinical trial listings on advocacy group websites. This will help to enhance the conversations that patients have with their providers regarding clinical trials of interest.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

The primary purpose of ClinicalTrials.gov for our organizations is to utilize a limited range of studies, specifically studies for the different types of cancers. When searching for these limited range of studies, it would be helpful to be able to see a tiered list of studies that includes 1) the studies that only the disease indication that is searched is being studied 2) any all-comer/solid tumor trials that are also matches.

Within the limited range of studies, it would be helpful to have criteria to further limit the list of studies. Limiting criteria should include required/excluded biomarkers, required/excluded prior treatments, required type of cancer, required subtype of cancer, and the required stage of cancer. It would also be helpful to continue to be able to narrow down the results using the map feature to narrow in on a specific county and state. It is also helpful to be able to narrow down by a radius from a specific zip code.

When looking at the landscape of clinical trials available for cancer patients, it is also helpful to look a slightly broader range of studies that are cancer studies, including the geographic locations of the studies, the types of studies (interventional versus observational) and intervention types, such as immunotherapy versus chemotherapy.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

As previously mentioned, in 2018, ACS CAN issued a report that provided 23 recommendations for overcoming barriers to patient enrollment. These consensus recommendations identified areas that would benefit from improvement, including standardized syntax submissions, more structured data fields, the ability for sponsors to share “private” information, such as proprietary biomarkers that may not be listed in the text, but would allow for trial matching, and more accurate and consistent site information.

ClinicalTrials.gov is positioned to influence how future clinical trial protocols are both written and submitted. All clinical trial protocol design will be impacted by what ClinicalTrials.gov allows and mandates when clinical trial information is submitted to the site. ClinicalTrials.gov represents the single source of truth when it comes to clinical trial information, but some of the information continues to be inaccurate or incomplete due to current limitations.

As more sponsors recognize the importance of and gain the ability to provide structured data, it would be beneficial to offer multiple ways to enter data. This would provide sponsors who have the ability to enter structured data the opportunity to do so and create better records, while maintaining flexibility for those sponsors who would like to continue with the existing free-text entry or do not have the ability to presently change their process.

In regards to structured data, specific fields that would be helpful to have sponsors enter data in a structured way include: cancer type, cancer subtype, biomarker status, stage of cancer/grade of cancer/presence of metastases, number of prior therapies allowed/excluded, and categories of/names of excluded or required prior treatments.

It would be helpful to have a mechanism whereby sponsors can easily notify ClinicalTrials.gov when a Phase I/II trial switches from Phase I to Phase II. It makes it very difficult when there are different cohorts for each phase to know which phase is currently enrolling and what the current eligibility criteria is. If possible, please require or incentivize sponsors to update what portion of the trial they are currently recruiting for and update the eligibility for the current phase of the trial that is recruiting.

Regarding site information, there is both a lack of specificity and consistency in site names and contact information for the sites. In the figures in the attached supporting document, there are examples of non-specific (Figure 13) and specific (Figure 14) site names and contact information.

We suggest exploring if there is a universal facility number that already exists and could be used to create consistency in site names or exploring the creation of a structured table of sites for sponsors to pick from in order to bring more consistency to the site names. Furthermore, it would be tremendously helpful if sponsors were required to provide the actual site information, including contact information and zip code and not just the city and state.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

It may be helpful to show results in an order that lists the most recently updated clinical trials at the top of the list. This could incentivize sponsors to ensure their records are up to date.

While not directly an incentive to sponsors, it may be helpful to include some sort of direct feedback loop/reporting capability (maybe a button in the clinical trial record) to allow various stakeholders, including advocacy groups, patients, physicians, and or investigators to inform ClinicalTrials.gov of out-of-date information. This may serve as a way for the ClinicalTrials.gov staff to prompt the sponsor for updated information. Currently, when advocacy groups hear from patients that a trial is closed, a site contact information is wrong, or other incorrect information is listed on ClinicalTrials.gov, the advocacy groups are spending time to reach out to the sponsors or sites to gather the correct information. This information is shared with the patient who is inquiring but is not updated on ClinicalTrials.gov. Once more, this serves as unnecessary wasted time by advocacy groups that could be used for clinical trial patient navigation and education.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

We recommend creating capabilities to submit both free-text eligibility criteria and standard machine-coded criteria through separate data entry fields. This allows trial sponsors or reporting intermediaries who have more advanced capabilities to submit structured data, while still preserving the legacy free-text entry. It is critical that ClinicalTrials.gov allow advanced sponsors to increase the structure and utility of their data as much as possible, and not restrict website or database improvements based on the slowest adopting or least sophisticated trial sponsors.

In addition to/in place of free-form text field for “standard set” of eligibility, we recommend that ClinicalTrials.gov provide a list of dropdowns/checkboxes to indicate eligible or ineligible patient populations. One common area of clarification needed is around the use of the term “advanced disease” as an eligibility criterion. As mentioned previously, there is overlap in the use of “stage IV,” “metastatic,” and “advanced” as descriptions of cancer status. Having multi-select dropdown or checkboxes that only allow the selection of specific stages of disease, such as stage III and/or stage IV would mitigate this issue. Also, for all-comer trials in the solid tumor space, requiring a multi-select dropdown or checkboxes that only allow the selection of specific types of solid tumors such as pancreatic adenocarcinoma, non-small-cell lung carcinoma, etc., could mitigate some of the issues with solid tumor trials not appearing in results.

Having an improved search engine that recognizes the sameness between “pancreatic cancer” being a “solid tumor” and likely “pancreatic adenocarcinoma” (if a subtype was not provided) and better mapping of cancer types will also mitigate issues in search results.

Many patients are more likely to search for “pancreatic cancer” rather than “pancreatic adenocarcinoma,” so the mapping of cancer terms is imperative to account for variations in the health literacy of users, as healthcare providers and patient advocacy groups using the site are more likely to use the appropriate cancer type and subtype when searching.

Another area that would be helpful to capture structured data is around performance status. Some clinical trials provide ECOG performance scores, while others provide Karnofsky performance scores. Requiring that these fields be a structured dropdown selection and that both fields are required, will help with patient advocacy groups who utilize performance status in clinical trial matching.

As mentioned above, separating out the type of cancer, subtype of cancer and stage of cancer in to separate structured fields is ideal for assisting users in both entering the correct data for their trial and for users searching for appropriate trials for a patient.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

We recommend the utilization of “syntax standard” along with a universal data standard to improve data quality. ACS CAN has convened a diverse set of stakeholders, including staff from ClinicalTrials.gov to develop a pragmatic “syntax standard” which could be implemented in the near term while longer-term database modifications and investigator infrastructure changes are being made to accommodate machine-readable standards. This syntax standard would continue to be text based, but syntax and terminology rules would dictate the form in which the criteria were presented with the goal of creating unambiguous phrases that are more easily interpreted by natural language processing (NLP), while retaining human readability. NLP is increasingly being used to translate free text into more structured data in an automated way. The workgroup is currently developing the syntax framework and hopes to pilot test and validate the end product by the end of 2020. The collaborative community will share results of that project when completed.

In parallel to the syntax standard, we strongly recommend that ClinicalTrials.gov adopts a machine-readable data standard for eligibility criteria. For example, the new Minimal Common Oncology Data

Elements project or mCODE offers an example of an open source, non-proprietary data model for common data standards and language. This collaboration between ASCO and the MITRE corporation serves as an example of accessible interconnectivity and data standards across different systems. The group of stakeholders convened by ACS CAN and the mCODE group are willing to work together with the ClinicalTrials.gov staff to assist in the adoptions of these standards. We also suggest working with other groups outside of cancer that are working on standardization for other disease areas. EHRs continue to use different nomenclatures, so if ClinicalTrials.gov moves in the direction of standards, it will influence and activate others to move in the same direction.

Attachment: RFI ClinicalTrials.gov Modernization_Final.docx

BY ELECTRONIC DELIVERY

Patricia Flatley Brennan, RN, PhD
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

RE: Request for Information (RFI), ClinicalTrials.gov Modernization

Dear Director Brennan:

On behalf of the 15 undersigned organizations, we welcome your request for our input on the efforts of the National Library of Medicine (NLM) on behalf of the National Institutes of Health (NIH) to modernize ClinicalTrials.gov. Representing the stakeholder groups of individuals with cancer, their families, and cancer advocacy organizations, we request that you include our recommended changes designed to reduce patient barriers to reliable clinical trial information. While our recommendations are targeted specifically to cancer clinical trials, it is important to note that cancer clinical trials encompass between 40% and 50% of all clinical trials conducted in the United States [1, 2].

We encourage you to incorporate these recommendations into the overall modernization activities of ClinicalTrials.gov. We stand ready to work with your team on specific recommendations and offer our collective expertise. Thank you for your efforts to modernize ClinicalTrials.gov and we look forward to our work together.

Listed below are comments that focus on the topic areas outlined specifically in the RFI.

Website Functionality

New Uses

The outcome of a January 2019 clinical trial matching summit sponsored by American Cancer Society Cancer Action Network (ACS CAN), was a consensus of 9 recommendations created to improve trial matching, many of which are relevant to ClinicalTrials.gov [3]. One proposed solution is to provide basic trial screening capabilities using currently required functionality of electronic health records (EHRs), which exist already in nearly all care settings. This “blue button” functionality would enable one-button clinical trial matching within EHRs by providers or by patients themselves through patient portal access to their medical record. Today most cancer clinical trial participants are identified and screened by their provider or treating institution, but the screens that occur are typically only conducted for clinical trials open at that particular institution. Small institutions may not screen patients at all if they do not offer trials, and larger institutions rarely bother to look for offsite trials if a patient does not match to an onsite trial. This means that often many interested patients are never made aware of available trials that may be located at neighboring institutions. This narrow confinement of screening to onsite trials also means that over half of patients will not have any clinical trial opportunities presented to them by their provider [4].

Enabling easy site-agnostic trial screening is critical to changing this paradigm, and ClinicalTrials.gov can play a critical role in this change.

The matching would be realized through the export of a select number of standardized deidentified patient clinical data points to external matching services as well as the receipt back into the EHR of the resulting trials. ACS CAN is leading a workgroup that has identified six high-value clinical criteria and are working on the data standards and protocol for export, with a proof-of-principal pilot expected by late summer of 2020. ClinicalTrials.gov could serve as one of the external matching services that receives data from EHRs and returns matching trials, paving the way for others.

The ability to search by cancer type, cancer subtype and cancer stage/grade via separate fields would be ideal. Currently, these three fields are grouped together in the condition field. Examples of trial finders that match based on separate fields for cancer type, cancer subtype and cancer stage/grade include the Pancreatic Cancer Action Network (<https://clinicaltrials.pancan.org>), BreastCancerTrials.org, and LUNGevity Foundation (<https://clinicaltrials.lungevity.org/>).

Below are screenshots from the Pancreatic Cancer Action Network's (PanCAN's) trial database and trial finder that illustrate suggested functionality.

| What type of pancreatic cancer does the patient have ? | | |
|--|--|--|
| Exclude (Drives Search) | Neutral (Drives Search) | Include (Drives Search) |
| | <input type="checkbox"/> Adenocarcinoma <input type="checkbox"/> Adenocarcinoma <input type="checkbox"/> Neuroendocrine carcinoma <input type="checkbox"/> Gastrinoma <input type="checkbox"/> Glucagonoma <input type="checkbox"/> Insulinoma <input type="checkbox"/> Nonfunctional Islet Cell Tumor <input type="checkbox"/> Not sure of the type of neuroendocrine carcinoma <input type="checkbox"/> Other Pancreatic Neuroendocrine Tumor <input type="checkbox"/> Somatostatinoma <input type="checkbox"/> VIPoma <input type="checkbox"/> Not Sure <input type="checkbox"/> Not Sure type of pancreatic cancer <input type="checkbox"/> Other <input type="checkbox"/> Acinar Cell Carcinoma <input type="checkbox"/> Adenosquamous Carcinoma <input type="checkbox"/> Giant Cell Carcinoma <input type="checkbox"/> Intraductal Papillary Mucinous Neoplasm (IPMN) <input type="checkbox"/> Mucinous Cystic Neoplasm (MCN) <input type="checkbox"/> Other type of Pancreatic Cancer <input type="checkbox"/> Pancreatic Intraepithelial Neoplasia (PanIN) <input type="checkbox"/> Pancreatic Lymphoma <input type="checkbox"/> Pancreatoblastoma <input type="checkbox"/> Serous Cystadenoma <input type="checkbox"/> Solid and Pseudopapillary Tumors | |
| <input type="button" value="Move to Exclude"/> | <input type="button" value="Move to Neutral"/> | <input type="button" value="Move to Include"/> |

Figure 1: Back-end structuring of pancreatic cancer subtype data from PanCAN's trial database

| What is the patient's current stage of pancreatic cancer ? Check one. | | |
|---|---|--|
| Exclude | Neutral | Include |
| | <input type="checkbox"/> Stage 0 <input type="checkbox"/> Stage I <input type="checkbox"/> Stage II <input type="checkbox"/> Stage III <input type="checkbox"/> Stage IV <input type="checkbox"/> Not Sure | |
| <input type="button" value="Move to Exclude"/> | <input type="button" value="Move to Neutral"/> | <input type="button" value="Move to Include"/> |

Figure 2: Back-end structuring of pancreatic cancer stage data from PanCAN's trial database

Enter Diagnosis Information

1. What type of pancreatic cancer does the patient have?

What are the different types? +

- Adenocarcinoma
- Pancreatic neuroendocrine tumors
- Other
- Not Sure

2. What is the current stage of the patient's pancreatic cancer?

What are the stages? +

- Surgically Removed
- Stage I
- Stage II
- Stage III
- Stage IV
- Not Sure

Figure 3: Front-end search by patient using structured data fields for subtype and stage

NARROW YOUR RESULTS

Type of Pancreatic Cancer

- Adenocarcinoma
- Pancreatic neuroendocrine tumors
- Gastrinoma
- Glucagonoma
- Insulinoma
- Non functional Islet Cell Tumor
- Somatostatinoma
- VIPoma
- Other Pancreatic Neuroendocrine Tumor
- Other
- Acinar Cell Carcinoma
- Adenosquamous Carcinoma
- Intraductal Papillary Mucinous Neoplasm (IPMN)
- Other type of Pancreatic Cancer

Request a Healthcare Provider account to access full Trial Find

View Details ▾

57 active and recruiting pancreatic cancer clinical trials

Pancreatic neuroendocrine t... X Other Type of Pancreatic Ca... X

[Clear All Filters X](#)

[Select All](#)

Phase I Study of Safety and Immunogenicity of Survivin Long P Vaccine (SurVaxM) in Patients With Metastatic Neuroendocrine (NETs)

Phase I First-in-Human Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of JNJ-Patients With Advanced Solid Tumors Harboring the KRAS G12

Phase I Study of Mesothelin-Targeted Immunotoxin LMB-100 in With Tofacitinib in Persons With Previously Treated Pancreatic Adenocarcinoma, Cholangiocarcinoma and Other Mesothelin E Solid Tumors

Figure 4: Front-end search by healthcare professional using structured data fields for subtype

Figure 5: Front-end search by healthcare professional using structured data fields for stage

The ability to search by biomarker status, which may be a subtype for some cancers, is increasingly important for clinical trial matching. It is necessary to be able to search by biomarkers that would exclude patients from clinical trials and biomarkers that are required to be identified for a patient to enroll.

Other important search functions are the ability to search by the categories and names of prior treatments that a patient has received and the number of lines of previous treatment. This would serve as helpful for both healthcare professionals searching on behalf of their patients and patients themselves who come to ClinicalTrials.gov to find clinical trials. Examples of trial finders that match based on prior treatment history include [clinicaltrials.pancan.org](#), [BreastCancerTrials.org](#), and the [JasonCarterClinicalTrialsProgram.org](#).

Below are examples of PanCAN's structured and searchable fields for number and type of prior treatments.

Figure 6: Back-end structuring of prior treatment data

| Prior Regimens | How many prior regimens has the patient received? | | |
|----------------|--|--|--|
| Exclude | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4+ | Neutral | |
| | | Include | |
| | <input type="button" value="Move to Exclude"/> | <input type="button" value="Move to Neutral"/> | <input type="button" value="Move to Include"/> |

Figure 7: Back-end structuring of lines of treatment data

4. More specifically, has the patient received treatment for their stage III or stage IV pancreatic cancer?

No
 Yes

All the therapies checked on question #3 have been solely for the treatment of the patient's advanced/metastatic disease

Please check all that apply

- Chemotherapy
- Targeted Therapy i
- Hormone Therapy i
- Immunotherapy i
- Surgery to remove pancreatic cancer
- Radiation
- Radiation together with Chemotherapy
- Irreversible Electroporation (NanoKnife®) i
- Other Treatments
- Not Sure

4a. From the treatment selected above, how many chemotherapy regimens has the patient received for their stage III or IV pancreatic cancer?

What is a chemotherapy regimen?

0
 1
 2

Figure 8: Front-end patient search by prior types and lines of treatment

| Line of Treatment | <input type="checkbox"/> Neoadjuvant | <input type="checkbox"/> Adjuvant | <input type="checkbox"/> First Line | <input type="checkbox"/> Second Line | <input type="checkbox"/> Third Line | <input type="checkbox"/> Beyond | <input type="checkbox"/> Maintenance | <input type="checkbox"/> Other | <input type="checkbox"/> Recurrence |
|-------------------|--------------------------------------|-----------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|--------------------------------|-------------------------------------|
|-------------------|--------------------------------------|-----------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|--------------------------------|-------------------------------------|

Figure 9: Back-end structuring of line of treatment studied in clinical trial

The screenshot shows a search interface for clinical trials. On the left, a sidebar titled 'NARROW YOUR RESULTS' contains a 'Line of Treatment' filter with options like Neoadjuvant, Adjuvant, First Line, Second Line (which is checked), Third Line, Beyond, Maintenance, Other, and Recurrence. A 'Continue' button is at the bottom of this sidebar. The main area displays a message: 'Request a Healthcare Provider account to access full Trial Finder features.' Below this is a heading: '122 active and recruiting pancreatic cancer clinical trials'. A green button labeled 'Second Line X' is present. Underneath are buttons for 'Select All', 'Download', 'Email', 'Print', and 'Save'. Three trial entries are listed: 'Pilot Study of Hepatic Resection for Metastatic Pancreatic Cancer', 'Pilot Study of Respiratory-gated Stereotactic Body Radiation Therapy for Borderline Resectable, Unresectable, or Recurrent/Residual Adenocarcinoma of the Pancreas or Periampullary Region', and 'Phase Ib Study of Treatment of Advanced Pancreatic Cancer With Anti-CD3 x Anti-EGFR-Bispecific Antibody Armed Activated T-Cells (BATS)'.

Figure 10: Front-end healthcare professional search by line of treatment studied in a clinical trial

HYPERLINK: "<https://www.breastcancertrials.org/BCTIncludes/FindATrial/GetStarted.html>"

Useful Resource Links

We recommend linking to websites of disease-focused patient advocacy groups that provide resources for clinical trial patient education, matching, and navigation. Many of these organizations provide educational materials and personal assistance to patients navigating their cancer care, including encouraging enrollment in clinical trials. As NLM understands, ClinicalTrials.gov cannot directly serve each disease community with pertinent information and this linkage provides an opportunity to navigate patients to respective expert communities. From the cancer perspective, some potential advocacy groups include:

- American Cancer Society (cancer.org)
- American Society for Clinical Oncology (<https://www.cancer.net/>)
- BreastCancerTrials.Org
- The Jason Carter Clinical Trials Program, offered by Be The Match® (<https://www.jasoncarterclinicaltrialsprogram.org/>)
- Leukemia & Lymphoma Society (LLS) (<https://www.lls.org/>)
- LUNGevity Foundation (<https://lungevity.org/>)
- PanCAN (pancan.org and clinicaltrials.pancan.org)
- Susan G. Komen (<https://ww5.komen.org/>)

Similar examples of such links to external groups from NIH websites include:

<https://supportorgs.cancer.gov/home.aspx?js=1> and <https://www.ninds.nih.gov/Disorders/All-Disorders/Sleep-Apnea-Information-Page/2794/organizations/1256>

In addition to advocacy groups, government-funded education materials related to clinical trials, such as the resources on cancer.gov, would also be helpful links to educate patients on clinical trials.

Linking to publications of the published and presented results from completed clinical trials, including both positive and negative results, would be beneficial resources for not only researchers and clinicians, but also for patients considering clinical trial enrollment. Transparency in clinical trial

results will continue to move research forward. Additionally, it would be helpful to explore the linking of publications and meeting abstracts automatically on the results tab by referencing the national clinical trial (NCT) numbers often included in these publications.

Current Uses

Use of the Application Programming Interface (API)

For patient advocacy groups who utilize the ClinicalTrials.gov API to access and download posted data on ClinicalTrials.gov studies, there is limited structured information provided. This requires that each of the advocacy groups download the data into their databases and manually curate it in order to make it structured and to make the data useable for clinical trial matching. This serves as very redundant work done by multiple advocacy groups. In addition to structuring the data, the advocacy groups also write patient-friendly summaries for each of the clinical trials and reach out to sponsors to ask clarifying questions of the vague eligibility criteria as well as gather important details on the trials for patients, such as the frequency of visits to the site to participate in the trial. For example, both BreastCancerTrials.org and PanCAN estimate that it takes 3-5 people hours per clinical trial to structure the data for matching, to write patient-friendly summaries, and to correspond with the sponsors to verify and gather additional information that is needed for patient matching and decision-making.

Given the labor and resources involved in this curation, our primary request is to increase the number of structured fields in the database. Increased structure assists not only third-party search services that utilize ClinicalTrials.gov data, but it can also increase the site's own native search functions. For example, the ability to search on non-patient clinical characteristics, such as patient preference fields like study type, study location, study phase, funder type, and access to study protocols is a very useful feature. These filter options are possible because of the structure of the underlying data. A multi-stakeholder group has identified high-priority data fields that would be most useful to have structured for oncology trials. These specific fields that would be helpful to have sponsors enter data in a structured way and include: 1) cancer type, 2) cancer subtype, 3) biomarker status, 4) stage/grade of cancer/presence of metastases, 5) number of prior therapies allowed/excluded, and 6) categories of or names of excluded or required prior treatments.

The lack of consistency in trial sites and names when trials are offered at the same institution also creates extra work for patient advocacy groups utilizing the API. For example, because of the lack of consistency in the sites within the ClinicalTrials.gov record, PanCAN does not utilize the site information through the API and instead maintains a consistent list of sites within their clinical trial database. From there, PanCAN staff must manually add these sites and the site contacts to each trial that is added to the database. Sites must also be manually removed from trial records in the PanCAN database as sites close. For the National Cancer Institute (NCI) National Clinical Trial Network (NCTN) group trials, which can include hundreds to a thousand sites, this can take up to 20 people hours for a single NCTN trial. Having consistency in site records on ClinicalTrials.gov will allow advocacy group resources to be better spent in patient education and navigation of clinical trial matching and ultimately, lead to more enrollments. See the images below for inconsistencies in both site name and contact information.

Information from the National Library of Medicine



To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT04229004**

Locations

United States, New York

New York University Langone Medical Center - Perlmutter Cancer Center Recruiting
New York, New York, United States, 10016
Contact: Keith Kallas 929-455-2433 keith.kallas@nyumc.org

United States, Washington

Virginia Mason Hospital & Seattle Medical Center Recruiting
Seattle, Washington, United States, 98101
Contact: Vincent Picozzi 206-223-6193 vincent.picozzi@vmmc.org
Contact: Anas Najjar 206-287-6271 anas.najjar@virginiamason.org

Allegheny General Hospital Recruiting

Pittsburgh, Pennsylvania, United States, 15212
Principal Investigator: Dulabh Monga, MD

United States, Texas

Baylor College of Medicine Recruiting
Houston, Texas, United States, 77030
Principal Investigator: Ben Musher, MD

Renovatio Clinic Recruiting
The Woodlands, Texas, United States, 77380
Principal Investigator: Mary Crow, MD

United States, Washington

Virginia Mason Medical Center Recruiting
Seattle, Washington, United States, 98101
Principal Investigator: Vincent Picozzi, MD

University of Washington Medical Center Recruiting
Seattle, Washington, United States, 98195
Principal Investigator: Elena Gabriela Chiorean, MD

Figures 11 a and b: The same facility is represented in multiple ways within the ClinicalTrials.gov database

For both the API utilization and when viewing trial records when searching on ClinicalTrials.gov, we recommend adding the ability to easily identify the clinical trials that have had impactful modifications to the eligibility criteria and the arms without combing through the history of changes. Many times, records indicate that there has been a change, but when looking at the history of

changes, there have simply been minor formatting changes and not changes to the actual criteria. This serves as unnecessary wasted time by users of ClinicalTrials.gov, including the advocacy groups utilizing the API that would be better spent in patient education and navigation.

Using the website

ClinicalTrials.gov serves as the most used search engine by oncology professionals when looking beyond their own facility for clinical trials for their patients. In the preliminary analysis of a recent survey conducted by several of the undersigned organizations, it overwhelmingly was cited as the go-to resource for providers, regardless of practice size or setting.¹ When speaking with advocacy groups, patients also report the use of ClinicalTrials.gov to locate clinical trials for which they may be eligible. Advocacy groups also rely on ClinicalTrials.gov to find clinical trial information for patients to whom they are providing personalized assistance.

The ability to download search results of trials of interest is a helpful feature for healthcare professionals, patients and advocacy groups. This allows users to be able to have a list of matched trials when discussing clinical trial options during patient and healthcare professional communications. It also makes it relatively easy for advocacy groups to share a curated list of clinical trials for which a patient may qualify to that individual patient.

The world map feature is a valuable tool for patients to understand the location of trials beyond just those close to a given zip code. Patients may have extended networks of friends and family that could serve as host locations for a patient to stay during a trial, or the trial may be located close to an available hospitality house like the [Hope Lodge](#) network. Limiting trials to proximity of one single zip code, therefore, restricts the ability for mobile patients to explore alternate sites. The map provides a useful interface for that exploration.

As previously mentioned, the ability to search on non-patient clinical characteristics, such as patient preference fields like study type, study location, study phase, funder type, and access to study protocols is a very useful feature. To augment, we suggest including more of these features, including the ability to search by frequency and number of study visits, access to consent forms, and pre-enrollment requirements. As just-in-time sites become more common for clinical trials, it would also be helpful to be able to search for clinical trials that are designed to open a study site at the patient's treating facility.

Listed in *Appendix A* is a sampling of cancer type choices available from the ClinicalTrials.gov drop-down menu. These choices combine the cancer type, subtype and stage into one category. As prior mentioned, it would be more useful for website users and API users, to separate these into separate selection criteria. Also, the descriptions listed have some overlap in terms of disease descriptions, and while the search engine utilizes a synonym function to search against multiple terms, not all synonyms are recognized. For example, a recent search for Phase III trials actively recruiting for metastatic pancreas cancer returned 10 results. A search for Phase III trials actively recruiting for pancreas cancer stage IV resulted in no trials. Stage IV cancer, by definition, is metastatic so these

¹ The results are presently being analyzed and will be published later in 2020 by several of the undersigned organizations.

searches should have yielded the same results but did not. We recommend more work to improve mapping synonyms.

Other disease relationship functions need to be similarly improved. For example, searching for clinical trials for pancreas cancer does not yield trials open to any solid tumor even though pancreas cancer is a type of solid tumor. Increasingly cancer trials are open to multiple tumor types, so this lack of sophistication in understanding the mapping of cancer types to broader categories means patients are not being exposed to potential matching trials. At the same time, it would also be very helpful to have functionality for users to be able to filter out solid tumor trials if they would specifically like to find trials that are only studying their specific cancer diagnosis, as this is a desire for some patients.

Currently, the synonym mapping that is done is viewable in the search details tab which is not intuitive to users. Meaning, users may not know that they can view which search terms and synonyms were searched based on their own search terms. It would be helpful to have that information more visible to users, such as in the scenario below, stating “Also searched for Pancreatic Neoplasm, Neoplasm and 24 other terms – See Search Details.”

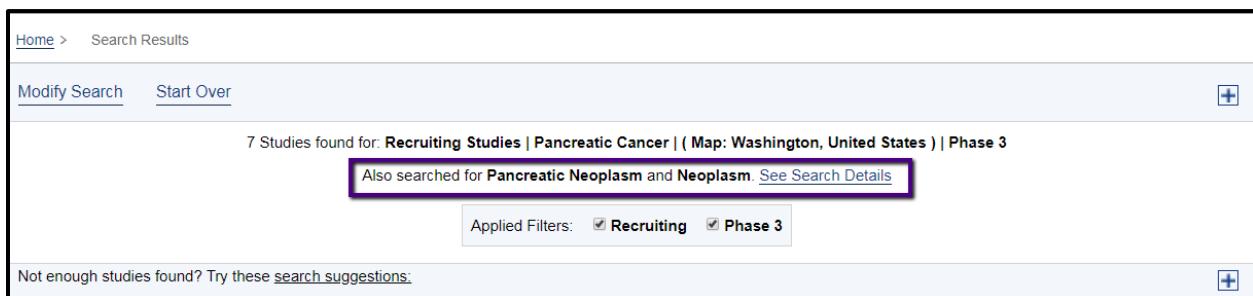


Figure 12: Depiction of synonyms used in search

In addition to improved synonym mapping, the functionality to search by multiple terms in a single field could also mitigate the current shortcomings of the mapping of cancer types. For example, this could allow users to search by breast cancer and breast carcinoma at the same time, potentially yielding more accurate results.

Better functionality is needed to be able to search for keywords in the “other terms” search box. For example, in searching for pancreatic cancer trials in the second-line setting that are actively recruiting in the United States, the search results yielded only four clinical trials. However, when using PanCAN’s clinical trial finder (clinicaltrials.pancan.org), where trial information about the line of treatment being studied is structured, the search yields 119 clinical trials. This is an example of where structured data on the line(s) of therapy being studied would assist users in finding applicable trials.

There is a lack of patient-friendly descriptions of the clinical trials, especially when describing the purpose of the clinical trial, the arms being studied in the clinical trial and eligibility criteria. One option is to add a new field labeled lay summary for clinical trial sponsors to submit lay-level descriptions and eligibility criteria for their trials. Another option would be to explore collaborations with disease advocacy groups who already create patient-friendly versions of the clinical trial listings to explain the design and purpose of the trial and the eligibility criteria and include links in the clinical

trial posting that will direct to these clinical trial listings on advocacy group websites. This will help to enhance the conversations that patients have with their providers regarding clinical trials of interest.

Current uses

The primary purpose of ClinicalTrials.gov for our organizations is to utilize a limited range of studies, specifically studies for the different types of cancers. When searching for these limited range of studies, it would be helpful to be able to see a tiered list of studies that includes 1) the studies that only the disease indication that is searched is being studied 2) any all-comer/solid tumor trials that are also matches.

Within the limited range of studies, it would be helpful to have criteria to further limit the list of studies. Limiting criteria should include required/excluded biomarkers, required/excluded prior treatments, required type of cancer, required subtype of cancer, and the required stage of cancer. It would also be helpful to continue to be able to narrow down the results using the map feature to narrow in on a specific county and state. It is also helpful to be able to narrow down by a radius from a specific zip code.

When looking at the landscape of clinical trials available for cancer patients, it is also helpful to look a slightly broader range of studies that are cancer studies, including the geographic locations of the studies, the types of studies (interventional versus observational) and intervention types, such as immunotherapy versus chemotherapy.

Information Submission

Registration improvements

As previously mentioned, in 2018, ACS CAN issued a report that provided 23 recommendations for overcoming barriers to patient enrollment. These consensus recommendations identified areas that would benefit from improvement, including standardized syntax submissions, more structured data fields, the ability for sponsors to share “private” information, such as proprietary biomarkers that may not be listed in the text, but would allow for trial matching, and more accurate and consistent site information.

ClinicalTrials.gov is positioned to influence how future clinical trial protocols are both written and submitted. All clinical trial protocol design will be impacted by what ClinicalTrials.gov allows and mandates when clinical trial information is submitted to the site. ClinicalTrials.gov represents the single source of truth when it comes to clinical trial information, but some of the information continues to be inaccurate or incomplete due to current limitations.

As more sponsors recognize the importance of and gain the ability to provide structured data, it would be beneficial to offer multiple ways to enter data. This would provide sponsors who have the ability to enter structured data the opportunity to do so and create better records, while maintaining flexibility for those sponsors who would like to continue with the existing free-text entry or do not have the ability to presently change their process.

In regards to structured data, specific fields that would be helpful to have sponsors enter data in a structured way include: cancer type, cancer subtype, biomarker status, stage of cancer/grade of

cancer/presence of metastases, number of prior therapies allowed/excluded, and categories of/names of excluded or required prior treatments.

It would be helpful to have a mechanism whereby sponsors can easily notify ClinicalTrials.gov when a Phase I/II trial switches from Phase I to Phase II. It makes it very difficult when there are different cohorts for each phase to know which phase is currently enrolling and what the current eligibility criteria is. If possible, please require or incentivize sponsors to update what portion of the trial they are currently recruiting for and update the eligibility for the current phase of the trial that is recruiting.

Regarding site information, there is both a lack of specificity and consistency in site names and contact information for the sites. In the figures below, there are examples of non-specific (Figure 13) and specific (Figure 14) site names and contact information.

The screenshot shows a study page for NCT03521154. The 'Contacts' section lists a general contact for AstraZeneca. The 'Locations' section shows two research sites in the United States: one in Santa Rosa, California, and another in Vallejo, California. Both sites are listed under the heading 'United States, California' and are categorized as 'Recruiting'. A yellow box highlights 'No facility name' and 'No customized contact for each facility'. Another yellow box highlights the lack of specific facility names and contact information for each site.

Figure 13: Sites lack names and contact information

The screenshot shows a study page for NCT02869789. The 'Contacts' section provides specific contact information for recruiting sites. The 'Locations' section lists two sites: one in Alabama (Birmingham) and one in Arizona (Chandler). Each site has a unique name ('Alabama Oncology' and 'Arizona Oncology Assoc, PC-Hal') and specific contact details ('Contact: Ira Gore, Site 0121 205-263-9746' and 'Contact: Abhimanyu Ghose, Site 0148 928-204-4198'). Yellow boxes highlight 'Specific facility name' and 'Specific facility contact info'.

Figure 14: Sites include full name and unique contact information

We suggest exploring if there is a universal facility number that already exists and could be used to create consistency in site names or exploring the creation of a structured table of sites for sponsors to pick from in order to bring more consistency to the site names. Furthermore, it would be tremendously helpful if sponsors were required to provide the actual site information, including contact information and zip code and not just the city and state.

Credits, incentives and recognition for submission of accurate and timely information

It may be helpful to show results in an order that lists the most recently updated clinical trials at the top of the list. This could incentivize sponsors to ensure their records are up to date.

While not directly an incentive to sponsors, it may be helpful to include some sort of direct feedback loop/reporting capability (maybe a button in the clinical trial record) to allow various stakeholders, including advocacy groups, patients, physicians, and/or investigators to inform ClinicalTrials.gov of out-of-date information. This may serve as a way for the ClinicalTrials.gov staff to prompt the sponsor for updated information. Currently, when advocacy groups hear from patients that a trial is closed, a site contact information is wrong, or other incorrect information is listed on ClinicalTrials.gov, the advocacy groups are spending time to reach out to the sponsors or sites to gather the correct information. This information is shared with the patient who is inquiring but is not updated on ClinicalTrials.gov. Once more, this serves as unnecessary wasted time by advocacy groups that could be used for clinical trial patient navigation and education.

Data Standards

Balancing standards while retaining flexibility in submitted information

We recommend creating capabilities to submit both free-text eligibility criteria and standard machine-coded criteria through separate data entry fields. This allows trial sponsors or reporting intermediaries who have more advanced capabilities to submit structured data, while still preserving the legacy free-text entry. It is critical that ClinicalTrials.gov allow advanced sponsors to increase the structure and utility of their data as much as possible, and not restrict website or database improvements based on the slowest adopting or least sophisticated trial sponsors.

In addition to/in place of free-form text field for “standard set” of eligibility, we recommend that ClinicalTrials.gov provide a list of dropdowns/checkboxes to indicate eligible or ineligible patient populations. One common area of clarification needed is around the use of the term “advanced disease” as an eligibility criterion. As mentioned previously, there is overlap in the use of “stage IV,” “metastatic,” and “advanced” as descriptions of cancer status. Having multi-select dropdown or checkboxes that only allow the selection of specific stages of disease, such as stage III and/or stage IV would mitigate this issue. Also, for all-comer trials in the solid tumor space, requiring a multi-select dropdown or checkboxes that only allow the selection of specific types of solid tumors such as pancreatic adenocarcinoma, non-small-cell lung carcinoma, etc., could mitigate some of the issues with solid tumor trials not appearing in results.

Having an improved search engine that recognizes the sameness between “pancreatic cancer” being a “solid tumor” and likely “pancreatic adenocarcinoma” (if a subtype was not provided) and better mapping of cancer types will also mitigate issues in search results.

Many patients are more likely to search for “pancreatic cancer” rather than “pancreatic adenocarcinoma,” so the mapping of cancer terms is imperative to account for variations in the health literacy of users, as healthcare providers and patient advocacy groups using the site are more likely to use the appropriate cancer type and subtype when searching.

Another area that would be helpful to capture structured data is around performance status. Some clinical trials provide ECOG performance scores, while others provide Karnofsky performance scores. Requiring that these fields be a structured dropdown selection and that both fields are required, will help with patient advocacy groups who utilize performance status in clinical trial matching.

As mentioned above, separating out the type of cancer, subtype of cancer and stage of cancer in to separate structured fields is ideal for assisting users in both entering the correct data for their trial and for users searching for appropriate trials for a patient.

Names and references to specific standards

We recommend the utilization of “syntax standard” along with a universal data standard to improve data quality. ACS CAN has convened a diverse set of stakeholders, including staff from ClinicalTrials.gov to develop a pragmatic “syntax standard” which could be implemented in the near term while longer-term database modifications and investigator infrastructure changes are being made to accommodate machine-readable standards. This syntax standard would continue to be text based, but syntax and terminology rules would dictate the form in which the criteria were presented with the goal of creating unambiguous phrases that are more easily interpreted by natural language processing (NLP), while retaining human readability. NLP is increasingly being used to translate free text into more structured data in an automated way. The workgroup is currently developing the syntax framework and hopes to pilot test and validate the end product by the end of 2020. The collaborative community will share results of that project when completed.

In parallel to the syntax standard, we strongly recommend that ClinicalTrials.gov adopts a machine-readable data standard for eligibility criteria. For example, the new [Minimal Common Oncology Data Elements](#) project or mCODE™ offers an example of an open source, non-proprietary data model for common data standards and language. This collaboration between ASCO and the MITRE corporation serves as an example of accessible interconnectivity and data standards across different systems. The group of stakeholders convened by ACS CAN and the mCODE™ group are willing to work together with the ClinicalTrials.gov staff to assist in the adoptions of these standards. We also suggest working with other groups outside of cancer that are working on standardization for other disease areas. EHRs continue to use different nomenclatures, so if ClinicalTrials.gov moves in the direction of standards, it will influence and activate others to move in the same direction.

In closing, we would like to thank you for the opportunity to share our experiences and recommendations for improving ClinicalTrials.gov. The website and database are valuable national resources that have assisted countless patients and providers in their quests to find clinical trial opportunities. As cancer clinical trials become more specialized and restrictive, it is more critical than ever to have state-of-the-art matching capabilities for patients to understand their options. While ClinicalTrials.gov was not originally designed or intended for patient matching, the reality is that today it is the go-to site for this function.

While the site must continue to serve its statutory role as a trial registry, it should also embrace its dual role in helping patients find clinical trials to participate in. We encourage NLM to be forward looking in its approach to the database architecture and website functionality of ClinicalTrials.gov and create an infrastructure that will allow the most advanced sponsors to submit trial records with greater structure and utility. Updates to ClinicalTrials.gov must not be tailored with the least sophisticated or slowest technology adopters as the primary design consideration. Instead, modernization should facilitate progress while continuing to provide a way for slow adopters to fulfil their registration obligations until they are capable of submitting more structured data.

We have developed a collaborative community of cancer organizations focused on the challenges of matching patients to clinical trials, and we offer ourselves as an ongoing resource as you carry out the modernization process. If you have any questions, please do not hesitate to contact either Cassadie Moravek (cmoravek@pancan.org) or Mark Fleury (mark.fleury@cancer.org). Once more, we applaud your efforts!

Sincerely,

American Cancer Society Cancer Action Network (ACS CAN)

American Cancer Society (ACS)

American Society of Clinical Oncology (ASCO)

Association of American Cancer Institutes (AACI)

Association of Community Cancer Centers (ACCC)

BreastCancerTrials.org (BCT)

Friends of Cancer Research (Friends)

Leukemia & Lymphoma Society (LLS)

LUNGevity Foundation

Massive Bio, Inc.

National Brain Tumor Society (NBTS)

Oncology Nursing Society (ONS)

Pancreatic Cancer Action Network (PanCAN)

SignalPath

The Jason Carter Clinical Trials Program, offered by Be The Match® (JCCTP)

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3. Fightcancer.org-- <https://www.fightcancer.org/policy-resources/patient-facing-clinical-trial-matching-summit-summary>
4. Unger 1--Unger JM, R Vaidya, DL Hershman, LM Minasian, ME Fleury. 2019.” Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation,” Journal of Natl. Cancer Inst. 111(3): 245-255.

Appendix A: Cancer type drop-down menu choices

ClinicalTrials.gov Search Results

| <i>Solid Tumor Examples</i> | | |
|---|---|---|
| Bladder | Liver | Skin |
| Bladder Cancer; Bladder Cancer Stage; Bladder Cancer Stage 0; Bladder Cancer Stage I; Bladder Cancer Stage II; Bladder Cancer Stage IV; Bladder Cancer TNM Staging Primary Tumor (T) T2A; Bladder Cancer TNM Staging Primary Tumor (T) T2B; Bladder Cancer TNM Staging Primary Tumor (T) T3A; Bladder Cancer TNM Staging Primary Tumor (T) T3B | Liver Cancer; Liver Cancer, Adult; Liver Cancer, Adult Primary; Liver Cancer, Childhood, Group I; Liver Cancer, Childhood, Group II; Liver Cancer, Childhood, Group IV; Liver, Cancer of, Non-Resectable; Liver, Cancer of, Primary; Liver Cancer Pediatric; Liver Cancer Stage IV | Skin Cancer; Skin Cancer, Basal Cell; Skin Cancer Face; Skin Cancer Melanoma; Skin Cancer, Non-Melanoma; Skin Cancer Metastatic; Skin Cancer, Recurrent; Skin Cancer, Squamous Cell; Skin Cancer Stage III; Skin Cancer Stage IV; |
| Breast | Lung | Thyroid |
| (BREAST CANCER SEARCH RESULTS): Breast Cancer; Breast Cancer Female; Breast Cancer Lymphedema; Breast Cancer Stage; Breast Cancer, Stage 0; Breast Cancer Stage I; Breast Cancer Stage II; Breast Cancer Stage IIA; Breast Cancer Stage III; Breast Cancer Stage IV; (BREAST CANCER STAGE SEARCH RESULTS): Breast Cancer Stage; Breast Cancer Stage 0; Breast Cancer Stage I; Breast Cancer Stage II; Breast Cancer Stage IIIA; Breast Cancer Stage IIIB; Breast Cancer Stage IIIC; Breast Cancer Stage IV | (LUNG CANCER SEARCH RESULTS): Lung Cancer; Lung Cancer Metastatic; Lung Cancer, Nonsmall Cell; Lung Cancer Non-small Cell Stage IV; Lung Cancer Recurrent; Lung Cancer, Small Cell; Lung Cancer Stage I; Lung Cancer Stage II; Lung Cancer Stage III; Lung Cancer Stage IV (LUNG CANCER STAGE SEARCH RESULTS): Lung Cancer Stage I; Lung Cancer Stage II; Lung Cancer Stage III; Lung Cancer Stage IV; | Thyroid Cancer; Thyroid Cancer, Anaplastic; Thyroid Cancer, Hurthle Cell; Thyroid Cancer, Medullary; Thyroid Cancer Metastatic; Thyroid Cancer, Papillary; Thyroid Cancer, Recurrent; Thyroid Cancer Stage I; Thyroid Cancer Stage II; Thyroid Cancer Stage IV |
| Colon and Rectum | Pancreas/Pancreatic | Uterine Cervix |
| (COLON CANCER SEARCH RESULTS): Colon Cancer; Colon Cancer Duke; Colon Cancer Metastatic to Liver; Colon Cancer Liver Metastasis; Colon Cancer Stage; Colon Cancer Stage I; Colon Cancer Stage II; | (PANCREAS CANCER SEARCH RESULTS): Pancreas Cancer; Pancreas Cancer, Acinar Cell Adenocarcinoma; Pancreas Cancer Cellular Diagnosis; Pancreas Cancer, Duct Cell Adenocarcinoma; | (UTERINE CERVIX CANCER SEARCH RESULTS): Uterine Cervix Cancer; Uterine Cervix Cancer, Stage 0; Uterine Cervix Cancer Stage I; Uterine Cancer, Stage IA; Uterine Cancer, Stage IB; Uterine Cervix Cancer Stage II; |

| | | |
|--|---|--|
| Colon Cancer Stage III; Colon Cancer Stage iv; Colon Cancer Stage 4; <i>(COLORECTAL CANCER SEARCH RESULTS):</i> Colorectal Cancer; Colorectal Cancer, Genetics of; Colorectal Cancer Metastatic; Colorectal Cancer Recurrent; Colorectal Cancer Somatic; Colorectal Cancer Stage 0; Colorectal Cancer Stage I; Colorectal Cancer Stage II; Colorectal Cancer Stage III; Colorectal Cancer Stage IV; <i>(RECTAL CANCER SEARCH RESULTS):</i> Rectal Cancer; Rectal Cancer, Adenocarcinoma; Rectal Cancer Dukes D; Rectal Cancer Metastatic; Rectal Cancer Recurrent; Rectal Cancer Stage I; Rectal Cancer Stage II; Rectal Cancer Stage III; | Pancreas Cancer, Metastatic; Pancreas Cancer, Recurrent; Pancreas Cancer, Stage 1; Pancreases Cancer, Stage II; Pancreas Cancer, Stage III; Pancreases Cancer, Stage IV <i>(PANCREAS CANCER STAGE SEARCH RESULTS):</i> Pancreas Cancer Stage I; Pancreas Cancer Stage II; Pancreas Cancer Stage III; Pancreas Cancer Stage IV; <i>(PANCREATIC CANCER SEARCH RESULTS):</i> Pancreatic Cancer; Pancreatic Cancer, Adult; Pancreatic Cancer Metastatic; Pancreatic Cancer Non-resectable; Pancreatic Cancer, Resectable; Pancreatic Cancer Stage; Pancreatic Stage III; Pancreatic Stage II; Pancreatic Cancer Stage IV; Pancreatic Cancer Stage IVA <i>(PANCREATIC CANCER STAGE SEARCH RESULTS):</i> Pancreatic Cancer Stage; Pancreatic Cancer Stage I; Pancreatic Cancer, Stage IA; Pancreatic Cancer, Stage IB; Pancreatic Cancer Stage II; Pancreatic Cancer, Stage IIA; Pancreatic Cancer, Stage IIB; Pancreatic Cancer Stage III; Pancreatic Cancer Stage IV; Pancreatic Cancer Stage IVA | Uterine Cerix Cancer, Stage IIB; Uterine Cervix Cancer, Stage III; Uterine Cervix Cancer, Stage IV; Uterine Cervix Cancer, Stage IVA; <i>(CERVICAL CANCER SEARCH RESULTS):</i> Cervical Cancer; Cervical Cancer Stage; Cervical Cancer Stage IB2; Cervical Cancer Stage II; Cervical Cancer Stage IIa; Cervical Cancer Stage IIB; Cervical Cancer Stage IIIA; Cervical Cancer Stage IIIB; Cervical Cancer Stage IVA; Cervical Cancer Stage IVB; <i>(CERVIX CANCER SEARCH RESULTS):</i> Cervix Cancer; Cervix Cancer Recurrent; Cervix Cancer, Stage 0; Cervix Cancer, Stage I; Cervix Cancer, IA; Cervix Cancer Stage IB; Cervix Cancer Stage II; Cervix Cancer, Stage III; Cervix Cancer, Stage IV; Cervix Cancer, Stage IVA |
| Kidney and Renal Pelvis <i>(KIDNEY CANCER SEARCH RESULTS):</i> Kidney Cancer; Kidney Cancer, Clear Cell Carcinoma; Kidney Cancer Metastatic; Kidney Cancer Recurrent; Kidney Cancer Stage I; Kidney Cancer Stage II; Kidney Cancer Stage III; Kidney Cancer Stage IV; <i>(RENAL CANCER SEARCH RESULTS):</i> Renal Cancer; Renal Cancer Metastatic; Renal Cancer Recurrent; Renal Cancer Stage I; | Prostate Prostate Cancer Adenocarcinoma; Prostate Cancer Aggressiveness; Prostate Cancer Metastatic; Prostate Cancer Metastatic to Bone; Prostate Cancer Recurrent; Prostate Cancer Stage; Prostate Cancer Stage I; Prostate Cancer Stage II; Prostate Cancer Stage III | |

| Renal Cancer Stage II; Renal Cancer Stage III; Renal Cancer Stage IV | | |
|---|--|--|
| <i>Blood Cancer Examples</i> | | |
| ALL | DLBCL | MDS |
| ALL, Childhood ALL, Adult ALL in Remission ALL, L1 Adult ALL, L2 Adult ALL, Recurrent, Adult ALL, Adult T Cell ALL, Adult B Cell ALL, L2 Childhood | Dlbcl-Ci DLBCL Unclassifiable DLBCL Activated B-Cell Type DLBCL Germinal Center B-Cell Type DLB | MDS-EB MDS/MPN MDS-RS MDS-EB-2 Mds-Mld MDS-EB-1 MDS/MPN-U MDS-Rs-Mld MDS/MPN with Ring Sideroblast and Thrombocytosis |
| AML | Leukemia | Myeloma |
| AML AML, adult AML/MDS AML M3 AML M4 AML M6 AML Childhood AML in remission AML FAB-M1 AML with Maturation | Leukemia Leukemia, Myeloid Leukemia, Chronic Leukemia, Acute Leukemia, Myeloid, Acute Leukemia, Lymphocytic Leukemia, Lymphoblastic Leukemia, T Cell Leukemia, B-Cell Leukemia Relapse | Myeloma Multiple Myeloma, Solitary Myeloma, Smoldering |
| CLL | Lymphoma | NHL |
| CLL/SLL CLL Progression CLL Transformation CLLS2 CLL Stage 1 CLL Stage 0 CLL, Relapsed CLL, Refractory CLL Stage II | Lymphoma Lymphoma, Non-Hodgkin Lymphoma, B-Cell Lymphoma, Follicular Lymphoma, T-Cell Lymphoma, Nonhodgkin Lymphoma, Mantle-Cell Lymphoma, Hodgkin Lymphoid Leukemia Lymphoma, High-Grade | NHL NHL, Adult NHL, Childhood NHL, Burkitt's NHL, Lymphoblastic NHL, Indolent, nos NHL, Metastatic Adult NHL, Stage I Adult NHL, Aggressive, nos NHL, Relapsed, Adult |
| T-Cell | | |
| T-cell Lymphoma T-cell Leukemia T-cell Prolymphocytic Leukemia T-Cell Lymphocytosis T-Cell Large Granular Lymphocyte Leukemia T-Cell Lymphoma Stage IV T-Cell Lymphoma Stage III T-cell Childhood Acute Lymphoblastic Leukemia T-cell Lymphoma Adults T-Cell ALL | | |

Submission No.: 249

Date: 3/14/2020

Name: Anonymous

Name of Organization: N/A

1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

With the new MDR regulations, sponsors are constantly trying to demonstrate equivalence and gather data (including other manufacturer's data) to support keeping our product on the market for patients. I wonder if it would be beneficial if CT.gov could allow sponsors/manufactures to somehow pool similar product/devices together or do some type of linkage so it's easier for companies to find equivalent product to support keeping product/devices on the market. Perhaps linking to the EUDAMED database?

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

With the new MDR regulations, sponsors are constantly trying to demonstrate equivalence and gather data (including other manufacturer's data) to support keeping our product on the market for patients. I wonder if it would be beneficial if CT.gov could allow sponsors/manufactures to somehow pool similar product/devices together or do some type of linkage so it's easier for companies to find equivalent product to support keeping product/devices on the market. Or have it automatically pooled together behind the scenes. Perhaps linking to the EUDAMED database?

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

We currently use CT.gov to keep our studies in compliance with evolving regulations/requirements and to keep the public/medical community informed. The consumer has gotten very savvy at looking things up on the internet. CT.gov gives patients the opportunity to find trials to participate in that they may have not been aware of before. Also, I have had physicians from other countries reach out to see if their patient qualifies for compassionate use. We've also had physicians contact us to express their interest in being a study site. Existing features that work well: flags to bring your attention to an item that requires your attention, instructions on what elements are required in a certain field. Improvements: It is extremely time consuming to manually enter in all the site's information, AEs/SAEs, other information. It would be nice if CT.gov had a way for sponsors to upload a PDF/locked excel spreadsheet of this information so users could read information that way instead of relying on sponsors to manually enter everything in CT.gov. Or it would be nice if CT.gov had the capability to upload information from sponsor's EDC systems.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of

studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

We rely on a wide range of studies, such as different types, intervention types and geographical locations because we are a large manufacturer, therefore we are required to report on all of these items.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

In my experience the PRS staff seem to lack the clinical study knowledge to adequately review the submitted records. As a result, we get flagged or we receive questions from them that don't make any sense so we are left struggling to interpret their questions/comments, which results in delays trying to seek clarity from them. We also try to call, but it's very difficult to reach someone live and when we do finally reach someone, they also don't understand our questions because they don't have any clinical study background/knowledge. Please find staff that understand clinical studies. Also, CT.gov doesn't really allow for the results reporting of two investigational devices approved under one study. The one size fits all model forces you to get creative when you are trying to report these results of two investigational products approved under one study. CT.gov needs to have a little more flexibility with this. It isn't always clear which studies are required to be registered on CT.gov. It would be nice if there was a decision tree that guided you to the right decision to either register or not register. Also, the request to delay results isn't super intuitive either. It would be nice to have more examples or guidance around that type of submission/request.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

It is extremely time consuming to manually enter in all the site's information, AEs/SAEs, other information. It would be nice if CT.gov had a way for sponsors to upload a PDF/locked excel spreadsheet of this information so users could read information that way instead of relying on sponsors to manually enter everything in CT.gov. Or it would be nice if CT.gov had the capability to upload information from sponsor's EDC (electronic data capture)/ETMF (electronic trial master file) systems.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

I'm not aware of any.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

I use the ClinicalTrials.gov Results Data Element Definitions for Interventional and Observations Studies and ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies on your website. These links, and others, are extremely useful.

- 2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**

Maybe if sponsors/manufacturers have a history of having complete, accurate and timely registration, they could go to the top of the list when there is a queue of studies/submissions to review.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

No comment.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

No comment.

Submission No.: 250

Date: 3/14/2020

Name: Christina Eldredge

Name of Organization: University of South Florida

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I currently use ClinicalTrials.gov publicly available adverse event data to study hypersensitivity and adverse allergic reactions in clinical cancer trials. Potential improvements involve the data point of the clinical trial arm intervention when it involves multiple drug therapy. There are limits to linking the reported adverse event to one specific drug in the multi-drug therapy regimen in sequential clinical cancer therapy trials. For example, the use of certain controlled terminologies or classification systems such as MedDRA do not report the drug allergen, the terminology only reports the type of hypersensitivity event. In multi-drug therapy, it is not possible to determine which drug in the arm intervention was the most likely etiology for the adverse event or if it was due to contrast or another unrelated event such as food.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

My use involves cancer therapy interventions and adverse immune events.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

CTCAE's grading levels are useful in my type of research to report on adverse immune events in clinical cancer trials.

Submission No.: 251

Date: 3/14/2020

Name: Cassadie Moravek

Name of Organization: Pancreatic Cancer Action Network (PanCAN)

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

There is a need to improve clinical trial matching for patients diagnosed with cancer. As outlined in the response from the American Cancer Society Cancer Action Network (ACS CAN), ClinicalTrials.gov can play a critical role in providing a website that enables easy clinical trial matching and screening. The Pancreatic Cancer Action Network (PanCAN), maintains a clinical trial database and clinical trial finder that enables pancreatic cancer patients, their families and healthcare professionals to find pancreatic cancer clinical trials easily using a few structured data fields. Adapting this type of functionality would facilitate enhanced trial matching on ClinicalTrials.gov for patients, families and healthcare professionals.

Separating the current fields grouped together in the condition field of ClinicalTrials.gov to allow the ability to search by cancer type, cancer subtype and cancer stage as unique fields would be ideal. In the attached supplementary materials are screenshots (Figures 1 through 5) from PanCAN's clinical trial database and clinical trial finder that illustrate our current functionality for structuring pancreatic cancer subtypes and stages. This type of functionality could be adapted to structure key data fields in ClinicalTrials.gov.

In the age of precision medicine, another unsupported new use of ClinicalTrials.gov that would benefit the cancer community is the ability to easily search clinical trials by biomarkers required in order to participate in a clinical trial. Structuring biomarker eligibility data and providing the ability to search by biomarker status via a dedicated biomarker field that allows searching for multiple biomarkers at once is increasingly important for clinical trial matching. PanCAN recently partnered with GenomOncology, <https://www.genomoncology.com/>, to fill the gap in the PanCAN's clinical trial finder functionality when it comes to matching to biomarker-driven site agnostic/solid tumor clinical trials. There are other organizations who have included a molecular target field in their clinical trial search functionality, such as Mary Crowley Cancer Research, <https://www.marycrowley.org/clinical-trials/>. Adopting this type of functionality would make searching for clinical trials requiring specific biomarkers much easier for users.

It is also important in clinical trial matching to search by the categories and names of prior treatments that a patient has received and the number of lines of previous treatment. In the attached document are screenshots (Figures 6 through 10) from our clinical trial database and clinical trial finder that illustrate our current functionality for structured fields for number and type of prior treatments. Including this type of functionality or at least starting with functionality allowing users to narrow searches to trials that either do allow or do not allow any prior treatment will immensely help in narrowing down the clinical trial search results on ClinicalTrials.gov.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

We would like to see linking to websites of disease-focused patient advocacy groups, such as PanCAN (<https://www.pancan.org/>), who provide resources for clinical trial patient education, matching and navigation. PanCAN's team can provide educational materials and personalized assistance to pancreatic cancer patients navigating their cancer care, including the importance of considering clinical trials as an option for care. This personal touch from advocacy organizations is an added benefit for patients who are navigating the clinical trial space.

Linking to published manuscripts and abstracts presented at national conferences (both positive and negative results) would also be helpful, as many patients pursuing clinical trials have questions about results of earlier clinical trials with the intervention being studied, including adverse events, side effects and outcomes of the prior clinical trials. Linking to this information will serve to better educate patients on the results of previous studies, assisting them in making informed decisions about their care, including the choice to enroll in a clinical trial.

The linking of terms within the ClinicalTrials.gov summaries, such as the specific drugs being studied, to the definitions in the NCI Drug Dictionary would further help users of ClinicalTrials.gov with understanding unfamiliar terms associated with the individual clinical trials. Some sponsors provide definitions of drugs within the listing summary, but others do not, so linking to the NCI Drug Dictionary would allow users to be able to educate themselves on the terms used and the drugs being studied, also assisting them in making informed decisions about enrolling in a clinical trial.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

PanCAN currently utilizes the ClinicalTrials.gov API to access and download posted data on ClinicalTrials.gov studies. It is extremely helpful to have the existing data available through the API, however, there is limited structured information provided. This requires our staff to manually curate the information posted in order to make it structured and usable for clinical trial matching in our clinical trial database and clinical trial finder. Because the information in ClinicalTrials.gov trial listings is not patient-friendly, PanCAN staff also writes patient-friendly summaries for each of the clinical trials that we curate. Finally, PanCAN staff also reaches out to sponsors to ask clarifying questions about the often vague eligibility criteria and gather other details about each clinical trial that is important to patients, such as the frequency of visits to the site for trial participation. We estimate that it takes 3-5 people hours per clinical trial to structure the data for matching, write patient-friendly summaries and to correspond with sponsors.

Given the resources involved in the curation, we would like to see an increase in the structured fields in the database and available through the API. As noted in the response provided by ACS CAN, structuring the following eligibility fields would be most useful: cancer type, cancer subtype, biomarker status, stage/grade of cancer/presence of metastases, number of prior therapies allowed/excluded, and categories of or names of excluded or required prior treatments. Additionally, PanCAN would also find it helpful to improve the number of keywords provided through the API and to have more subcategories in the study types. For example, there are many subcategories to interventional trials, including treatment

trials, supportive care trials, and diagnostic/screening trials. Having this additional level of detail will help with the structuring of clinical trial data to drive better clinical trial matching both through third parties and on ClinicalTrials.gov itself. People with a cancer diagnosis are often looking for treatment clinical trials or supportive care clinical trials to support their quality of life while receiving standard treatments. People at a high risk of cancer due to family history or other factors are often looking for studies that are testing diagnostic or screening procedures. Being able to filter by these subtypes of interventional trials will narrow down the list of trials users must look through to find applicable trials.

The other challenging area for PanCAN is the lack of consistency in trial sites and names when trials are offered at the same institution. Because of this lack of consistency, PanCAN does not utilize the site information through the API and instead maintains a consistent list of sites within our clinical trial database. PanCAN staff manually adds the sites and site contacts to each trial that is added to our database. We must also manually remove sites as they halt recruitment. For National Cancer Institute (NCI) National Clinical Trial Network (NCTN) group trials, which can include hundreds to a thousand sites, this can take up to 20 people hours for a single trial. Additionally, some trials listed on ClinicalTrials.gov do not have any sites listed at all, creating extra work to contact the trial sponsor to obtain the specific sites so that we are able to let patients know which trials are close to them.

Improving the structure and consistency of each of these areas will allow advocacy groups to access better data through the API and shift resources to the high-touch areas of patient education and navigation of clinical trial matching and enrollment.

PanCAN has also utilized ClinicalTrials.gov to search for clinical trials that are not curated in our clinical trial database in order to assist patients in finding solid tumor trials they may be eligible for, and specifically clinical trials studying a specific biomarker population. In using the website for this purpose, the save studies functionality has been very useful. However, our staff has run into a few challenges, including clearing saved studies, studies not saving and issues with having multiple browser windows open preventing the list of saved studies from remaining consistent. Despite these challenges, the ability to save a list of trials and download that list is very helpful when sharing a personalized list of trials with a patient for them to take to discuss with their doctor.

In searching for clinical trials for our patient population, we often filter out the pediatric trials using the very useful Age Group filter. However, we have noticed that when applying only the Adult and Older Adult filters, some pediatric trials are still showing up in the search results. This may be a result of more pediatric trials extending the age range of participants to patients up to 21 years of age. Having the ability to structure these the Age Groups based on the intended study population of the trial rather than age ranges allowed would mitigate this issue.

Other filters that are very helpful when searching for clinical trials for patients include the filters that provide the ability to search on non-patient clinical characteristics, such as patient preference fields like Recruitment Status, Study Type, Study Documents and Phase. These filters allow our staff to easily narrow down the list of trials when we are looking for trials for a patient. To augment this existing set of filters, we suggest including more of these features, including the ability to search by frequency and number of study visits, access to consent forms, and pre-enrollment requirements. As just-in-time sites become more common for clinical trials, it would also be helpful to be able to filter for clinical trials that can open a study site at the patient's treating facility.

The map feature is very helpful when narrowing down a list of trials to a specific country or state in the United States. It is also helpful to be able to search by a city and a radius around that city. However, not all cities are listed, so functionality to allow users to search by a zip code (and multiple zip codes at a time) is a much-needed improvement in this search functionality. Also, the website currently limits the radius of up to 300 miles— it would be helpful to have greater radius options. Also, when returning results within a geographic area, within the clinical trial record, it would be helpful to highlight the sites within that geographic area, or sort them to the top of the location list so the user isn't searching through hundreds of sites within the trial listing to find the one within the search radius they are looking.

Within the clinical trial record, the table indicating the condition, intervention and phase of the clinical trial is very helpful to see at-a-glance these key pieces of information. As cancer clinical trials become more sophisticated, especially in the use of biomarkers as eligibility criteria, it would also be helpful to see the biomarker and classification of the drug in this table. This could be another opportunity to link to the NCI Drug Dictionary.

The History of Changes section of the clinical trial record is also very helpful to determine what has changed in the record. However, it would be an improvement in this feature if there was a way to indicate if there were meaningful changes in the trial record, such as changes to eligibility criteria that would change the patient population or the addition of new arms to the trial, versus only changes to the formatting of the information.

For PanCAN staff, the RSS Feed is a very helpful way to be notified of new trials, including pancreatic cancer, gastrointestinal cancer, and solid tumor trials with an expansion cohort in pancreatic cancer that would be relevant to include in our clinical trial database and clinical trial finder.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

PanCAN currently utilizes a limited range of studies, limited to those studies specifically for pancreatic cancer, gastrointestinal cancers (that include pancreatic cancer), solid tumors with a pancreatic cancer cohort, and solid tumor with a specific biomarker population. Limiting to these trials helps us narrow in on the clinical trials that are most applicable to the specific population that we serve, pancreatic cancer patients. Within this limited list of trials, it is also imperative to narrow down the list with additional criteria including the stage of disease, subtype of pancreatic cancer, biomarker population being studied, location of the trial, prior treatments allowed, phase of the trial and study design. These additional criteria would allow PanCAN staff to provide a more limited and more easily navigated list of clinical trials for patients. It would also serve patients, families and healthcare professionals utilizing the tool to find trials for a patient.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

PanCAN echoes the response provided by ASC CAN that standardized syntax submissions, more structured data fields, the ability for sponsors to share “private” information, such as proprietary biomarkers that would allow for trial matching and more accurate and consistent site information would benefit from improvement. Regarding site information, as mentioned above, there is an opportunity to require more specific site names and contact information from sponsors as to which sites are enrolling patients for their trials.

It would be also helpful to allow sponsors to easily notify ClinicalTrials.gov when a Phase I/II trial switches from Phase I to Phase II so that the record can be updated appropriately. When there are multiple cohorts with varying eligibility criteria, the way the data is currently presented makes it difficult to know which phase is currently enrolling and what the current eligibility criteria is. If possible, please require or incentivize sponsors to update what portion of the trial they are currently recruiting for and update the eligibility for the current phase of the trial that is recruiting.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

PanCAN echoes the response provided by ACS CAN regarding incentivizing sponsors to provide updated information for their trials. Clinical trial records with consistently updated information should appear at the top of the list of matched trials.

PanCAN also supports including a direct feedback loop to inform ClinicalTrials.gov staff when we come across out-of-date information. PanCAN regularly learns of incorrect information in the ClinicalTrials.gov record from patients, clinical trial sites and sometimes clinical trial sponsors. We correct the information in our own database and would happily welcome a way to easily share that information with the ClinicalTrials.gov team so that they may follow up with the sponsor to report updated information. Keeping the ClinicalTrials.gov record updated will not only help users of ClinicalTrials.gov but will also help other third-party groups using this public data, preventing multiple groups from wasting time correcting the same data in multiple places.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

PanCAN recommends in addition to providing fields to enter free-form text, that ClinicalTrials.gov also provides a list of dropdowns/checkboxes for key criteria to indicate eligible or ineligible populations. For example, one common eligibility criteria that is indicated is that patients must have “advanced” disease. However, when following up with sponsors of clinical trials, some sponsors indicate this is only stage IV pancreatic cancer, while other sponsors indicate they are allowing both stage III and stage IV pancreatic

cancer. Having a multi-select dropdown or checkboxes for sponsors to select specific stages of disease, such as stage III or stage IV, would mitigate this issue.

As mentioned above, separating out the type of cancer, subtype of cancer and stage of cancer into separate structured fields would also be helpful when sponsors are entering information about the eligibility criteria for their trials.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

In participating in workgroups led by ACS CAN, PanCAN has had the opportunity to work with a group of stakeholders to develop a “syntax standard” provided in the ACS CAN response. This syntax would be helpful in the short term to make the open text in the records more easily interpreted by natural language processing (NLP), which still retaining human readability while longer-term solutions mentioned in this response are put into place. In parallel to the syntax standard, we strongly recommend that ClinicalTrials.gov adopts a machine-readable data standard for eligibility criteria.

As part of the ACS CAN workgroups, PanCAN also vets, selects and implements a machine-readable data standard for eligibility criteria, such as the example mentioned in the ACS CAN response, the Minimal Common Oncology Data Elements project.

Attachment: RFI ClinicalTrials.gov Modernization_PanCAN Supplementary Materials.docx

RFI: ClinicalTrials.gov Modernization PanCAN Supplementary Materials

What type of pancreatic cancer does the patient have ?

| Exclude (Drives Search) | Neutral (Drives Search) | Include (Drives Search) |
|---|---|-------------------------|
| <input type="checkbox"/> Adenocarcinoma | <input type="checkbox"/> Adenocarcinoma | |
| <input type="checkbox"/> Neuroendocrine carcinoma | | |
| <input type="checkbox"/> Gastrinoma | | |
| <input type="checkbox"/> Glucagonoma | | |
| <input type="checkbox"/> Insulinoma | | |
| <input type="checkbox"/> Nonfunctional Islet Cell Tumor | | |
| <input type="checkbox"/> Not sure of the type of neuroendocrine carcinoma | | |
| <input type="checkbox"/> Other Pancreatic Neuroendocrine Tumor | | |
| <input type="checkbox"/> Somatostatinoma | | |
| <input type="checkbox"/> VIPoma | | |
| <input type="checkbox"/> Not Sure | | |
| <input type="checkbox"/> Not Sure type of pancreatic cancer | | |
| <input type="checkbox"/> Other | | |
| <input type="checkbox"/> Acinar Cell Carcinoma | | |
| <input type="checkbox"/> Adenosquamous Carcinoma | | |
| <input type="checkbox"/> Giant Cell Carcinoma | | |
| <input type="checkbox"/> Intraductal Papillary Mucinous Neoplasm (IPMN) | | |
| <input type="checkbox"/> Mucinous Cystic Neoplasm (MCN) | | |
| <input type="checkbox"/> Other type of Pancreatic Cancer | | |
| <input type="checkbox"/> Pancreatic Intraepithelial Neoplasia (PanIN) | | |
| <input type="checkbox"/> Pancreatic Lymphoma | | |
| <input type="checkbox"/> Pancreatoblastoma | | |
| <input type="checkbox"/> Serous Cystadenoma | | |
| <input type="checkbox"/> Solid and Pseudopapillary Tumors | | |

Figure 1: Back-end structuring of pancreatic cancer subtype data

What is the patient's current stage of pancreatic cancer ? Check one.

| Exclude | Neutral | Include |
|---------|------------------------------------|---------|
| | <input type="checkbox"/> Stage 0 | |
| | <input type="checkbox"/> Stage I | |
| | <input type="checkbox"/> Stage II | |
| | <input type="checkbox"/> Stage III | |
| | <input type="checkbox"/> Stage IV | |
| | <input type="checkbox"/> Not Sure | |

Figure 2: Back-end structuring of pancreatic cancer stage data

Enter Diagnosis Information

1. What type of pancreatic cancer does the patient have?

What are the different types?



- Adenocarcinoma
- Pancreatic neuroendocrine tumors
- Other
- Not Sure

2. What is the current stage of the patient's pancreatic cancer?

What are the stages?



- Surgically Removed
- Stage I
- Stage II
- Stage III
- Stage IV
- Not Sure

Figure 3: Front-end search by patient using structured data fields for subtype and stage

NARROW YOUR RESULTS

Type of Pancreatic Cancer

Adenocarcinoma
 Pancreatic neuroendocrine tumors
 Gastrinoma
 Glucagonoma
 Insulinoma
 Non functional Islet Cell Tumor
 Somatostatinoma
 VIPoma
 Other Pancreatic Neuroendocrine Tumor
 Other
 Acinar Cell Carcinoma
 Adenosquamous Carcinoma
 Intraductal Papillary Mucinous Neoplasm (IPMN)
 Other type of Pancreatic Cancer

Request a Healthcare Provider account to access full Trial Find

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57 active and recruiting pancreatic cancer clinical trials

Pancreatic neuroendocrine t... X Other Type of Pancreatic Ca... X

Clear All Filters X

Select All Download Email Print

Phase I Study of Safety and Immunogenicity of Survivin Long P Vaccine (SurVaxM) in Patients With Metastatic Neuroendocrine (NETs)

Phase I First-in-Human Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of JNJ-Patients With Advanced Solid Tumors Harboring the KRAS G12

Phase I Study of Mesothelin-Targeted Immunotoxin LMB-100 in With Tofacitinib in Persons With Previously Treated Pancreatic Adenocarcinoma, Cholangiocarcinoma and Other Mesothelin Solid Tumors

Figure 4: Front-end search by healthcare professional using structured data fields for subtype

NARROW YOUR RESULTS

Stage of Pancreatic Cancer

- Resected
- Stage I
- Stage II
- Stage III
- Stage IV

Continue

Request a Healthcare Provider account to access full Trial Finder features.

[View Details](#)

184 active and recruiting pancreatic cancer clinical trials

Select All [Download](#) [Email](#) [Print](#) [Save](#)

Pilot Proof of Mechanism Study of BXCL701, a Small Molecule Inhibitor of Dipeptidyl Peptidases (DPPs), in Patients With Pancreatic Cancer [»](#)

Pilot Study of Hepatic Resection for Metastatic Pancreatic Cancer [»](#)

Figure 5: Front-end search by healthcare professional using structured data fields for stage

Prior Treatment **Has the patient received prior treatment ?**

Exclude Neutral Include

Patient has had prior treatment (yes)
 Patient has not had prior treatment (no)

[Move to Exclude](#) [Move to Neutral](#) [Move to Include](#)

Lines of Treatment **What treatments has the patient received for their pancreatic cancer ? (Check all that apply)**

Exclude Neutral Include

| |
|---|
| Chemotherapy |
| 5-Fluorouracil (5-FU) |
| Capecitabine (Xeloda®) |
| Carboplatin (Paraplatin®) |
| Cisplatin (Platinol®) |
| Cyclophosphamide (Cytoxan® or Neosar®) |
| Dacarbazine (DTIC-Dome®) |
| Docetaxel (Taxotere®) |
| Doxorubicin (Adriamycin® or Rubex®) |
| Etoposide (Toposar®, VePesid®, or Etopophos®) |
| Gemcitabine (Gemzar®) |
| Irinotecan (Camptosar®) |
| Irinotecan liposome injection (ONIVYDE™) |
| Mitomycin-C (Mutamycin®) |
| Nab-paclitaxel (Abraxane®) |
| Other |
| Oxaliplatin (Eloxatin®) |
| Paclitaxel (Taxol®) |
| Streptozocin (Zanosar®) |
| Temozolamide (Temodar®) |
| Hormone Therapy |
| Lanreotide (Somatuline® Depot) |
| Octreotide (Sandostatin®) |
| Other |
| Immunotherapy |

Figure 6: Back-end structuring of prior treatment data

Prior Regimens **How many prior regimens has the patient received?**

Exclude Neutral Include

| |
|----|
| 0 |
| 1 |
| 2 |
| 3 |
| 4+ |

[Move to Exclude](#) [Move to Neutral](#) [Move to Include](#)

Figure 7: Back-end structuring of lines of treatment data

4. More specifically, has the patient received treatment for their stage III or stage IV pancreatic cancer?

No

Yes

All the therapies checked on question #3 have been solely for the treatment of the patient's advanced/metastatic disease

Please check all that apply

- Chemotherapy
- Targeted Therapy i
- Hormone Therapy i
- Immunotherapy i
- Surgery to remove pancreatic cancer
- Radiation
- Radiation together with Chemotherapy
- Irreversible Electroporation (NanoKnife®) i
- Other Treatments
- Not Sure

4a. From the treatment selected above, how many chemotherapy regimens has the patient received for their stage III or IV pancreatic cancer?

What is a chemotherapy regimen? +

0

1

2

Figure 8: Front-end patient search by prior types and lines of treatment

| | | | |
|-------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Line of Treatment | <input type="checkbox"/> Neoadjuvant | <input type="checkbox"/> Second Line | <input type="checkbox"/> Maintenance |
| | <input type="checkbox"/> Adjuvant | <input type="checkbox"/> Third Line | <input type="checkbox"/> Other |
| | <input type="checkbox"/> First Line | <input type="checkbox"/> Beyond | <input type="checkbox"/> Recurrence |

Figure 9: Back-end structuring of line of treatment studied in clinical trial

NARROW YOUR RESULTS

Line of Treatment

- Neoadjuvant
- Adjuvant
- First Line
- Second Line
- Third Line
- Beyond
- Maintenance
- Other
- Recurrence

Continue

Request a Healthcare Provider account to access full Trial Finder features.

View Details ▾

122 active and recruiting pancreatic cancer clinical trials

Second Line X

Select All     

Pilot Study of Hepatic Resection for Metastatic Pancreatic Cancer 

Pilot Study of Respiratory-gated Stereotactic Body Radiation Therapy for Borderline Resectable, Unresectable, or Recurrent/Residual Adenocarcinoma of the Pancreas or Periampullary Region 

Phase Ib Study of Treatment of Advanced Pancreatic Cancer With Anti-CD3 x Anti-EGFR-Bispecific Antibody Armed Activated T-Cells (BATS) 

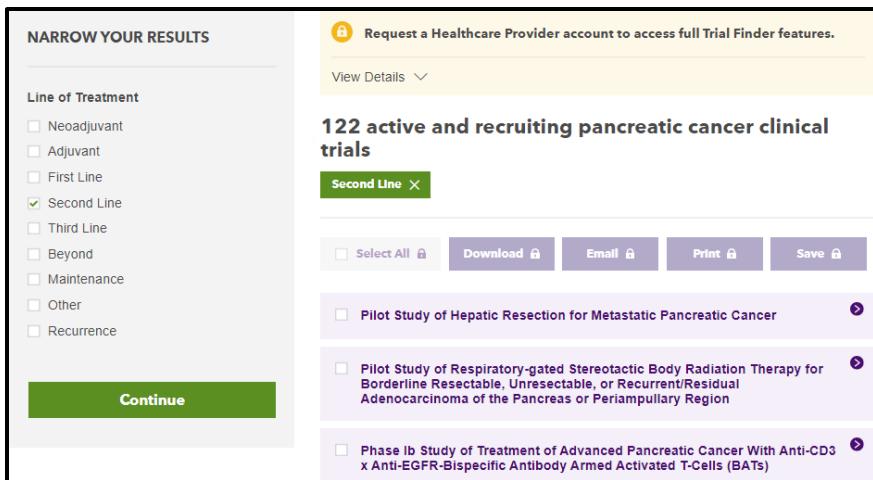


Figure 10: Front-end healthcare professional search by line of treatment studied in a clinical trial

Submission No.: 252

Date: 3/14/2020

Name: Perrine Janiaud

Name of Organization: Meta-research Innovation Center at Stanford

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

We would recommend linking ClinicalTrials.gov to the Drugs@FDA database for all trial interventions with a New Drug Application (NDA) and Biologics License Application (BLA) identification number. For consistency, we would also recommend linking the approval packages of biologics approved by the Center for Biologics Evaluation and Research (CBER), although no formal database exists for those interventions. Such linking would give direct access to the FDA approval packages as well as the drug labels and prescriber information, which would be valuable to patients and clinicians, and also to researchers of the drug development and approval process. Likewise, it would be very useful and increase consistency and transparency, if the clinical trial IDs used in the FDA drug approval documents referred to the ClinicalTrial.gov NCT entry IDs, rather than the protocol ID assigned by the applicant.

Some repositories for study protocols and data already exist, such as the YODA project. We would recommend that any registered trial should be linked to such data repositories when available.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

We primarily use ClinicalTrials.gov for research purposes, including systematic reviews and meta-analyses.

One important research focus is the type of evidence used by the FDA to approve drugs, which requires the identification of pivotal and supportive studies. However, it is difficult to cross-check information and identify such trials due to the lack of consistent trial ID names across platforms. A label or tag such as “pivotal study” or “supportive study” could help clinicians, patients and researchers better understand on what evidence base a drug has been approved.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
- 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

The current outcome reporting requirements, as stipulated in the 2007 FDA Amendment Act and the FDA Final Rule in 2016, could be strengthened. We see two main areas of improvement to the current

reporting requirements (1) and (2), and we have a further proposal (3) on how to increase the transparency and openness of trials registered at ClinicalTrials.gov:

1) Adverse events: Currently there is a 5% reporting threshold for the reporting of harms. This arbitrary cutoff may prevent important results from being disseminated that may also never be published in peer-reviewed medical journals, as such journals often introduce reporting thresholds as well. We recommend requiring the full reporting of adverse events, without any cutoffs.

2) “Key secondary outcomes”: Currently, “key secondary outcomes” must be reported alongside the primary outcomes. It is not defined in the current legislation what constitutes a “key secondary outcome”, and furthermore it seems that investigators may report not-prespecified outcomes rather than the pre-specified outcomes, also known as outcome switching (Chang et al. 2004, Goldacre et al. 2019). We recommend the reporting of all prespecified primary and secondary outcomes. This will allow for the most unbiased reporting of trial results and it will mitigate selective reporting and outcome switching.

If the investigators are allowed to report the results in whichever format they want, provided that they adhere to a minimum standard reporting requirement (as proposed above), we anticipate that there should be no additional burden to the investigators reporting the results, despite the strengthened requirements.

3) Clinical Study Reports: This issue particularly pertains to industry studies conducted for new drug applications that are registered in the database. Currently, FDA does not release clinical trial data from new drug applications, also known as clinical study reports (CSRs) (module 5 in the marketing authorisation dossier). Other major drug regulatory agencies, such as Canada Health and the European Medicines Agency (EMA) have begun prospectively to release such data. EMA began releasing clinical study reports upon request with the introduction of policy 0043 in 2010 and then began with the prospective release of data from newly approved drugs with policy 0070 in 2015 (<https://clinicaldata.ema.europa.eu/web/cdp/home>). Canada Health began prospectively releasing clinical data for newly approved drugs in 2019 (<https://clinical-information.canada.ca/search/ci-rc>). FDA launched in 2018 a pilot program, “Clinical Data Summary Program”, about prospective release of CSRs from newly approved drugs (<https://www.fda.gov/drugs/development-approval-process-drugs/clinical-data-summary-pilot-program>). We envision ClinicalTrials.gov could operate as the main entry point for such trial data, if the FDA began prospectively or retrospectively releasing such trial data.

We have one concrete idea for a research project to elucidate current limitations and challenges related to trial registration and results reporting, which may help identify additional areas that could be improved. It would be valuable to survey principal investigators and other relevant users of ClinicalTrials.gov about their experiences of the database and particularly to assess current problems. It would especially be valuable to get information from principal investigators of trials that have not reported results at all, or within the 12-month time frame to identify common problems or mechanisms for delayed or absent reporting.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

Institutional review boards across the country can be powerful allies in enforcing trial registration on ClinicalTrials.gov by making it a prerequisite to an IRB submission. In addition, many IRBs have their own online submission system requiring similar data entry as ClinicalTrials.gov. There is an unique opportunity to streamline the process by enhancing the interoperability between the different platforms.

Make the data submission process simpler - make sure that the form is clean and that anyone with minimal methodologic knowledge can fill it. If this is not possible, provide a service to pay for a specialist to fill it in for you.

At the moment, one of the most substantial barriers in registering a trial and its results on ClinicalTrials.gov, is the arduous process of signing up with ClinicalTrials.gov and filling in the required forms. We recommend that this process stripped down to its absolute basics, that all questions come with clear explanations of what information is sought, since the same term may mean very different things to different people.. At the moment, there is plenty of information at different pages on the website, which are difficult to find and synthesize. We propose to gather all necessary information where users will most need it,i.e. right at the form. A source of inspiration for creating user-friendly forms may be www.typeform.com. ClinicalTrials.gov could also invest in creating a quick Coursera course with the aim to teach users about the registration and results reporting.

Many clinical trialists use standard software to manage their clinical trials, such as Microsoft Excel. Unfortunately, this software was not designed for managing such studies, it leads to non-standard methods of accumulating and communicating data and is error prone. Some use purposely-built software, but this does not directly integrate into ClinicalTrials.gov. We suggest ClinicalTrials.gov invests in creating a software for managing clinical trials, that helps researchers manage their clinical trial and at the same time knows how to communicate with and populate ClinicalTrials.gov with the appropriate results.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Clinical trials have diversified over time in terms of type of intervention/treatment and other parameters. Consequently, many trials do not fit predefined categories, resulting in many uncategorized trials, labeled "Other". One solution would be to organize a "ClinicalTrials.gov Data Mapping Challenge" or similar to extract categories from the data already in the database and provide future researchers with an opportunity to select from a wider range of categories when they register their trials.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

We have four suggestions to incentivize the registration and reporting of trial results on the ClinicalTrials.gov website:

Providing a DOI (digital object identifier) number for all registered trials with adequately reported results. We believe that providing a DOI for all registered trials with reported results would help incentivize researchers to submit complete, accurate and timely results. In addition, a DOI would allow

the trial registration to be cited by the scientific community, thus providing recognition to the researcher/sponsor of the trial.

Recognizing trial registration and results reporting with ORCID: Researchers and investigators may be incentivized to register and report results, if they could claim credit for this work through their ORCID profiles. Similarly, researchers and/or investigators could declare in Publons all the trials they have registered as it represents an important contribution to the research community.

Requiring results reporting as a condition for publication in ICMJE journals: The requirement of trial registration as a condition for publication in any member journal of the International Committee of Medical Journal Editors (ICMJE) resulted in a rapid increase of registered trials at ClinicalTrials.gov. The requirement of timely reporting of results on ClinicalTrials.gov before consideration of publication in a ICMJE journal may likely result in a similar increase in results reporting.

Integrating results reporting in the funding mechanism: For publicly funded studies by NIH, or other governmental funding bodies, the person time needed to fulfill the requirement of posting the results on ClinicalTrials.gov should be integrated and planned in the funding request. The posting of results will thus no longer be perceived as an additional burden by the research team but will be integrated into the research process. Another incentive would be to withhold a percentage of funding until publication of the study results on ClinicalTrials.gov. For example, this strategy is used by the Wellcome Trust to ensure that certain milestones are met by researchers.

Attachment: CTgov-Modernization-Response.pdf

Responders:

Perrine Janiaud, Postdoctoral Fellow at the Meta-Research Innovation Center at Stanford

Kim Boesen, PhD Student at the Nordic Cochrane Centre in Copenhagen, Denmark and visiting scholar at the Meta-Research Innovation Center at Stanford, Stanford University

Stelios Serghiou, PhD Student in the Epidemiology and Clinical Research at the Department of Health Research and Policy, Stanford University School of Medicine and at the Meta-Research Innovation Center at Stanford

Valentin Danchev, Postdoctoral Fellow at the Meta-Research Innovation Center at Stanford, Stanford University

Sarah Wieten, Clinical Ethics Fellow at the Stanford Center for Biomedical Ethics, and Postdoctoral Affiliate at the Meta-Research Innovation Center at Stanford

Carole Frederico, Postdoctoral Fellow at the Stanford Center for Biomedical Ethics and Postdoctoral Affiliate at the Meta-Research Innovation Center at Stanford

Janneke van 't Hooft, Postdoctoral Fellow at the Meta-Research Innovation Center at Stanford, Stanford University

The main challenge in the modernization of ClinicalTrials.gov is to find the balance between increasing the number of registered trials and increasing the quality and standardization of the information submitted. Presently, although it has yet to be quantified, the burden of trial registration and result submission may be a main hurdle to having all trials registered and timely reported. Investigators may consider it as duplication of the work already put in the writing of the protocol, study reports and published articles. If the aim of the modernization of ClinicalTrials.gov is to increase the rate of registered trials and in particular to improve the proportion of timely reported trials, we recommend allowing investigators to upload their own documents, such as protocols, results documents and similar, while keeping the required registration items to a minimum. This would likely improve trial registration and results reporting. From our experience, the current manual data entry of study results is time consuming and prone to errors. From a research perspective, the current format of study results does not make it easier to extract data for inclusion in systematic reviews and meta-analyses. We therefore recommend allowing investigators to upload their own tables and/or study reports. To ensure harmonization of the uploaded documents it would be very useful to define a minimum required standard of items to be included in the tables, similar to other reporting checklists, such as CONSORT. A common standard for clinical trial registry entries would be particularly useful if it was also adopted by other major clinical trial registries such as European Union Clinical trial Register (EUCTR), ISRCTN, and other registries. However, we, as researchers, believe that the lack of registration and of results reporting is likely more harmful than having non-standardized reporting.

The quality of the reporting and of the posting of results will benefit from the implementation of new technologies but they are conditioned that there is sufficient staff to oversee them. We can therefore only stress the importance for ClinicalTrials.gov to be adequately staffed.

Submission No.: 253

Date: 3/14/2020

Name: Simone Kraemer

Name of Organization: Bristol-Myers Squibb

Attachment: CTgov Modernization_Comments_final March 2020.docx

| | Topic | Comments |
|--|--|--|
| Website Functionality NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API); see https://clinicaltrials.gov/api/gui | 1.a. List specific examples of unsupported, new uses of the CT.gov website; include names and references for any systems that serve as good models for those uses. | <ul style="list-style-type: none"> Allow for upload of Plain Language Summaries in a way that allows lay public to find and access them easily; sponsors would have the opportunity to upload same PLS as will be uploaded to the European CTIS, as well as for studies not reported on the CTIS; this would allow the public to find PLS for trials in one central, public source. Consider enhancements that improve the user friendliness for public/patients: e.g., patient friendly view of the protocol information, including graphical icons and patient friendly language separate; on home page of CT.gov, list "recruiting" only as a radio button for patients; add "Illness" as an additional term for condition or disease and on advanced search page add "illness" as an additional term on advanced search page, under status; highlight or bold term "recruiting" and/or point an arrow and list "recruiting first; for "Expanded Access" (EA) options, include a brief definition of what EA is/means. Enable patients to find recruiting sites in their area through, e.g., interactive map of site locations, or the ability to find nearest trial-sites by zip-code/address Search feature for uploaded documents (e.g., protocols, SAPs, PLSs) Consider addition an option to support language options/translations of key information for public (e.g., ability to search for key words or eligibility criteria in Spanish) Add an option/ feature that allows to add reference (links) to other registries (same trial, local language) Consider adding a tooltip mouse over glossary of medical terms Consider making a mobile responsive website and/or mobile app available Consider option to identify biomarkers that are being evaluated, where explicit in study design/endpoints or exploratory. |
| Website Functionality NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API); see https://clinicaltrials.gov/api/gui | 1.b. Describe resources for possible linking from CT.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful. | <ul style="list-style-type: none"> Currently ClinicalTrials.Gov automatically includes publication that list the NCT number in the ClinicalTrials.Gov record in the section of publications. However, there are published abstracts and presentations that are not indexed in PubMed and are NOT included in the list of publications. Flexibility to link to a publication not indexed in PubMed as long as a DOI (Digital Object Identifier) and/or citation is provided would be ideal. Consider adding links to the ClinicalTrials.Gov site to patient advocacy groups based on conditions listed (i.e., MDS Foundation, PanCan, etc...). Consider adding an area on CTgov on which links to major databases for de-identified Individual Patient Data (IPD) are present, to improve awareness. |

| | | |
|---|---|--|
| <p>Website Functionality NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API); see https://clinicaltrials.gov/api/gui</p> | <p>1.c. Provide specific examples of how you currently use the CT.gov website, including existing features that work well and potential improvements.</p> | <p><u>What works well:</u></p> <ul style="list-style-type: none"> • In general, searching for a trial using the advanced search. • User can configure columns of trial data to view. <p>Searches performed include: by Study Number, NCT number, EudraCT number, search endpoints on how they are used in various studies; search by sponsor's; search for eligible studies for potential study participants. Suggest discontinuing use of MESH for condition since they are not known by patients, or allow for addition of more common terms in the conditions field.</p> <p><u>Improvement opportunities:</u></p> <ul style="list-style-type: none"> • Searching and reporting features are somewhat limited. Consider indexing studies similar to PubMed indexing. • Enhanced search functionality that accommodates trials with complex designs, e.g., for multiple indications • Add ability to search for trials that have indication for IPD sharing set to 'yes' • Allow for search/sorting by Study Completion Date • Under "study type", add "healthy volunteer" in the drop down menu as an option. • Add "brief description" under all of the targeted search fields. • Add the study start date in the public site report; allow public site report to include every data field inputted; add a Healthy Volunteer Column; add a pediatric column; include a column for "Final Results Release" Date <p><u>Specific Data Improvements (available for downloads):</u></p> <ul style="list-style-type: none"> • Bulk download of trials (CSV or XML) should include full study information, specifically LOCATION details that are only available for download of a single trial • Location # (or Site #) should be an additional new attribute. It should be received from Sponsor, and defaulted to a sequence if not received. Some sponsors use other fields like Degree to populate. This improves data consistency between sponsor CTMS systems and the submission to PRS/Ct.gov. • Reference data for Investigators and Institutions based on identifiers so that duplicates can be identified and eventually enable search based on investigators and institutions; consider option to capture IDs like Golden Number or NPI. |
| <p>Website Functionality NLM seeks broad input on the ClinicalTrials.gov website, including its application</p> | <p>1.d. Describe if your primary use of CT.gov relies on (1) a wide range of studies, such as different study types,</p> | <p>As a study sponsor, the use is primarily option number 1. The search helps us provide the potential participants with the options of various studies available to them.</p> |

| | | |
|--|---|--|
| <p>programming interface (API); see https://clinicaltrials.gov/api/gui</p> | <p>intervention types, or geographical locations of (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.</p> | |
| <p>Information Submission NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy of and timeliness of information submitted through the CT.gov Protocol Registration and Results System (PRS).</p> | <p>2.a. Identify steps in the CT.gov registration and results information submission process that would most benefit from improvements.</p> | <ul style="list-style-type: none"> • The existing validations for registrations could be refined, implementation of validations that check for consistency within result disclosure form would be helpful (i.e., error or warning indication prior to actual submission for PRS review) • Consider adding the ability to identify and manage a 'do-not-post-prior-to date' for registrations, to allow for submission and review of registrations well in time, while still allowing sponsor the ability to determine posting time, as long as regulation timelines will be met. • On the PRS registration/results, rename "Outcome Measures (OCM)" to Endpoints. • In the "eligibility criteria", improvement in the format of the special characters; improvement in the format of the inclusion/exclusion information. • Within the results module, please consider increasing the number of characters allowed in the Participant Flow "Comment Fields"; in the description fields within the baseline characteristic (BLC) module and if a BLC needs to include "categories", increase the number of characters. • Also, allow additional characters within the outcome measure descriptions, the time frame within the OCM section, and the AE section. • For initial registration, a more consistent review process would be helpful, comments received could have less variability. |
| <p>Information Submission NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy of and timeliness of information submitted through the CT.gov Protocol Registration and Results System (PRS).</p> | <p>2.b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.</p> | |

| | | |
|---|---|---|
| <p>Information Submission NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy of and timeliness of information submitted through the CT.gov Protocol Registration and Results System (PRS).</p> | <p>2.c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the CT.gov website.</p> | |
| <p>Information Submission NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy of and timeliness of information submitted through the CT.gov Protocol Registration and Results System (PRS).</p> | <p>2.d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.</p> | <ul style="list-style-type: none"> • Consider providing specific examples within the data element definition document (for example; an endpoint/outcome measure) including the title, description, timeframe; give specific examples of observational studies including Group, Cohort Description. Please include an examples of a cohort. |
| <p>Information Submission NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy of and timeliness of information submitted through the CT.gov Protocol Registration and Results System (PRS).</p> | <p>2.e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate and timely registration and result information submission.</p> | |
| <p>Data Standards NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for</p> | <p>3.a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.</p> | |

| | | |
|--|--|--|
| inclusion and exclusion criteria). | | |
| <p>Data Standards NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).</p> | <p>3.b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.</p> | |

Submission No.: 254

Date: 3/14/2020

Name: Nicolle Gatto, PhD

Name of Organization: Aetion

Attachment: NLM RFI ClinicalTrials.gov Modernization_Aetion Response.pdf

AETION

March 14, 2020

Rebecca J Williams, PharmD, MPH
Acting Director, ClinicalTrials.gov
National Library of Medicine, National Institutes of Health in Bethesda, MD

RE: NOT-LM-20-003 "ClinicalTrials.gov Modernization"

Dear Acting Director of ClinicalTrials.gov Williams,

As the National Library of Medicine (NLM) is looking into how best to operationalize its 2017–2027 Strategic Plan along the four “FAIR principles of making information Findable, Accessible, Interoperable, and Re-usable” pertaining to ClinicalTrials.gov (CT.gov), Aetion welcomes the opportunity to respond to the RFI on “ClinicalTrials.gov Modernization” and share the perspectives and priorities of observational researchers and regulatory scientists. We especially appreciate the timeliness of this RFI, which might uncover synergies with the FDA RFC on “Modernizing the Food and Drug Administration’s Data Strategy”, that Aetion has also responded to².

Please find our specific suggestions below.

- 1. Website Functionality. NLM seeks broad input on the [ClinicalTrials.gov website](#), including its [application programming interface \(API\)](#).**
 - a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**
 - i. *Integrate CT.gov entries with RxClass identifiers at the drug, drug class, and disease level for FDA approved prescription medications:* RxClass³ (also maintained by the NLM) is a medical/ clinical ontology navigator that links drug classes of several drug sources (including ATC, EPC, MoA, FDB, MeSH, MED-RT, SNOMED-CT and TC among others) to their RxNorm⁴ drug members (*i.e.*, prescription medications approved for human use in the US). Of all these hierarchical drug class and disease identifiers, CT.gov currently recommends, but does not require, the use of MeSH & SNOMED-CT vocabularies when registering the clinical trial ‘Condition or Disease’ of interest⁵. Accordingly, (1) CT.gov queries of ‘Condition or Disease’ can be inconsistent or not

¹ A Platform for Biomedical Discovery and Data-Powered Health: National Library of Medicine Strategic Plan 2017–2027 – Report of the NLM Board of Regents; https://www.nlm.nih.gov/pubs/plan/lrp17/NLM_StrategicReport2017_2027.pdf

² RFC on Modernizing the Food and Drug Administration’s Data Strategy (FDA-2019-N-5799); <https://www.federalregister.gov/documents/2020/01/08/2020-00071/modernizing-the-food-and-drug-administrations-data-strategy-public-meeting-request-for-comments>

³ RxClass: About; <https://mor.nlm.nih.gov/RxClass/>

⁴ RxNorm: What does the RxNorm model look like; <https://www.nlm.nih.gov/research/umls/rxnorm/overview.html>

⁵ ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies, 2019 Mar 7; <https://prsinfo.clinicaltrials.gov/definitions.html>

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comprehensive hindering thorough secondary research, and (2) queries at the pharmacologic class level are unsupported. Both of these functionalities can be enabled by a standard registration requirement to use RxClass identifiers, and/or by linking to RxClass from within CT.gov entries upon regulatory approval. This would be of immense value to trialists/ regulatory scientists/ observational researchers, who currently have to rely on independently curated ontologies, cross-walking tables, or other resource-intensive research workflows⁶; e.g., when studying pre-approval vs. post-approval drug-related safety events at the pharmacologic class level⁷. ENCePP/EU-PAS Register is a good reference, where the search functionality allows filtering for ‘Study drug> Substance Class (ATC Index)⁸.

b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

- i. *Tag completed trials where individual participant data (IPD) is made available besides aggregated clinical study results:* Vivli.org is an independent, non-profit organization that has developed a global data-sharing and analytics platform with a focus on sharing IPD from completed clinical trials, as well as Study Protocols, Statistical Analysis Plans, and Clinical Study Reports⁹. Each vivli.org entry maps to a respective NCT entry, but registrants are currently not required to reference this pairing in CT.gov. Whenever an NCT entry references such a pairing, this information is contained in the ‘More Information’ section as free-form text, which is not queryable under CT.gov’s ‘Advanced Search’ function¹⁰. Requiring registrants to enter this information when available, implementing an ‘IPD available’ tag, and creating a respective filter under ‘Advanced Search> Additional Criteria> Study Documents’ would facilitate locating available IPD, which would significantly expedite secondary research. For example, historical IPD from completed clinical trials may serve as external controls to directly augment clinical trials and/ or indirectly inform related clinical development programs¹¹. An advanced iteration of this suggestion is for CT.gov itself to host IPD under respective NCT entries wherever available.

⁶ Using the RxNorm System, NIH Collaboratory Living Textbook of Pragmatic Clinical Trials, 2015 Oct 26; <https://rethinkingclinicaltrials.org/resources/using-the-rxnorm-system/>

⁷ An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System, FDA, 2018 Apr 10; <https://www.fda.gov/files/about%20fda/published/Drug-Safety-Surveillance-and-the-FDA-Adverse-Event-Reporting-System-%28PDF--1.31MB%29.pdf>

⁸ ENCePP/EU-PAS Register; <http://www.encepp.eu/encepp/studySearch.htm>

⁹ About Vivli: Overview; <https://vivli.org/about/overview-2/>

¹⁰ NCT04102150; <https://clinicaltrials.gov/ct2/show/NCT04102150>

¹¹ Characterizing the Use of External Controls for Augmenting Randomized Control Arms and Confirming Benefit, FOCR, Nov 2019; https://www.focr.org/system/files_force/pdf/Panel-1_External_Control_Arms2019AM.pdf

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- ii. *Tag completed trials of approved drugs based on pivotal status:* As part of an overall FDA effort to make demographic data from pivotal clinical trials more available and transparent, the FDA has been releasing a Drug Trials Snapshot “for every New Molecular Entity approved since January 2015 within 30 days of the approval date”, which includes concise information about who participated in clinical trials that supported the approval of new drugs (a.k.a. pivotal trials)¹². While, in select instances, FDA Drug Trials Snapshots identify the respective NCT entries of pivotal trials (e.g., “The FDA approved ACCRUFER based on evidence from three clinical trials (Trial 1/NCT01252221, Trial 2/NCT01340872 and Trial 3/NCT02968368”)¹³, currently there is no cross-identification available on CT.gov. Requiring such tagging consistently by registrants upon approval and/or enabling cross-database linking would significantly expedite regulatory science and observational research¹⁴.

c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

 - i. *Comprehensively map registered standard study elements to ‘Advanced Search’ query filters:* For trialists/ regulatory scientists/ observational researchers, a highly valuable CT.gov search functionality is the ability to analyze query results in bulk via the ‘Download All Available Columns in CSV format’ option allowing data manipulation and additional filtering not available in the ‘Advanced Search’ interface otherwise, since not all registered study elements have respective ‘Advanced Search’ query filters. For example, one can currently query ‘Advanced Search> Study Type> Observational Studies’, but cannot query this subset based on different available observational models (Case-only/ case-control/ cohort/ other) or time perspectives (prospective/ retrospective/ cross-sectional/ other) even though these study element values are standardized. Re-designing ‘Advanced Search’ query filter options to comprehensively map to all registered study elements with standard values would improve the utility of CT.gov.

d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

¹² Whyte J, Woodcock J, Wang J. Review of the Drug Trials Snapshots Program of the US Food and Drug Administration: Women in Cardiovascular Drug Trials. *JAMA Intern Med.* 2017 May 1;177(5):724–727. doi: 10.1001/jamainternmed.2017.0033. PubMed PMID: 28288256; PubMed Central PMCID: PMC5470354.

¹³ Drug Trials Snapshots: ACCRUFER;

<https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-accruf>

¹⁴ Pepitone K, Kamat S. Challenges in identifying published registration studies for FDA-approved pharmaceuticals, 10th Annual Meeting of ISMPP, 2014 Apr 7-9;

https://www.ismpp.org/assets/docs/Education/AnnualMeeting/10thAM/Abstract_Posters/19_pepitone_10am_poster_final.pdf

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2. **Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).**
 - a. **Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**
 - b. **Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.**
 - c. **Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.**
 - d. **Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.**
 - e. **Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.**
 - i. *Tag trials or studies registered in response to postmarketing requirements (PMRs) or postmarketing commitments (PMCs) of approved medical products:* The FDA maintains a Postmarketing Requirements and Commitments Database, where each PMR/ PMC of an approved medical product is assigned a unique identifier¹⁵. Currently there is no streamlined way of identifying respective NCT entries of PMRs/ PMCs that requested clinical trials or studies, or whether a registered NCT was in response to a specific PMR/PMC. Requiring such tagging consistently by registrants and/or enabling cross-database linking would significantly facilitate monitoring how manufacturers are delivering on their post-approval regulatory requirements and commitments, and expedite regulatory science¹⁶. ENCePP/EU-PAS Register is a good reference, where the search functionality allows filtering for 'Study requested by a regulator'¹⁷.

¹⁵ FDA Postmarketing Requirements and Commitments; <https://www.accessdata.fda.gov/scripts/cder/pmc/>

¹⁶ Wallach JD, Luxkaranayagam AT, Dhruba SS, Miller JE, Ross JS. Postmarketing commitments for novel drugs and biologics approved by the US Food and Drug Administration: a cross-sectional analysis. BMC Med. 2019 Jun 17;17(1):117. doi: 10.1186/s12916-019-1344-3. PubMed PMID: 31203816; PubMed Central PMCID: PMC6572730

¹⁷ ENCePP/EU-PAS Register; <http://www.encepp.eu/encepp/studySearch.htm>

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3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).
 - a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.
 - i. *Enable 'embargo' function until planned public release date when registering retrospective cohort studies:* As previously discussed in detail at the 2019 ISPOR Breakout Session “To register or not register (the protocol). That is the question in observational and big data studies, economic models, and cost-effectiveness analysis”¹⁸, when registering retrospective cohort studies and detailed protocols, there is concern amongst registrants around protecting publication rights, since a publicly available retrospective database study protocol can easily be executed by other parties assuming underlying data availability. An agreed-upon ‘embargo date’, until when a registered retrospective database study protocol should not be publicly released, would help protect any IP rights of the registrants, and thus serve to incentivize consistent reporting and transparency. A similar regulation to learn from pertains to how the FDA is required under FDAAA § 916 to publish the Action Package of Approval of a New Molecular Entity (including the FDA’s multi-discipline review of the application) not later than 30 days after the approval date¹⁹. This provision defines a time window when the FDA and the applicant can consult and agree on, e.g., which parts of the multi-discipline review should be censored before public release to prevent potential IP infringement.

b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

- i. *Incentivize standardized registration of observational studies using real-world data, such as cohort studies leveraging real world data:* Under current legislation, observational research is not subject to the registration and results submission requirements described in FDAAA § 801 and codified in 42 CFR Part 11, since they do not meet the criteria for ‘applicable clinical trials’ as defined in PHSA Section 402(j)²⁰. While lack of such legislation unavoidably led to inconsistent and not comprehensive reporting of observational research on the part of registrants to date, multiple stakeholders “did not let perfect be the enemy of good” and have developed standards and best practices for internal alignment and wider adoption.

¹⁸ ISPOR, 2019 May; https://www.ispor.org/docs/default-source/ispor-2019/ispor-2019-032119.pdf?sfvrsn=d7c79a46_2

¹⁹ FDAAA § 916; <https://www.govinfo.gov/content/pkg/PLAW-110publ85/html/PLAW-110publ85.htm>

²⁰ Which trials must be registered on ClinicalTrials.gov? <https://clinicaltrials.gov/ct2/manage-recs/fdaaa>

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As recently discussed in detail at the ISPOR 2019 Summit²¹ (where NLM also presented its forward looking perspective), and then documented in the ensuing white paper co-authored by ISPOR, ISPE, NPC, and Duke Margolis Center for Health Policy; “standardized (observational) study registration – particularly for hypothesis evaluating treatment effectiveness (HETE) studies leveraging real-world data (RWD) sources – has been proposed as an important mechanism for improving transparency and trust into real-world evidence (RWE) generation since existing study registries such as ENCePP/EU-PAS and ClinicalTrials.gov are either oriented toward studies involving primary data collection such as (randomized) controlled trials, or they lack many of the features that should be incorporated in a study registry system designed to improve transparency and trust for studies performed on secondary, non-interventional data”²².

The summary table below from the white paper outlines the rationale, goals, and some potential solutions that pertain to CT.gov registration, as well as specific concerns that are unique to real-world evidence studies performed on secondary data. We encourage NLM to refer to the full publication for further reference.

| Rationale | Goals | Potential solutions |
|--|---|---|
| Decision makers see lack of transparency regarding how evidence is generated in hypothesis evaluating treatment studies using secondary data as a major barrier to using RWE for high-stakes decisions. | Researcher: First encourage transparency of study processes, including reporting on study design and implementation prior to study start, including posting of results when available Recipient: Over time – increase confidence of decisions makers in these studies, elevating the credibility All: Provide insight into the totality of evidence so reviewers can gauge reproducibility and replicability as part of the credible use of RWE | Post a study protocol reporting key study parameters (see below for further details) so that a decision-maker can be confident that they understand how the study arrived at its findings. Use structured reporting templates to improve readability, encourage completeness of reporting, and increase efficiency for researchers and reviewers by making it clear what to look for and where to look for it. |

²¹ Building Trust in Real-World Evidence: The Role of Study Registration, ISPOR, 2019 Oct; <https://www.ispor.org/conferences-education/conferences/past-conferences/isporsummit-2019>

²² Improving Transparency in Non-Interventional Research for Hypothesis Testing—WHY, WHAT, and HOW: Considerations from The Real-World Evidence Transparency Initiative, 2019 Sep 18; https://www.ispor.org/docs/default-source/strategic-initiatives/improving-transparency-in-non-interventional-research-for-hypothesis-testing_final.pdf

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| Specific concerns include | | |
|--|--|--|
| <p>Results-driven selection of study parameters</p> <p>Ease of rerunning analyses with altered study parameters</p> | <p>Provide clarity about the degree to which study parameter selection could have been driven by results.</p> <p>Revisions to the initial plan are often necessary when working with secondary data and need to be clearly reported.</p> | <p>Date-stamp the deposited study protocol with attestation regarding the nature of data prelooking (e.g. feasibility numbers to support power calculation vs outcome rates by exposure)</p> <p>Date-stamp all revisions to the protocol with rationale for changes</p> |
| <p>Selective reporting of favorable findings</p> <p>A non-randomly selected denominator of studies makes it difficult to conduct comprehensive evidence reviews</p> | <p>Avoid selective reporting of studies so that evidence aggregators and decision makers can conduct balanced evidence summaries.</p> | <p>Establish a comprehensive repository containing date-stamped protocols and results tables for all studies that are initiated to facilitate evaluation of publication bias</p> <p>Create incentives to register hypothesis-evaluating RWE studies like the requirements that journal editors have placed on RCTs, and EMA for PAS studies.</p> |

As exemplified by the NCT entry for the observational study “Replication of the CANVAS Diabetes Trial in Healthcare Claims (NCT03936010)²³ that is part of the RCT DUPLICATE initiative of the Brigham and Women’s Hospital, Harvard Medical School²⁴, core elements of standardized retrospective cohort study registrations should include:

- Full code and algorithm definitions
- Detailed and time-stamped study protocol; *i.e.*, eligible study population definition, eligible cohort entry dates, inclusion/exclusion criteria, primary and secondary outcome measures (including time frame of observation)
- Statistical Analysis Plan
- Results tables

²³ NCT03936010; <https://clinicaltrials.gov/ct2/show/NCT03936010>

²⁴ RCT DUPLICATE; <https://www.rctduplicate.org>

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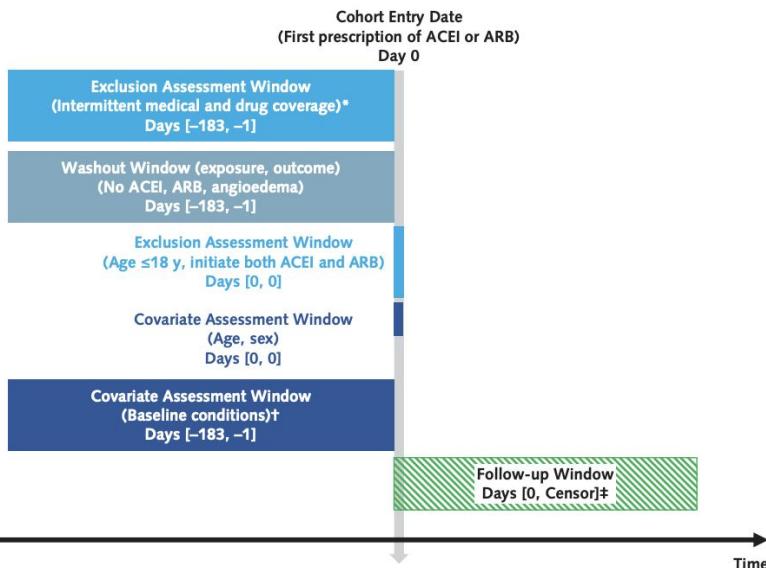
- ii. *Incentivize standardized graphical depiction of longitudinal study designs within observational study protocols:* Longitudinal health care database studies can yield robust real-world evidence (RWE), however lack of standard reporting and registration guidelines hamstring data review and study reproducibility – an area of active research among regulators, academia, and the industry²⁵. “To address this gap, we propose a simple framework of graphical representation that visualizes longitudinal database study design implementations in a comprehensive, unambiguous, and intuitive way; contains a level of detail that enables reproduction of key study design variables; and uses standardized structure and terminology to simplify review and communication to a broad audience of decision makers. Visualization of design details will make database studies more reproducible, quicker to review, and easier to communicate to a broad audience of decision makers”²⁶. The rest of this suggestion quotes, and includes an example graphical depiction from Schneeweiss *et al.*, 2019. We encourage NLM to refer to the full publication for further reference.

The proposed standardized longitudinal design diagrams (see below) “include bracketed numbers representing time intervals anchored on the Cohort Entry Date (day 0). Following conventional mathematical notation, we indicate open intervals (which do not include the endpoints) with parentheses and closed intervals (which do include the endpoints) with square brackets. First-order time anchors (defined in patient event time; specifying study entry or index date) are represented as columns indicating a date on the patient timeline, whereas second-order anchors (defined in patient event time, relative to first-order anchor) are represented as separate boxes. Boxes are placed in different rows so that overlap can be easily distinguished. The steps to create the analytic cohort from data tables in the longitudinal source are laid out sequentially from top to bottom in the design diagram. Attrition tables could be incorporated into these diagrams, with patient counts inserted in the relevant rows for exclusion criteria. We used standardized structure and terminology to provide examples of graphical representation for several designs that can be used in nonrandomized database studies, including cohort designs; designs that sample from cohorts (case– control, case– cohort, and 2-stage sampling); and self-controlled study designs.

²⁵ REPEAT Initiative; <https://www.repeatinitiative.org>

²⁶ Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, Dal Pan G, Goettsch W, Murk W, Wang SV. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398–406. Doi: 10.7326/M18-3079. Epub 2019 Mar 12. PubMed PMID: 30856654.

Figure 2. Exposure-based cohort entry where the cohort entry date is selected before application of exclusion criteria.



This work is licensed under CC BY, and the original versions can be found at www.repeatinitiative.org/projects.html. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

* Up to 45-d gaps in medical or pharmacy enrollment were allowed.

† Baseline conditions included allergic reactions, diabetes, heart failure, ischemic heart disease, and use of nonsteroidal anti-inflammatory drugs.

‡ Earliest of outcome of interest (angioedema), switching or withdrawing study drugs, death, disenrollment, 365 d of follow-up, or end of study period.

- iii. Align retrospective cohort study elements to be registered in CT.gov with the FDA RWE submission cover letter (once finalized): As already highlighted in Aetion's response to the FDA RFC on "Submitting Documents Using Real-World Data and Real-World Evidence to the Food and Drug Administration for Drugs and Biologics; Draft Guidance for Industry; Availability (FDA-2019-D-1263)"²⁷, we see value in capturing detailed real-world study elements to facilitate transparent, auditable, and reproducible real-world evidence generation.

The summary table below from Aetion's aforementioned response outlines the proposed fields and subfields in the RWE submission cover letter that are also applicable to CT.gov registration, as well as the rationale behind these proposals. Aligning retrospective cohort study elements registered in CT.gov with the final FDA RWE submission cover letter would not only enable streamlined transparency, but also reduce administrative burden for the registrants. We encourage NLM to refer to Aetion's full response for further reference.

²⁷ Submitting Documents Using Real-World Data and Real-World Evidence to the Food and Drug Administration for Drugs and Biologics; Draft Guidance for Industry; Availability (FDA-2019-D-1263); <https://www.regulations.gov/contentStreamer?documentId=FDA-2019-D-1263-0005&attachmentNumber=1&contentType=pdf>

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| Field | Subfield | Change from the FDA's sample presentation | Rationale |
|---|--|--|--|
| Study design | <input type="radio"/> Randomized (pragmatic) trial | Changed from 'Randomized clinical trial' | It specifies use of RWD and that randomization is in a real-world setting |
| | <input type="radio"/> Single arm trial with external control arm | Inserted 'with external control arm' | It specifies reliance on RWD; we recommend the use of 'external control arm' over 'synthetic control arm' because it is more generic and allows for a variety of approaches |
| | Non-randomized study | Changed from 'Observational study' | To more clearly distinguish between randomized and non-randomized designs, we recommend against the word 'observational', as even in RCTs, there is an observational phase (that is, patients are generally observed prospectively immediately following baseline randomization) |
| | <input type="radio"/> Cohort study | Inserted the types of non-randomized studies | Specificity is valuable |
| | <input type="radio"/> Case-control study | | |
| | <input type="radio"/> Cross-sectional study | | |
| | <input type="radio"/> Self-controlled case series | | |
| RWD source(s) used to generate RWE | <input type="checkbox"/> Data derived from electronic health records; specify data set(s): _____ | Inserted 'specify data set(s)' | We believe that distinguishing among specific types of RWD will be valuable for purposes of interpretation and planning |
| | <input type="checkbox"/> Medical claims and/or billing data; specify data set(s): _____ | | |
| | <input type="checkbox"/> Product, disease, and/or pregnancy registry data; specify data set(s): _____ | Inserted 'pregnancy' and 'specify data set(s)' | The FDA's recent efforts to provide clinically relevant human safety data to inform health care providers ² ; as above, specificity is valuable |
| | <input type="checkbox"/> Patient-generated data (e.g., wearable, patient-reported outcome); specify data set(s): _____ | Insertion | Consistent capture and analysis of use can inform a regulatory framework for emerging clinical data generation/use |
| | <input type="checkbox"/> Other data source; specify data set(s): _____ | Removed 'that can inform on health status' | Implied if the intent is to support regulatory decision-making |
| | <input type="radio"/> Yes; specify software platform and evidence of its scientific validation: _____ | Insertion | A validated RWE software platform can address many concerns about transparency, reproducibility, and scientific validity (see below) |
| | <input type="radio"/> No, specify software program used for one-off line programming: _____ | | |



Conclusion

Aetion thanks the NLM for the opportunity to respond to the RFI on “ClinicalTrials.gov Modernization” (NOT-LM-20-003). We appreciate the institute’s commitment to innovation and its interest in soliciting the perspectives and priorities of diverse ClinicalTrials.gov users, including observational researchers and regulatory scientists.

Aetion looks forward to our continued collaboration with the NLM to help inform the successful implementation of the institute’s strategic plans that pertain to modernizing ClinicalTrials.gov. Please contact Nicolle Gatto, PhD, at nicolle.gatto@aetion.com with any questions regarding these responses or other issues related to increasing the utility of ClinicalTrials.gov.

Sincerely,

Nicolle Gatto, PhD
SVP, Research, Aetion

Submission No.: 255

Date: 3/14/2020

Name: Anthony Keyes

Name of Organization: Johns Hopkins University

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Johns Hopkins University appreciates the opportunity to respond to this ClinicalTrials.gov Modernization Request for Information. We have had a dedicated ClinicalTrials.gov Program since June 2016, maintaining nearly 2,000 records, registering, updating and submitting results for hundreds of records annually. ClinicalTrials.gov remains an important part of our overall mission to ensure transparency of our clinical research studies, although there are challenges our investigators face with using the system. We applaud the efforts of the National Library of Medicine (NLM) to solicit information in support of improving the functionality of the system.

We recognize NLM leadership is faced with a choice to continue small scale remedies and enhancements to a 20-year old system or to invest the time and resources necessary to build a truly modern interface. The huge volume of clinical and non-clinical trials as well as the increasing complexity of trial design could not have been fully appreciated during the system's design and implementation. Either way, such an important system needs to have the required funding commitments. While we do not have the full details of the technical aspects of the website we recommend that leadership strongly consider a total rebuild. We also recommend that a separate website be built to handle the intervention studies focusing on biological mechanisms that are now considered clinical trials with the NIH definition. Researchers in this area will not be well served by the current website. The current website is not ready to support the multiple study designs that are common in early clinical research. Researchers in this area will require substantial administrative support to comply and users of the data will also not be able to easily interpret the study results.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

Our use of ClinicalTrials.gov encompasses a broad range of different studies.

- 2. Information Submission.** NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
 - 2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.**

Updated sections of a record should be seen when completed entries are approved by an administrator (instead of seeing them after clicking “Release”)

The actual updates or changes made should be highlighted (including changes in results section if applicable)

A personal pronoun detector should be built into study description section

An in text citation detector should be built into study description section

We suggest that outcome measures with multiple time points, although not assessing a change and are not pharmacokinetic measures, should be allowed to be listed as one outcome measure if results can be reported in different rows for the specified time points within the same listed measure. In a situation where 5 outcome measures are listed with each having 5 time points for assessment, this will have to be broken down into 25 outcomes which gives the study teams a lot of work to do and more work for the PRS team to review 25 outcomes rather than 5.

The review criteria specifies that “The Intervention Name(s) are specific, unless the study record clearly indicates that the study is not evaluating a specific intervention or exposure.” There are studies that specify that some drugs are being evaluated but for the purposes of the study the drug names will have to remain blinded. Such submissions are returned with comments even when the intervention description specifically states that drug names need to remain blinded. The studies however get registered after some discussion with the ClinicalTrials.gov PRS Team. We suggest that the review criteria be revised to make room for such submissions.

2b. Describe opportunities to better align the PRS submission process with your organization’s processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

For most universities it remains cost prohibitive to build IT systems that set up useful interfaces between clinical research systems like the eIRB or CTMS systems and ClinicalTrials.gov. The open API for ClinicalTrials.gov is useful. Future systems should encourage low cost ways ClinicalTrials.gov could take advantage of university clinical research applications.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

We have found that a substantial percentage of the delay in posting results is due to prolonged review by clinicaltrials.gov staff. We would propose a change to the process unless NLM can increase staff. Posting of results within 30 days—study teams should be given a chance to respond to comments within 5 days and if they don’t respond then study is posted with comments.

At the end of completion of the entry for a field within a section e.g. when one clicks on save after entering results information for an outcome measure, there could be a display of a checklist that asks about the outcome measure title, description, time frame, unit of measure listed, clarifying differences in overall numbers analyzed with analysis population description (e.g. overall numbers analyzed appear to be less than numbers reported to have started in participant flow, please revise or verify numbers and explain discrepancy in analysis population description) etc.

A prompt to enter information in pre-assignment details if enrollment and number started are not same.

System could have a way of detecting errors when time frames specify a certain duration but data reported in weeks, months, years etc. goes beyond that duration.

For arms and interventions section:

Once a drug is listed for intervention, a prompt that says “please include information on the dose of the drug”

For outcome measure section:

The information in the Help and Definitions links are very helpful. However people are not clicking on them and outcome measures continue to produce a lot of comments. In order to make this information more readily available, we suggest adding an example at the top of the page.

For the example, “Title” in the displayed example can be made “Title: What is being assessed?” with text box below it having an example of a title in the preferred format.

“Description” can be “Description: How will this be assessed or what tool will be used in the assessment?” with text box below it having an example of a description in the preferred format.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Useful

Planning report

PRS user guide

Spelling feature to detect potential spelling mistakes and unexpanded acronyms

Major comments list

Definitions and Help feature within sections

We are not sure what triggers the informational message in the Outcome Measure section which states, “If reporting a score on a scale, please include the unabridged scale site, the minimum and maximum values, and whether higher scores mean a better or worse outcome.” The message doesn’t always appear even when a scale is entered. We however think that is a very useful prompt that should be displayed for any outcome measure that mentions a questionnaire, scale, score or index.

Other materials that could be added

Common QC comment scenarios addressed by ClinicalTrials.gov staff could be compiled into best practices and posted to the website.

The Planning Report page should default to “All records” rather than “action expected”

Show or hide columns tab for Planning Report should have a “Select all” option rather than having to manually select all 38 options

The following should be added to the Planning Report; “Collaborators”, “Problems”, “Start Date Type” (i.e. “Anticipated” or “Actual”).

The Planning Report should have dates of each release and reset. These dates are currently available only within the “PRS Review History” of each record. When performing analysis on success rates, review cycles and time in review, these can only be gathered by opening each record and manually entering the dates onto a separate spreadsheet.

The PRS home page should have “FDAAA status” in the “Show/Hide Columns”

The PRS should flag studies that are late to report results per NIH like how studies are currently flagged as “Late Results per FDAAA”.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

ClinicalTrials.gov should develop ways to easily summarize organizational performance on registration and results reporting. It is the responsibility of the scientific community (funders, research leaders, research teams) to identify how to reward good performers and penalize poor performers. ClinicalTrials.gov could provide summary data on the performance of organizations by calculating the percentage of total number of public records needing attention. This percentage could be displayed in the top corner of any study that is registered by the institution. This could also be a separate link on the ClinicalTrials.gov homepage that says “Organizational Compliance”.

We recognize that the “Last Update Posted” date is displayed on records. This date could be changed to a font color of red and/or flagged with a statement that says this record has not been updated in the last 12 months if there’s been no update in 12 months or more.

Submission No.: 256

Date: 3/14/2020

Name: Fred Jorgensen

Name of Organization: Booz Allen Hamilton

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

While not officially designated a High-Impact Service Provider, the ClinicalTrials.gov operations team may wish to self-identify as one and still adopt the Customer Experience (CX) and Service Delivery guidelines set forth in OMB Circular A-11 Section 280. ClinicalTrials.gov faces a challenge to deliver streamlined customer service experiences that measure up with commercial entities like Airbnb and Zappos, who have set a new standard for user expectations because of their emphasis on the end-to-end customer journey. Patients, families, and researchers will carry these same expectations when they engage with the platform.

Proposed features that will support this goal of placing users at the center of strategy, business, design decisions, include:

* Formal Adoption of CX Methodologies: Through an understanding of user and stakeholder needs, the ClinicalTrials.gov operations team will be better able to design the service around a “North Star” and establish the key metrics that prove the platform’s contribution to the public and clinical research community.

Critical to the success of any CX initiative is the application of a cross-discipline CX methodology, involving Human-Centered Designers, Data Scientists, and Digital Analysts. This team will help identify opportunities for short-term service recovery and long-term systems improvement. Armed with data, along with a closeness to the customer journey (and those moments that matter most), cross-functional CX teams are then able to uncover emerging trends, remove barriers, and recommend new workflows that heighten satisfaction among ClinicalTrials.gov users.

* Strategic use of Machine Learning / Artificial Intelligence: Toward more effectively fostering connections between patients, families, and researchers, the website operations team may wish to consider a human analysis of existing taxonomy and metadata as well as potential taxonomy drawn from other medical fields related to clinics and their studies. Combining human expertise with the power of Machine Learning / Artificial Intelligence capabilities would help to create new connections that could increase clinic and patient/volunteer collaboration.

A tactical example of metadata that can help in this regard is the appending of national and international disease classification protocols. Specifically, standardized diagnosis codes such as the World Health Organization’s International Classification of Diseases—ICD-10 (and soon-to-be-released ICD-11), as well as, the Centers for Medicare and Medicaid Services’ ICD-10 Clinical Modification, can assist in the flagging of possible clinical trials at the time of diagnosis or treatment by a clinician.

* Practice of Sound Digital Communications Techniques: To ensure the highest possible credibility among the public and industry, it's imperative ClinicalTrials.gov employ fundamentally sound and proven digital communications techniques. The 21st Century Integrated Digital Experience Act (IDEA) and the U.S. Digital Services Playbook are watershed frameworks that set new conditions for how agencies deploy citizen experiences: understand what users need, make it simple, and communicate expectations step-by-step.

Regular usability studies, plain language analyses (terminology mapping), key performance indicators, and routine enhancements for greater accessibility (regardless of time, location, or device) are all paramount to ensuring such the highly-visible ClinicalTrials.gov is achieving the needs of its stakeholders—on both the researcher and patient fronts. Additionally, the consistent release of features and upgrades in an open and Agile fashion is the most effective route for ClinicalTrials.gov to keep pace not only with fluid user preferences, but also a dynamic regulatory environment.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Any modernization initiative for ClinicalTrials.gov means NLM and program stakeholders must chart a clear path for the platform and be willing to invent, experiment, and iterate regularly on the product—while balancing the competing priorities and disparate needs of researchers, patients, and families.

To do this, NLM may wish to apply the emerging operational method of lean product management. Lean product management is the formal organizational function that ensures ClinicalTrials.gov remains laser-focused on understanding user needs, as well as, developing goal-driven, outcome-focused features to validate those needs.

Working in small, cross-functional teams, quick prototypes are built, tested and then iterated upon - and ultimately proven out by their utilization and growth in key performance indicators. The incremental and iterative releases of these features (done in close collaboration with users), shortens the time to realize value vis-a-vis improved information quality and timely submission of results, as well as, other desired behaviors among ClinicalTrials.gov stakeholders.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

An ancillary, but key, benefit of the lean product management methodology is the imperative to assemble a cross-functional product team amid a collaborative team environment. To overcome the barriers preventing timely and complete submission of study results, the product manager of ClinicalTrials.gov should involve the contributions of Social Scientists and Behavioral Economists. These disciplinary experts can glean behavioral insights from the various stakeholder groups to inform design elements used on ClinicalTrials.gov - including choice architecture, message framing, and other default options that are likely to improve clinical trial registration and results outcomes.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

NLM may wish to consider the creation of flexible submission forms and APIs for data submission. Assuming the use of controlled vocabulary terms for ClinicalTrials.gov was adopted, the flexibility of these items would allow 1) a submitted term existing in the adopted standard vocabulary to be used as-is, 2) if a recognized synonym, the term could be mapped to use the preferred controlled vocabulary term, and 3) if neither, allow the use of the term - but flag it as non-standard, for possible curation downstream. This would allow substantial flexibility, but would still ensure that the information relevant to the submitter's study protocol and analysis plan is always captured.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

Industry encourages ClinicalTrials.gov to implement standards for unambiguous reporting of at least a core set of measures to support clinically and scientifically important secondary use of the ClinicalTrials.gov repository. Adopting more standardization will improve data quality and efficiency, enhance the ability to share data, streamline processes, and improve traceability.

Currently, ClinicalTrials.gov's field definitions are mostly adapted from 42 CFR Part 11, but only refer to the use, if available, of appropriate descriptors from descriptors from NLM's Medical Subject Headings (MeSH)-controlled vocabulary thesaurus or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus—and that only for Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study. For Adverse Event Reporting Description and for Adverse Event Term Additional Description in Trial Results, a field for the Source Vocabulary Name for Table Default in which to state from what controlled vocabulary the terms are derived (SNOMED CT and MedDRA 10.0 are given as examples).

Also of note, CDISC (<https://www.cdisc.org/>) has a Protocol Representation Model (PRM) that provides a standard for planning and designing a research protocol with focus on study characteristics such as study design, eligibility criteria, and requirements from the ClinicalTrials.gov, World Health Organization (WHO) registries, and EudraCT registries. There is an accompanying Controlled Terminology, and it is related to a Study/Trial Design Model in XML (SDM-XML) which will allow machine-readable interchangeable descriptions of the designs of their clinical studies, including treatment plans, eligibility and times and events. Considering the inclusion of ClinicalTrials.gov requirements, it would seem that adoption of this model, its XML version, and use of the Protocol Entities as Controlled Vocabulary would be advantageous for the standardization of clinical trial study information when used beyond ClinicalTrials.gov. Controlled Terminology is used throughout the clinical research process, from data collection through analysis and submission.

For results, examples for successful terminology standardization would include LOINC (<https://loinc.org/>) for lab results and the Observational Medical Outcomes Partnership (OMOP; <https://www.ohdsi.org/data-standardization/>) for medical records.

Perhaps even simpler for initial implementation would be to make use of the existing mappings in a CDISC standard released in 2016, Clinical Trial Registry (CTR) XML (<https://www.cdisc.org/standards/data-exchange/ctr-xml>). This standard makes it possible to build applications that generate submissions for multiple, global clinical trial registries; specifically the World Health Organization (WHO), European Medicines Agency (EMA) and to ClinicalTrials.gov from a single file, based upon the common elements mapped between the registries, and includes Study/Trial Design Model (SDM-XML) content.

The HL7 FHIR specification, an emerging standard for exchanging healthcare information electronically which also defines a set of operations for searching for health record data and currently being encouraged to be used widely at NIH by NLM, includes mappings for ClinicalTrials.gov in the ResearchStudy resource (<https://www.hl7.org/fhir/researchstudy.html>). It has additional terms beyond those mapped and might be advantageous to add some or all of them to ClinicalTrials.gov to enhance FHIR interoperability.

A last suggestion is that as precision medicine continues to grow, ClinicalTrials.gov consider adding fields designed to couple genomic and other -omic data with clinical parameters for reporting trial results, using Global Alliance for Genomics and Health (GA4GH; <https://www.ga4gh.org>) standards, where appropriate.

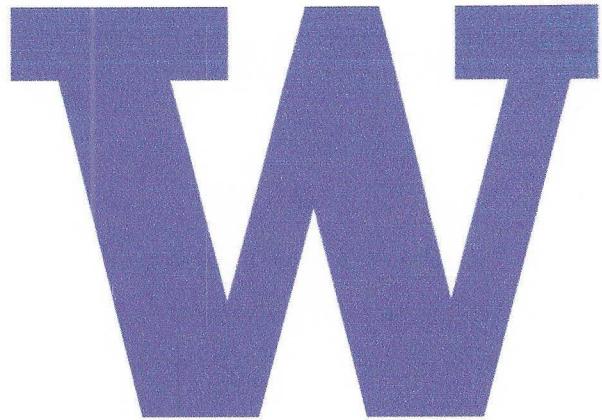
Submission No.: 257

Date: 3/14/2020

Name: Taylor Zimmermann

Name of Organization: University of Washington

Attachment: CTG_Response_RFI_UW_14MAR2020.pdf



ClinicalTrials.gov Information Team
National Library of Medicine
National Institutes of Health
8600 Rockville Pike
Bethesda, MC 20894

March 14, 2020

Submitted to: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Re: Request for Information (RFI): ClinicalTrials.gov Modernization, Notice Number: NOT-LM-20-00

The University of Washington appreciates the opportunity to respond to the ClinicalTrials.gov modernization RFI with regards to updating the ClinicalTrials.gov platform. The information gathered from the RFI comments will be extremely valuable toward reducing researcher registration and reporting burden into ClinicalTrials.gov, thus increasing transparency of accurate clinical trials information and data. It is the hope that the ClinicalTrials.gov modernization initiative will serve the need to meet the standards of a multitude of users and the current day digital era.

Through primary research input efforts from researchers and administrators at the University of Washington and Fred Hutchinson Cancer Research Center associated with the ClinicalTrials.gov registration and reporting process, a variety of themes were presented to be problematic with the current website as well as potential solutions raised. These ranged from ClinicalTrials.gov and PRS usability, the registration and results reporting process not being efficiently inclusive for all disciplines of applicable clinical trials, and burdensome data management and entry for researchers.

Considerations for the ClinicalTrials.gov modernization include the following:

- **Utilize improved current day digital technology for navigating the ClinicalTrials.gov website.** This may include video, audio, interactive assistants and enhanced data visualization tools associated with a project for the audience wanting to learn more about a study. Specific to the public, enhancing education in real-time while browsing through research studies would reduce burden and increase understanding efficiency. This can be done through defining scientific research vocabulary and explaining scientific research concepts directly from the study pages, via additional pop-up box options when the cursor hovers over certain words and sections, as well as helpful links attached to the study pages. Study transparency to the masses will only be as effective as the understanding of the study material is.
- **Create a community of practice peer-to-peer ClinicalTrials.gov forum.** This will be central to expanding the support hub, allowing users to communicate directly with one another and troubleshoot potential burdens that researchers may be having. By allowing users to

communicate directly with one another, a forum space will be vital for open ideas and user autonomy with navigating the ClinicalTrials.gov system. The forum platform may be divided into a "public" space and a "researcher" space, with sub-forums being created per discipline. This flow of feedback, questions and answers, intellectual property and guides will allow users to moderate their own inquiries, placing increased ownership onto the public realm, and to take some of the support burden off the ClinicalTrials.gov team. Additionally, this space can become a space for researchers to communicate and discuss progressive scientific research, potentially furthering conceptual understanding and fostering novel approaches to scientific research.

- **Create a results reporting compliance dashboard on the ClinicalTrials.gov website.** Due to the NIH/NLM being taxpayer funded, transparency of clinical trials is a vital resource that is owed to the public. In an effort to increase the compliance and transparency of clinical trials results (negative and positive results alike), a dashboard that may be accessed from the ClinicalTrials.gov website that provides data metrics on that compliance will give the public transparency on this important matter. It will allow the public to see registration and results reporting compliance measures from an industry level, institutional level and researcher level. Top compliance performers may be celebrated, perhaps highlighted within a quarterly ClinicalTrials.gov newsletter, and thus bringing reputational notoriety and promotion. The purpose to this initiative would be not to shame those not in compliance, yet to encourage compliance through positive reinforcement and creating further public trust by providing the complete transparency that they are owed.
- **Utilize API (Application Programming Interface) technology for synching project timepoint reminders for results reporting and quality control compliance, as well as for interfacing data between researcher and ClinicalTrials.gov.** By not only automating timeline window reminders to enforce compliance of the Final Rule using API technology with study projects, API synchronization has the ability to do so with project data essential to the results reporting process as well. This idea would require ClinicalTrials.gov PRS to communicate with a project data template, or data management interface, in order to update data and results in real time as changes to the project are made. This would reduce inconsistent data or "forgetfulness" of reporting changed data. Utilizing API technology in conjunction with data management templates will greatly assist researcher results reporting burden and aid consistency with study outcomes and data results reporting. Furthermore, the quality standards for study registration and results reporting need to remain consistent within the PRS.

- **Expand the PRS results reporting to interface with a variety of templates and external modules.** With an effort to decrease researcher data entry burden and redundancy, enabling data management templates and modules to interact with the PRS during registration and results reporting will bring greater fluidity to the process. API technology has the potential to bridge this interface communication. Another possibility is to allow a variety of different file formats for upload into the PRS, allowing templated file formats to interact and auto-populate fields within the PRS. For example, importing data from an electronic data capture system, a clinical trials management system or a data management template into the PRS with the intent of populating the necessary registration and results reporting fields is within the current day realm of technological capability, eliminating much of the manual burden. Syncing systems and programs to interface and communicate with one another, such as through API technology, will achieve this level of automation.
- **Establish a stakeholder working group for the development and implementation of the ClinicalTrials.gov modernization update.** This should be devised from representatives in a wide variety of disciplines, including academia, industry and non-research affiliated. Stakeholders from different fields of applicable clinical trials should serve this working group so that a voice may be heard going forward to include improvements for all kinds of different clinical trials going forward. The ClinicalTrials.gov modernization initiative should be viewed as a fluid process and indefinite going forward; thus, feedback and input to progress the evolution of the ClinicalTrials.gov platform may continue, even after the modernization changes associated with this RFI are implemented. A stakeholder working group, meeting quarterly or biannually, will have the ability to foster continuous improvement to the website and advance ideas for greater clinical trials compliance and transparency.
- **Improvement to clarity and specificity of status updates.** Providing more clear differentiation between overall recruitment status options would be incredibly helpful. Particularly, the definitions for the *Suspended* and *Active, not recruiting* statuses are vague enough that it's not always clear which option is the most appropriate status to use. Updating a trial status to *Active, not recruiting* prompts the user to update the total enrollment number and toggle from "anticipated" to "actual" (though it does not fully require that the enrollment be updated at that time). If the status definitions cannot be updated within PRS to be clearer, it would be helpful to users if the system (or resource materials) provided examples of the different scenarios where *Suspended* and/or *Active, not recruiting* would be appropriate. For example, should a study that is temporarily halting recruitment due to a gap in funding, but plans to enroll more participants, be updated to *Suspended* or *Active, not recruiting*?

By implementing measures that build public trust and interactivity, encourage compliance through positive reinforcement and support reducing researcher burden of all study types, as well as supporting public education and understanding, ClinicalTrials.gov will be taking another progressive step in its evolution to serve the public and scientific community.

Furthermore, please note that the University of Washington is in full support of the AAU/COGR response and the University of Michigan Medical School response. The University of Washington appreciates the opportunity to be involved with providing input on the ClinicalTrials.gov modernization efforts and applauds the NLM with putting RFI response considerations into action going forward. Please contact Taylor Zimmermann, Health Sciences Library Clinical Trials Specialist, at Tayzimm@uw.edu or (206) 616-1106 with any inquiries.

Sincerely,

A handwritten signature in black ink, appearing to read "Taylor Zimmermann".

Taylor Zimmermann
Clinical Trials Specialist
University of Washington

Submission No.: 258

Date: 3/14/2020

Name: Donna M. Ludwinski

Name of Organization: Solving Kids' Cancer

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

How I use the website:

As a research advocate for a pediatric cancer charity, I help families navigate the pediatric cancer clinical trial landscape, and stay abreast of open clinical trials for the more common pediatric tumors. We also fund clinical trials so I pay attention to unmet needs in specific tumors to identify areas for requests for proposals. As a reviewer for the NCI Pediatric CIRB I also check the site for competing trials and background for trials I review (either disease specific or agent specific).

Existing features that work well:

I appreciate the column selection and download feature to create spreadsheets that can be sorted.

Occasionally I use the map feature which is great for presentations on trials.

I often use the "History of Changes" to find out when a trial eligibility changed, or recruitment, etc.

Potential improvements:

Keywords for categories of intervention could be added for more broad characterization of the intervention. For example, cancer trials may be single agent or combinations of chemotherapy, radiation, targeted drug, or immunotherapy. (Immunotherapy can be further delineated as cellular therapy, antibodies, vaccines, etc.) This would make surveying the current landscape easier to assess for options, and identify gaps for certain tumor types.

For example, I did a search in Aug 2019 for recruiting and not yet recruiting interventional trials for neuroblastoma. To describe the current landscape I had to manually go through 104 clinical trials and categorize them based on the intervention. The "By Topic" tab returns unhelpful information -- see "Drug Interventions by Category"

https://clinicaltrials.gov/ct2/results/browse?recrs=ab&cond=Neuroblastoma&brwse=intr_cat

And the Drug Interventions (alphabetical) returns 193 drugs which doesn't easily lend itself to broad categories such as chemotherapy, radiation, targeted drug, immunotherapy.

See document accompanying this record.

If you wanted to know how many clinical trials have been completed or are open for pediatric cancers it is very difficult because the keywords are all over the place (pediatric, child, cancer, etc) with choosing

the age group filter -- a search like this returns many trials that are adult trials for breast, prostate, colon, lung cancer that have no age limit in the eligibility.

Lastly if there was a way to see accrual real-time that would be incredibly useful. (ie Is the phase I trial accruing at the 3rd dose level? etc)

Attachment: NB open trials Aug 10 2019.pdf

| | Immunotherapy -- targeted drug -- chemo combo -- radiotherapy -- frontline -- other | Interventions | Phase | Enrollment | Start Date | URL |
|----------------------|---|--|--------------|-------------------|---|---|
| Immunotherapy | Naxitamab for High-Risk Neuroblastoma Patients With Primary Refractory Disease or Incomplete Response to Salvage Treatment in Bone and/or Bone Marrow | Biological: GM-CSF + Naxitamab Drug: Ch14.18 Biological: NK Cells Drug: Lenalidomide Drug: Arsenic Trioxide Drug: Conventional induction chemotherapy Genetic: GINAKIT Cells Drug: Cyclophosphamide Drug: Fludarabine Biological: DNA vaccine Biological: Salmonella oral vaccine Drug: Lenalidomide | 2 | 37 | April 3, 2018 | https://ClinicalTrials.gov/show/NCT03363373 |
| Immunotherapy | Immunotherapy of Relapsed Refractory Neuroblastoma With Expanded NK Cells | 1 | 24 | November 16, 2018 | https://ClinicalTrials.gov/show/NCT02573896 | |
| chemo combo | Clinical Trial of Arsenic Trioxide Combined Chemotherapy in the Treatment of Stage 4 Neuroblastoma | 2 | 70 | January 1, 2019 | https://ClinicalTrials.gov/show/NCT03503864 | |
| Immunotherapy | GD2 Specific CAR and Interleukin-15 Expressing Autologous NKT Cells to Treat Children With Neuroblastoma | 1 | 24 | January 18, 2018 | https://ClinicalTrials.gov/show/NCT03294954 | |
| Immunotherapy | DNA Vaccination Against Neuroblastoma Metronomic Treatment in Children and Adolescents With Recurrent or Progressive High Risk Neuroblastoma | 1 | 12 | January 9, 2019 | https://ClinicalTrials.gov/show/NCT04049864 | |
| chemo combo | Phase II Study of Monoclonal Antibody ch14.18/CHO Continuous Infusion in Patients With Primary Refractory or Relapsed Neuroblastoma | Drug: metronomic therapy | 2 | 26 | October 2016 | https://ClinicalTrials.gov/show/NCT02641314 |
| Immunotherapy | Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma | Drug: dinutuximab beta | 2 | 40 | March 27, 2015 | https://ClinicalTrials.gov/show/NCT02743429 |
| Immunotherapy | Neuroblastoma Maintenance Therapy Trial | Biological: GD2-CART01 Drug: Difluoromethylornithine (DFMO) Drug: Vincristine Drug: Aldesleukin Drug: ch14.18/CHO Drug: Carboplatin Drug: Etoposide Drug: Cisplatin Drug: Cyclophosphamide Drug: Doxorubicin Drug: G-CSF Drug: Busulfan Drug: Melphalan | 1/2 | 42 | December 2017 | https://ClinicalTrials.gov/show/NCT03373097 |
| DFMO | High Risk Neuroblastoma Study 1.8 of SIOP-Europe (SIOPEN) | 2 | 258 | February 2016 | https://ClinicalTrials.gov/show/NCT02679144 | |
| frontline | Immunotherapy of Neuroblastoma Patients Using a Combination of Anti-GD2 and NK Cells | Biological: Anti-GD2 in combination with NK cells Drug: Thiotepa Drug: Cyclophosphamide Drug: Melphalan Drug: Etoposide Drug: Carboplatin Biological: Autologous Stem Cell Infusion Biological: Granulocyte colony stimulating factor | 3 | 3300 | February 2002 | https://ClinicalTrials.gov/show/NCT01704716 |
| Immunotherapy | Myeloablative Consolidation Therapy and Tandem Autologous Stem Cell Rescue in Patients With High-Risk Neuroblastoma | 1/2 | 5 | October 3, 2017 | https://ClinicalTrials.gov/show/NCT03242603 | |
| frontline | | | 2 | 12 | June 2016 | https://ClinicalTrials.gov/show/NCT02605421 |

| | | | | | |
|----------------------|---|--|-----|-----|--|
| | | Drug: cyclophosphamide Drug: topotecan Biological: hu14. 18K322A Procedure: peripheral blood stem cell harvest Procedure: surgical resection Drug: cisplatin Drug: etoposide Drug: doxorubicin Drug: vincristine Drug: busulfan Drug: melphalan Biological: peripheral blood stem cell transplantation Biological: natural killer cell infusion Radiation: radiation therapy Biological: GM- CSF Biological: G- CSF Drug: mesna Drug: levetiracetam Biological: interleukin-2 Drug: Isotretinoin Device: CliniMACS | 2 | 210 | July 5, 2013 https://ClinicalTrials.gov/show/NCT01857934 |
| frontline | Therapy for Children With Advanced Stage Neuroblastoma -- NB2012 | Drug: 67Cu-SARTATE α Peptide Receptor Radionuclide Therapy Administered to Pediatric Patients With High-Risk Neuroblastoma | 1/2 | 34 | November 2019 https://ClinicalTrials.gov/show/NCT04023331 |
| radiotherapy | Study of CAR T-Cells Targeting the GD2 With IL-15+iCaspace9 for Relapsed/Refractory Neuroblastoma | Biological: iC9.GD2.CAR. IL-15 T-cells Drug: Cyclophosphamide Drug: Fludarabine | 1 | 18 | July 15, 2019 https://ClinicalTrials.gov/show/NCT03721068 |
| Immunotherapy | Safety Evaluation of Peptide Receptor Radionuclide Therapy (PRRT) With 177Lu-DOTA0-Tyr3-Octreotate for Refractory or Recurrent Metastatic Neuroblastoma Expressing Somatostatin Receptors | Drug: PRRT with 177Lu-DOTATATE | 1 | 22 | January 2020 https://ClinicalTrials.gov/show/NCT03966651 |
| radiotherapy | Racotumomab in Patients With High-risk Neuroblastoma | Drug: Racotumomab | 2 | 39 | November 2016 https://ClinicalTrials.gov/show/NCT02998983 |
| Immunotherapy | Study Evaluating the Efficacy and Safety With CAR-T for Relapsed or Refractory Neuroblastoma in Children | Biological: GD2-targeted CAR-T cells Biological: Ex vivo Expanded and Activated Haploididentical Donor NK Cells Biological: Hu14.18-IL2 | N/A | 22 | September 2016 https://ClinicalTrials.gov/show/NCT02919046 |
| Immunotherapy | Treatment of Relapsed or Refractory Neuroblastoma With Expanded Haploididentical NK Cells and Hu14.18-IL2 | Biological: Hu14.18-IL2 | 1 | 6 | March 12, 2018 https://ClinicalTrials.gov/show/NCT03209869 |
| Immunotherapy | A Study of the Effect of Hu3F8/GM-CSF Immunotherapy Plus Isotretinoin in Patients in First Remission of High-Risk Neuroblastoma | Biological: Hu3F8 Drug: GM-CSF Drug: Isotretinoin Genetic: C7R-GD2.CART cells Drug: Cyclophosphamide Drug: Fludarabine | 2 | 59 | January 23, 2017 https://ClinicalTrials.gov/show/NCT03033303 |
| Immunotherapy | C7R-GD2.CART Cells for Patients With Relapsed or Refractory Neuroblastoma (GAIL-N) | | 1 | 34 | April 23, 2019 https://ClinicalTrials.gov/show/NCT03635632 |

| | | | | | |
|----------------------|--|--|--------|-----------|---|
| Immunotherapy | Phase I Study of Investigational Medicinal Products in Children With Relapsed/Refractory Neuroblastoma | Drug: Nivolumab Drug: Ch14.18/CHO Drug: Ceritinib Drug: dasatinib Drug: sorafenib Drug: vorinostat Drug: DFMO Radiation: External beam radiotherapy Radiation: proton beam RT Drug: Cisplatin Drug: Doxorubicin Drug: Etoposide Drug: Cyclophosphamide Drug: Ifosfamide Drug: Carboplatin Procedure: Tandem HDCT/auto-SCT Radiation: Radiotherapy Drug: Interleukin-2 Drug: Isotretinoin Radiation: MIBG Drug: Bevacizumab Drug: Temozolomide Drug: Irinotecan Drug: Topotecan | 1 2 | 36 500 | May 24, 2018 https://ClinicalTrials.gov/show/NCT02914405 |
| frontline | Pediatric Precision Laboratory Advanced Neuroblastoma Therapy | | | | September 2015 https://ClinicalTrials.gov/show/NCT02559778 |
| radiotherapy | Local Control With Reduced-dose Radiotherapy for High-Risk Neuroblastoma | | | 50 | September 2014 https://ClinicalTrials.gov/show/NCT02245997 |
| frontline | Response-based Treatment of High-risk Neuroblastoma | | 2 | 54 | April 2015 https://ClinicalTrials.gov/show/NCT02771743 |
| chemo combo | Activity Study of Bevacizumab With Temozolomide ± Irinotecan for Neuroblastoma in Children | | 2 | 160 | July 2013 https://ClinicalTrials.gov/show/NCT02308527 |
| radiotherapy | Standardized Protocol of Surgery and Radiation for Patients With Brain Metastases in Relapsed Neuroblastoma | Radiation: Cerebral Spinal (CS) radiation Radiation: Focal radiotherapy (SRS) | 20 | | September 1, 2019 https://ClinicalTrials.gov/show/NCT03406273 |
| frontline | European Low and Intermediate Risk Neuroblastoma Protocol | Drug: chemotherapy Drug: Irinotecan Drug: temozolomide Biological: Hu3F8 Drug: GM-CSF Drug: Carboplatin Biological: Autologous stem cell infusion Biological: Granulocyte colony stimulating factor Radiation: Radiation therapy Drug: Isotretinoin (13-cis-retinoic acid) Drug: Melphalan Drug: Etoposide Biological: IL-2 Biological: GD2Bi-aATC Biological: GM-CSF Other: laboratory evaluations of immune responses | 3 1 | 685 36 | December 2011 https://ClinicalTrials.gov/show/NCT01728155 |
| Immunotherapy | Study of Chemoimmunotherapy for High-Risk Neuroblastoma | | | | June 12, 2017 https://ClinicalTrials.gov/show/NCT03189706 |
| frontline | High Dose Chemotherapy and Autologous Transplant for Neuroblastoma | | 20 | | March 28, 2012 https://ClinicalTrials.gov/show/NCT01526603 |
| Immunotherapy | Activated T Cells Armed With GD2 Bispecific Antibody in Children and Young Adults With Neuroblastoma and Osteosarcoma | | 1/2 | 40 | November 2014 https://ClinicalTrials.gov/show/NCT02173093 |
| Immunotherapy | Combination Therapy of Antibody Hu3F8 With Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF) in Patients With Relapsed/Refractory High-Risk Neuroblastoma | Biological: Hu3F8 With GM-CSF | 1/2 | 224 | December 2012 https://ClinicalTrials.gov/show/NCT01757626 |

| | | | | | |
|---------------------------------|--|--|-----|---|---|
| chemo combo | Multimodal Molecular Targeted Therapy to Treat Relapsed or Refractory High-risk Neuroblastoma | Drug: Dasatinib Drug: Rapamycin Drug: Irinotecan Drug: Temozolamide Biological: adjuvant OPT-821 in a vaccine containing two antigens (GD2L and GD3L) covalently linked to KLH Biological: oral β -glucan | 2 | 114 | August 2013 https://ClinicalTrials.gov/show/NCT01467986 |
| Immunotherapy | Bivalent Vaccine With Escalating Doses of the Immunological Adjuvant OPT-821, in Combination With Oral β -glucan for High-Risk Neuroblastoma | | 1/2 | 260 | May 2009 https://ClinicalTrials.gov/show/NCT00911560 |
| scan | A Phase I/II Study of [124I]mIBG PET/CT in Neuroblastoma | Drug: [124I]meta-Iodobenzylguanidine Radiation: 131I-mIBG Drug: Topotecan Drug: Thiotepa Procedure: Autologous stem cell transplant Procedure: Biopsy Drug: Ceritinib Drug: Trametinib Drug: HDM201 Genetic: Next Generation Sequencing Procedure: Tumor Scans Radiation: X-ray Procedure: Bone marrow Tests Other: Physical Exam Other: Eye Exam Other: Labs Other: Pregnancy Test Behavioral: Interviews Other: ECG Other: Echocardiogram Drug: Ribociclib | 1/2 | 33 | February 2014 https://ClinicalTrials.gov/show/NCT02043899 |
| chemo combo radiotherapy | Trial Evaluating and Comparing Two Intensification Treatment Strategies for Metastatic Neuroblastoma Patients With a Poor Response to Induction Chemotherapy | Drug: Topotecan Drug: Thiotepa Procedure: Autologous stem cell transplant Procedure: Biopsy Drug: Ceritinib Drug: Trametinib Drug: HDM201 Genetic: Next Generation Sequencing Procedure: Tumor Scans Radiation: X-ray Procedure: Bone marrow Tests Other: Physical Exam Other: Eye Exam Other: Labs Other: Pregnancy Test Behavioral: Interviews Other: ECG Other: Echocardiogram Drug: Ribociclib | 2 | 150 | October 1, 2018 https://ClinicalTrials.gov/show/NCT03165292 |
| targeted drug | Next Generation Personalized Neuroblastoma Therapy | Drug: Ribociclib | 1 | 105 | July 2016 https://ClinicalTrials.gov/show/NCT02780128 |
| Immunotherapy | Anti-GD2 4th Generation CART Cells Targeting Refractory and/or Recurrent Neuroblastoma | Biological: Anti-GD2 CART | 2 | 30 | May 1, 2016 https://ClinicalTrials.gov/show/NCT02765243 |
| radiotherapy | Phase II Study of Proton Radiation Therapy for Neuroblastoma | Radiation: Proton Beam Radiation Therapy Drug: 131 I-Metaiodobenzylguanidine (131I-MIBG) Drug: Potassium iodide solution Drug: G-CSF Procedure: hematopoietic stem cell infusion | | 30 | June 2014 https://ClinicalTrials.gov/show/NCT02112617 |
| radiotherapy | MIBG for Refractory Neuroblastoma and Pheochromocytoma | Drug: cyclophosphamide Biologic: al: NK cells Biological: hu3F8 Drug: rIL-2 | 100 | December 2013 https://ClinicalTrials.gov/show/NCT01850888 | |
| Immunotherapy | Humanized Anti-GD2 Antibody Hu3F8 and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma | Drug: hu3F8 Drug: rIL-2 | 1 | 36 | January 2016 https://ClinicalTrials.gov/show/NCT02650648 |
| scans | 18F-Fluorodopamine PET Studies of Neuroblastoma and Pheochromocytoma | Drug: 18F-DA | 1 | 20 | March 14, 2019 https://ClinicalTrials.gov/show/NCT03541720 |

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|-----------------------------------|--|---|---|-----|---|
| | | Biological: Patient Derived CD171 specific CAR T cells expressing EGFRt (2nd generation T cells) Biological: Patient Derived CD171 specific CAR T cells expressing EGFRt (3rd generation T cells) Biological: Patient Derived CD171 specific CAR T cells expressing EGFRt (long spacer 2nd generation T cells) Drug: 131 I-Metaiodobenzylguanidine | 1 | 40 | November 25, 2014 https://ClinicalTrials.gov/show/NCT02311621 |
| Immunotherapy | Engineered Neuroblastoma Cellular Immunotherapy (ENCIT)-01 | | | | |
| radiotherapy | 131I-Metaiodobenzylguanidine (131I-MIBG) Therapy for Relapsed/Refractory Neuroblastoma | Drug: Potassium Iodide Drug: G-csf Radiation: 131I-MIBG Drug: Ch14.18 Monoclonal Antibody | 1 | 25 | May 28, 2019 https://ClinicalTrials.gov/show/NCT03649438 |
| radiotherapy immunotherapy | MIBG With Dinutuximab | Drug: Lorlatinib Drug: Cyclophosphamide Drug: Topotecan Genetic: GD2 T cells Biological: VZV vaccine Drug: Fludarabine Drug: Cyclophosphamide | 1 | 24 | September 5, 2018 https://ClinicalTrials.gov/show/NCT03332667 |
| targeted drug | Study of Lorlatinib (PF-06463922) | | 1 | 40 | September 1, 2017 https://ClinicalTrials.gov/show/NCT03107988 |
| Immunotherapy | iC9-GD2-CAR-VZV-CTLs/Refractory or Metastatic GD2-positive Sarcoma and Neuroblastoma Iodine I 131 Metaiodobenzylguanidine in Treating Patients With Recurrent, Progressive, or Refractory Neuroblastoma or Malignant Pheochromocytoma or Paraganglioma | Drug: Cyclophosphamide | 1 | 26 | April 2014 https://ClinicalTrials.gov/show/NCT01953900 |
| radiotherapy | | Radiation: iobenguane I 131 | 2 | 150 | May 2006 https://ClinicalTrials.gov/show/NCT00107289 |
| Immunotherapy chemo combo | Irinotecan Hydrochloride, Temozolomide, and Dinutuximab With or Without Eflornithine in Treating Patients With Relapsed or Refractory Neuroblastoma | Biological: Dinutuximab Drug: Eflornithine Drug: Irinotecan Biological: Sargramostim Drug: Temozolomide Radiation: 131I-MIBG Drug: Vincristine Drug: Irinotecan Drug: Vorinostat | 2 | 95 | May 28, 2019 https://ClinicalTrials.gov/show/NCT03794349 |
| radiotherapy chemo combo | 131I-MIBG Alone VS. 131I-MIBG With Vincristine and Irinotecan VS 131I-MIBG With Vorinostat | | 2 | 105 | July 2014 https://ClinicalTrials.gov/show/NCT02035137 |

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|----------------------|--|---|-----|-------------|---|
| | | Diagnostic Test: Initial fecal microbiome Diagnostic Test: Initial fecal volatile organic compounds Diagnostic Test: Initial breath volatile organic compounds Diagnostic Test: Microbiome under chemotherapy Diagnostic Test: Fecal volatile organic compounds under chemotherapy Diagnostic Test: Breath volatile organic compounds under chemotherapy Diagnostic Test: Final microbiome Diagnostic Test: Final fecal volatile organic compounds Diagnostic Test: Final breath volatile organic compounds | | | |
| microbiome | Investigating the Microbiome and Volatileome of Children With Neuroblastoma | | 20 | May 7, 2018 | https://ClinicalTrials.gov/show/NCT03545542 |
| radiotherapy | A Study of Therapeutic Iobenguane (131-I) for Relapsed, High-Risk Neuroblastoma Subjects | Drug: 131I-MIBG Genetic: 1RG-CART/m^2 (Dose Level 1) Genetic: 1RG-CART/m^2 (Dose Level 2) Genetic: 1RG-CART/m^2 (Dose Level 3) Genetic: 1RG-CART/m^2 (Dose Level 4) Drug: Cyclophosphamide Drug: Fludarabine Genetic: 1RG-CART/m^2 (Dose Level 5) | 2 | 65 | March 2019 https://ClinicalTrials.gov/show/NCT03561259 |
| Immunotherapy | A Cancer Research UK Trial of Anti-GD2 T-cells (1RG-CART) Study of the Safety and Efficacy of Humanized 3F8 Bispecific Antibody (Hu3F8-BsAb) in Patients With Relapsed/Refractory Neuroblastoma, Osteosarcoma and Other Solid Tumor Cancers | Biological: Humanized 3F8 Bispecific Antibody Other: Blood draw Drug: Carboplatin Other: Clinical Observation Drug: Cyclophosphamide Drug: Doxorubicin Hydrochloride Drug: Etoposide Other: Laboratory Biomarker Analysis Other: Pharmacological Study | 1 | 27 | February 2016 https://ClinicalTrials.gov/show/NCT02761915 |
| Immunotherapy | | | 1/2 | 30 | February 22, 2019 https://ClinicalTrials.gov/show/NCT03860207 |
| frontline | Response and Biology-Based Risk Factor-Guided Therapy in Treating Younger Patients With Non-high Risk Neuroblastoma | | 3 | 621 | July 28, 2014 https://ClinicalTrials.gov/show/NCT02176967 |

| | | | | | |
|---|--|--|-----|---|---|
| | | Biological: Aldesleukin Procedure: Autologous Hematopoietic Stem Cell Transplantation Drug: Carboplatin Drug: Cisplatin Drug: Cyclophosphamide Drug: Dexrazoxane Biological: Dinutuximab Drug: Doxorubicin Drug: Etoposide Radiation: External Beam Radiation Therapy Drug: Isotretinoin Drug: Melphalan Biological: Sargramostim Drug: Thiotepa Drug: Topotecan Drug: Vincristine | 2 | 45 | January 14, 2019 https://ClinicalTrials.gov/show/NCT03786783 |
| frontline Immunotherapy radiotherapy | Dinutuximab, Sargramostim, and Combination Chemotherapy in Treating Patients With Newly Diagnosed High-Risk Neuroblastoma Undergoing Stem Cell Transplant 131I-omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases | Biological: 131I-omburtamab Biological: Aldesleukin Procedure: Autologous Hematopoietic Stem Cell Transplantation Drug: Busulfan Drug: Carboplatin Drug: Cisplatin Drug: Crizotinib Drug: Cyclophosphamide Drug: Dexrazoxane Hydrochloride Biological: Dinutuximab Drug: Doxorubicin Hydrochloride Drug: Etoposide Phosphate Radiation: External Beam Radiation Therapy Radiation: Iobenguane I-131 Drug: Isotretinoin Other: Laboratory Biomarker Analysis Drug: Melphalan Other: Pharmacological Study Biological: Sargramostim Procedure: Therapeutic Conventional Surgery Drug: Thiotepa Drug: Topotecan Hydrochloride Drug: Vincristine Sulfate | 2/3 | 32 | December 11, 2018 https://ClinicalTrials.gov/show/NCT03275402 |
| frontline | Iobenguane I-131 or Crizotinib and Standard Therapy in Treating Younger Patients With Newly-Diagnosed High-Risk Neuroblastoma or Ganglioneuroblastoma | 3 | 813 | May 9, 2018 https://ClinicalTrials.gov/show/NCT03126916 | |

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|---------------|--|--|-----|-----|--|
| OMS | Opsoclonus Myoclonus Syndrome/Dancing Eye Syndrome (OMS/DES) in Children With and Without Neuroblastoma (NBpos and NBneg) Opsoclonus Myoclonus Syndrome/Dancing Eye Syndrome (OMS/DES) in Children With and Without Neuroblastoma (NBpos and NBneg) | Drug: Dexamethasone acetate Drug: dexamethasone and cyclophosphamide Drug: dexamethasone and rituximab Drug: Trametinib plus hydroxychloroquine in patients with NRAS Melanoma (Dose 1) Drug: Trametinib plus hydroxychloroquine in patients with NRAS Melanoma (Dose 2) Drug: Trametinib plus hydroxychloroquine in patients with NRAS Melanoma (Dose 3) Drug: 177Lu-DOTA-tyr3-OCTREOTATE Procedure: Peptide Receptor Radiotherapy (PRRT) | 3 | 100 | April 18, 2013 https://ClinicalTrials.gov/show/NCT01868269 |
| targeted drug | MEK and Autophagy Inhibition in Metastatic/Locally Advanced, Unresectable Neuroblastoma RAS (NRAS) Melanoma | | 29 | | September 30, 2019 https://ClinicalTrials.gov/show/NCT03979651 |
| radiotherapy | Dosimetry Guided PRRT With 177Lu-DOTATATE in Children | | 1/2 | 74 | July 1, 2019 https://ClinicalTrials.gov/show/NCT03923257 |
| radiotherapy | Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer | Radiation: iodine I 131 monoclonal antibody 8H9 Procedure: Computed Tomography Drug: Gallium Ga 68-DOTATATE Procedure: Positron Emission Tomography | 1 | 120 | July 2004 https://ClinicalTrials.gov/show/NCT00089245 |
| scan | An Investigational Scan (68Ga-DOTATATE PET/CT) in Diagnosing Pediatric Metastatic Neuroendocrine Tumors | | 1 | 20 | August 15, 2019 https://ClinicalTrials.gov/show/NCT04040088 |
| targeted drug | Trial of CUDC-907 in Children and Young Adults With Relapsed or Refractory Solid Tumors, CNS Tumors, or Lymphoma | Drug: CUDC-907 Radiation: 90Y-DOTA tyro3-Octreotide Diagnostic Test: 68Ga-DOTATOC PET Positron Emission Tomography (PET) whole body scan Drug: Amino Acids | 1 | 44 | October 2016 https://ClinicalTrials.gov/show/NCT02909777 |
| radiotherapy | Dosimetry-Guided, Peptide Receptor Radiotherapy (PRRT) With 90Y-DOTA- tyro3-Octreotide (90Y-DOTATOC) | Drug: Idasanutlin Drug: Venetoclax Drug: Cyclophosphamide Drug: Topotecan Drug: Fludarabine Drug: Cytarabine Drug: Intrathecal Chemotherapy | 2 | 46 | September 29, 2017 https://ClinicalTrials.gov/show/NCT03273712 |
| targeted drug | A Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Preliminary Activity of Idasanutlin in Combination With Either Chemotherapy or Venetoclax in the Treatment of Pediatric and Young Adult Participants With Relapsed/Refractory Acute Leukemias or Solid Tumors | Drug: 68Ga-DOTATOC PET/CT | 1/2 | 220 | October 26, 2019 https://ClinicalTrials.gov/show/NCT04029688 |
| scan | Impact of Ga-68 DOTATOC PET-CT Imaging in Management of Neuroendocrine Tumors | | 2 | 200 | September 2015 https://ClinicalTrials.gov/show/NCT02441062 |
| radiotherapy | Dose Escalation Study of CLR 131 in Children and Adolescents With Relapsed or Refractory Malignant Tumors Including But Not Limited to Neuroblastoma, Rhabdomyosarcoma, Ewings Sarcoma, and Osteosarcoma | Drug: CLR 131 | 1 | 30 | April 30, 2019 https://ClinicalTrials.gov/show/NCT03478462 |

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|---------------|--|---|-----|-----|--|
| targeted drug | Study Of Palbociclib Combined With Chemotherapy In Pediatric Patients With Recurrent/Refractory Solid Tumors | Drug: Palbociclib Drug: Temozolomide Drug: Irinotecan Drug: MM-398 (Irinotecan Sucrosofate Liposome Injection) plus cyclophosphamide Procedure: Allogeneic HCT Drug: Donor NK Cell Infusion | 1 | 100 | May 24, 2019 https://ClinicalTrials.gov/show/NCT03709680 |
| chemo combo | Phase 1 Study of MM-398 Plus Cyclophosphamide in Pediatric Solid Tumors | Drug: 18F-DOPA | 1 | 30 | December 2013 https://ClinicalTrials.gov/show/NCT02013336 |
| haplo | Phase 2 STIR Trial: Haploididential Transplant and Donor Natural Killer Cells for Solid Tumors | Procedure: Allogeneic HCT Drug: Donor NK Cell Infusion | 2 | 20 | March 2014 https://ClinicalTrials.gov/show/NCT02100891 |
| scan | 18F-DOPA PET Imaging: an Evaluation of Biodistribution and Safety | Drug: 18F-DOPA | 3 | 400 | June 29, 2017 https://ClinicalTrials.gov/show/NCT03042416 |
| chemo combo | A Study of the Safety and Pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients With Relapsed or Refractory Malignancies | Drug: chemotherapy Drug: venetoclax | 1 | 165 | November 8, 2017 https://ClinicalTrials.gov/show/NCT03236857 |
| targeted drug | Selumetinib Sulfate in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With Activating MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial) | Other: Laboratory Biomarker Analysis Drug: Selumetinib Drug: Selumetinib Sulfate | 2 | 49 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03213691 |
| targeted drug | Ensartinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With ALK or ROS1 Genomic Alterations (A Pediatric MATCH Treatment Trial) | Drug: Ensartinib Other: Laboratory Biomarker Analysis Other: Pharmacological Study | 2 | 98 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03213652 |
| targeted drug | Ulixertinib in Treating Patients With Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial) | Other: Pharmacokinetic Study Drug: Ulixertinib | 2 | 49 | October 1, 2018 https://ClinicalTrials.gov/show/NCT03698994 |
| targeted drug | Palbociclib in Treating Patients With Relapsed or Refractory Rb Positive Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With Activating Alterations in Cell Cycle Genes (A Pediatric MATCH Treatment Trial) | Other: Laboratory Biomarker Analysis Drug: Palbociclib Other: Pharmacological Study | 2 | 49 | June 22, 2018 https://ClinicalTrials.gov/show/NCT03526250 |
| targeted drug | Vemurafenib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With BRAF V600 Mutations (A Pediatric MATCH Treatment Trial) | Other: Laboratory Biomarker Analysis Drug: Vemurafenib | 2 | 49 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03220035 |
| targeted drug | Adavosertib and Irinotecan Hydrochloride in Treating Younger Patients With Relapsed or Refractory Solid Tumors | Drug: Adavosertib Drug: Irinotecan Drug: Irinotecan Hydrochloride Other: Laboratory Biomarker Analysis Other: Pharmacological Study | 1/2 | 154 | March 27, 2014 https://ClinicalTrials.gov/show/NCT02095132 |
| targeted drug | Olaparib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With Defects in DNA Damage Repair Genes (A Pediatric MATCH Treatment Trial) | Drug: Olaparib | 2 | 49 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03233204 |
| targeted drug | Larotrectinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With NTRK Fusions (A Pediatric MATCH Treatment Trial) | Drug: Larotrectinib Drug: Larotrectinib Sulfate | 2 | 49 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03213704 |

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|----------------------|--|--|-----|--|--|
| | PI3K/mTOR Inhibitor LY3023414 in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With TSC or PI3K/MTOR Mutations (A Pediatric MATCH Treatment Trial) | Other: Laboratory Biomarker Analysis Other: Pharmacological Study Drug: PI3K/mTOR Inhibitor LY3023414 | 2 | 144 | July 31, 2017 https://ClinicalTrials.gov/show/NCT03213678 |
| targeted drug | Erdafitinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With FGFR Mutations (A Pediatric MATCH Treatment Trial) | Drug: Erdafitinib Other: Laboratory Biomarker Analysis Other: Pharmacological Study Procedure: Biopsy Procedure: Biospecimen Collection Drug: Ensartinib Drug: Erdafitinib Other: Laboratory Biomarker Analysis Drug: Larotrectinib Procedure: Mutation Carrier Screening Drug: Olaparib Drug: Palbociclib Other: Pharmacological Study Drug: PI3K/mTOR Inhibitor LY3023414 Drug: Selumetinib Sulfate Drug: Tazemetostat Drug: Ulixertinib Drug: Vemurafenib | 2 | 49 | November 6, 2017 https://ClinicalTrials.gov/show/NCT03210714 |
| targeted drug | Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial) | Other: Laboratory Biomarker Analysis Drug: Tazemetostat | 2 | 1000 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03155620 |
| screen | Tazemetostat in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With EZH2, SMARCB1, or SMARCA4 Gene Mutations (A Pediatric MATCH Treatment Trial) | Device: Magnetic resonance high intensity focused ultrasound Drug: Lyso-thermosensitive liposomal doxorubicin Biological: Ipilimumab Other: Laboratory Biomarker Analysis Biological: Nivolumab Other: Pharmacological Study Device: Magnetic Resonance High Intensity Focused Ultrasound | 2 | 49 | July 24, 2017 https://ClinicalTrials.gov/show/NCT03213665 |
| targeted drug | A Phase I Study of Lyso-thermosensitive Liposomal Doxorubicin and MR-HIFU for Pediatric Refractory Solid Tumors | 1 | 34 | October 2016 https://ClinicalTrials.gov/show/NCT02536183 | |
| chemo + HIFU | Nivolumab With or Without Ipilimumab in Treating Younger Patients With Recurrent or Refractory Solid Tumors or Sarcomas | Biological: Ipilimumab Other: Pharmacological Study Device: Magnetic Resonance High Intensity Focused Ultrasound | 1/2 | 352 | February 2, 2015 https://ClinicalTrials.gov/show/NCT02304458 |
| Immunotherapy | MR-guided High Intensity Focused Ultrasound (HIFU) on Pediatric Solid Tumors | 1 | 14 | April 2014 https://ClinicalTrials.gov/show/NCT02076906 | |
| HIFU radiotherapy | MIBG Therapy for Patients With MIBG Avid Tumors | Drug: MIBG Drug: Cyclophosphamide Drug: Fludarabine Biological: Anti-NY ESO-1 TCR-transduced T cells | 2 | 65 | March 2014 https://ClinicalTrials.gov/show/NCT02378428 |
| Immunotherapy | T Cell Receptor-transduced T Cells Targeting NY-ESO-1 for Treatment of Patients With NY-ESO-1-Expressing Malignancies | 1 | 36 | April 2015 https://ClinicalTrials.gov/show/NCT02457650 | |

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|---------------|--|--|-----|--|--|
| | | Biological: second generation 4-1BB TM EGFR806-EGFRt Biological: second generation 4-1BB TM EGFR806-EGFRt and a second generation 4-1BB TM CD19-Her2tG | 1 | 36 | October 2019 https://ClinicalTrials.gov/show/NCT03618381 |
| Immunotherapy | EGFR806 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults | Drug: Simvastatin Drug: Cyclophosphamide Drug: Topotecan Drug: Myeloid growth factor Procedure: TCR ⁺ /CD19+ depleted Haploididential HSCT Drug: Zoledronate | 1 | 36 | February 2015 https://ClinicalTrials.gov/show/NCT02390843 |
| chemo combo | Simvastatin With Topotecan and Cyclophosphamide in Relapsed and/or Refractory Pediatric Solid and CNS Tumors | Alpha/Beta CD19+ Depleted Haploididental Transplantation + Zometa for Pediatric Hematologic Malignancy's and Solid Tumors | 1 | 22 | January 2016 https://ClinicalTrials.gov/show/NCT02508038 |
| haplo scan | Methionine PET/CT Studies In Patients With Cancer | Drug: Methionine Drug: Gemcitabine Drug: ribociclib Drug: sonidegib Drug: trametinib Biological: filgrastim | 2 | 650 | July 20, 2009 https://ClinicalTrials.gov/show/NCT00840047 |
| targeted drug | SJDAWN: St. Jude Children's Research Hospital Phase 1 Study Evaluating Molecularly-Driven Doublet Therapies for Children and Young Adults With Recurrent Brain Tumors | 1 | 108 | March 5, 2018 https://ClinicalTrials.gov/show/NCT03434262 | |
| targeted drug | Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors | Drug: Abemaciclib | 1 | 60 | February 2016 https://ClinicalTrials.gov/show/NCT02644460 |
| targeted drug | Safety, Tolerability, Efficacy and Pharmacokinetics of Copanlisib in Pediatric Patients | Drug: BAY806946 | 1/2 | 130 | April 30, 2018 https://ClinicalTrials.gov/show/NCT03458728 |
| targeted drug | Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations | Drug: Trametinib Drug: Dabrafenib | 1 | 142 | January 15, 2015 https://ClinicalTrials.gov/show/NCT02124772 |
| Follow-up | Pediatric Long-Term Follow-up and Rollover Study | Drug: dabrafenib Drug: trametinib | 4 | 250 | August 27, 2019 https://ClinicalTrials.gov/show/NCT03975829 |
| targeted drug | Study of the Bromodomain (BRD) and Extra-Terminal Domain (BET) Inhibitor BMS-986158 in Pediatric Cancer | Drug: BMS-986158 | 1 | 34 | June 30, 2019 https://ClinicalTrials.gov/show/NCT03936465 |
| chemo combo | Nab-paclitaxel in Combination With Gemcitabine for Pediatric Relapsed and Refractory Solid Tumors | Drug: Gemcitabine Drug: Nab-paclitaxel Drug: Cyclophosphamide Drug: Fludarabine Radiation: low dose total body irradiation Drug: Melphalan Drug: Tacrolimus Drug: Sirolimus Drug: Celecoxib Drug: Etoposide Drug: Cyclophosphamide | 1 | 24 | August 27, 2018 https://ClinicalTrials.gov/show/NCT03507491 |
| haplo | Reduced Intensity Haploidential BMT for High Risk Solid Tumors | 2 | 60 | March 27, 2013 https://ClinicalTrials.gov/show/NCT01804634 | |
| chemo combo | Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors | 2 | 60 | June 2015 https://ClinicalTrials.gov/show/NCT02574728 | |
| targeted drug | Study Of Entrectinib (Rxdx-101) in Children and Adolescents With No Curative First-Line Treatment Option, Recurrent or Refractory Solid Tumors And Primary Cns Tumors, With or Without Trk, Ros1, or Alk Fusions | Drug: Entrectinib | 1 | 65 | May 3, 2016 https://ClinicalTrials.gov/show/NCT02650401 |

Submission No.: 259

Date: 3/14/2020

Name: Deborah Collyar

Name of Organization: Patient Advocates In Research (PAIR)

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
- 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

Thank you for the opportunity to help ClinicalTrials.gov improve the way it collects and disseminates information about the many types of studies that are done in people.

Website functionality depends on whom you consider your ultimate audience. No matter who uses the site, it is ultimately there to improve people's health, as at least approximately 51% of your users indicate.

A main goal includes getting more people on clinical trials to answer questions about what happens in people (outcomes = results). Different audiences enter the system, so ClinicalTrials.gov needs to help them get to details in ways that make sense to each audience.

Here are some specific steps that would be useful if applied for ClinicalTrials.gov:

Throughout ClinicalTrials.gov

- Apply healthy literacy and plain language to all content.
 - o Encourage and/or require sponsors/submitters to take plain language training so they can provide study information that is easy to understand.
 - o Require sponsors/submitters to create a plain language statement about each clinical trial, including a simple title.
 - o The use of graphics, images, and video capabilities that explain clinical trials in general, and for individual studies, would help bring clinical trial data into the modern era. Also, providing a field for links to supporting materials would be useful.
 - ï,§ This includes graphic representation of data, not just numbers on a screen in tabular or text formats. For example, AEs and SAEs and how to interpret these data.
 - ï,§ Short instructional videos about how to conduct searches on CT.gov would help.
 - ï,§ A field for video summaries would also be helpful, explaining each trial, key findings and what they mean for people. Some sponsors currently create these.
 - o A list of adverse events (AE) and serious adverse events (SAE), with an explanation if the intervention is suspected as the cause or not, is also needed.

- Use a modern web platform/framework that allows 2020 standard features and has the flexibility to change to newer standards once they are established. For instance:
 - o Create submission formats based on web presentation, not paper formats. For instance, there should be no character limits in fields.
 - o Create a dashboard for each study that allows details to appear in hover boxes, drop down menus, and/or linked pages (both in text and in defined fields), and linked to detail pages for more information that also includes resources.
 - o Create fields for feedback and questions. This helps create a process for continual improvements, in addition to occasional surveys.
- Create a prominent place on each page to display the acronym/glossary list. All terms should have hover accessibility each time these terms and acronyms are used. The acronym/glossary list should also be printable, and possibly available at the side of each web page, so it is easy to refer back while reading the content in a study record.
 - o Lead with patient-oriented information. For instance, why is “study record manager” information listed first, before the term is displayed? This gives the wrong impression.
 - o There should also be an option to view the Glossary list by letter or categories to make it easier and more useful. Topics could include categories like body, therapy, type of studies, biomarker, etc.
 - o Add terms from other useful glossaries, such as the NCI Thesaurus and others by disease/NIH institution or FDA, OHRP and other HHS offices.
- Allow sponsors to enter plain language patient study calendars that help explain what is expected in each study in more graphic presentations. At a minimum, this should include number of study visits to research site, visits to more local/affiliated sites, labs, etc.
- Make sure that the same information is being requested and reported between original submissions and results reporting. Often, these numbers are different, with no explanation as to why. This can lead to mistrust of the process.
- Add information and interactive tools (e.g. graphics, video, audio) on how to use ClinicalTrials.gov information. This would include how to use results when considering them as health decisions are made.
- Provide feedback loops, focus groups, and user tests as improvements are made to ClinicalTrial.gov to ensure that changes work as intended for each audience.

Home page:

The home page should allow the user to select who they are, so the site can be tailored to their purpose and language, such as “patients/public” and “researchers”

- One possible model for separating patient and researcher tracks is the NCI website's “Cancer Types” section. Each type includes prominent links to a “Patient Version” and a “Health Professional Version.” See links in Section 1.b.

- There is too much wasted space in the banner, and the content in it can be combined with the left paragraph in a much simpler, plain language approach.

- Include hover capability or the “i” for all terms/acronyms through the website. For example, there is no definition for “NCT” on the home page or in advanced searches currently.

Find a study/search capability:

There should be only one search mechanism that uses the advanced search capabilities, which also need to be expanded and improved. The first search is basically worthless and gives people the impression that they must be ‘simple’ once they have to go to the advanced search function. People are used to scrolling, so that isn’t an issue anymore.

- Search functions need clear instructions on the same page (video could help) and could be reformatted to a Q&A format to use words that people are familiar with.

- o Alert users to whether search terms are combined using “and” or “or” operators or provide an option for either.

- Allow multiple searches to be saved by user.

- “œStatus” heading should show all choices that are listed in advanced search, similar to the way “country” currently works. The responsible party (sponsor/investigator) should update with a 2-factor authentication process that eliminates the need for your internal review.

- o There should also be a penalty for not updating location and contacts within a short specified time period for each study. This is woefully outdated for many patients who need this information.

- o Lead researchers and study sponsors should list complete contact information.

- Tailored searches that represent audience factors are needed instead of limiting to only study parameters.

- o For example, allow further categorization for diagnostics, prevention, therapy, diet, behavior, etc. within categories such as Intervention.

- o Improve filtering to include modern criteria for treatment, such as (but not limited to):

- i,§ Biomarker/mutation (include multiple options), then organ site (optional)

- i,§ Exclusion/inclusion criteria (patients with ongoing conditions know this)

- i,§ Site(s) of condition or metastasis

- i,§ Comorbidities

- Set and use structured data standards/requirements for how medical conditions/diseases are entered by sponsors. This will require multi-stakeholder discussions that include patients, but it is very important for searches and for comparison of studies, data sharing, etc. ClinicalTrials.gov should be a part of any existing initiatives, such as CDISC, mCODE and others.

- o Create a cross-reference to all possible conditions (no matter what term is entered in search) so that all relevant conditions are listed. This could also be a field for someone to check if they want all related terms to appear in their search.
- o Allow someone to search for “all metastatic cancers” or other multi-disease state conditions. Often, this is the only way to find some trials that do not have a specific diagnosis listed.
- o All fields should include indexed terms in drop down menus, such as the “country” field now works. Many of these fields should also allow multiple choices, including “country”.
 - Include a check field to receive update notifications on individual studies, including any status changes. The notification should also list the update type (e.g. eligibility, recruitment status). This is especially important for chronic conditions and metastatic diseases.
- o Include an alert for new or existing studies that match the user’s saved search criteria. Multiple searches should be able to be saved.
 - Add a ‘compare to’ button that allows unlimited comparisons between different studies. Allow at least 3 to be shown on the same screen (again, a dashboard would be useful, or allow users to choose the information they want to display) and allow multiple levels of comparison. This is similar to the way rental car company websites work.
- o Allow people to select their own data fields to compare multiple studies. For example, a specific side effect (adverse event), number of research visits, and brain metastasis.
- o The user could then save comparisons that would be re-listed together as they narrow down their choices. This is why multiple searches are also important.
 - ClinicalTrials.gov should also post public (plain language) trial result summaries that are created by sponsors, just as the EMA plans to do.
- o Until this is done (recognizing that the FDA is woefully behind in regulating this need), ClinicalTrials.gov should create a field that can house a link (or multiple links) that are provided and updated by the responsible party.
- o Create a field for Plain-language Summaries at the top of the Results tab/display (external link). A disclaimer will help people understand that it is an external link and that NLM is not responsible for content.
- o A parallel field should also be added on the Study Details tab for an external link to a plain language overview of the trial itself. This could link to, for example, the patient brochure content that is often created (and reviewed by IRBs/ethics) as recruitment material at the launch of a study, providing more complete information that introduces a trial to prospective participants.
 - Provide easy access to all clinical trial reports and summaries at the top of study pages (currently at the end, if available at all).
- o Require sponsors to upload their informed consent forms and make them easy to find.
- Create clear information that is searchable for Master Protocols. These need to be cross-referenced to all terms used for these types of trials, such as platform trials, umbrella, basket, and

others so related keywords can be included in searches if users so choose. These trials are valuable to patients, and flexible rules and search capabilities are needed.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

One possible model for separating patient and researcher tracks is the NCI website's "Cancer Types" section. Here, each cancer type includes prominent links to a "Patient Version" and a "Health Professional Version." This clear demarcation between audiences helps patients find understandable information without getting lost in content written by and for researchers. See:
<https://www.cancer.gov/types/bladder> and <https://www.cancer.gov/types/bladder/hp>.

An interactive map, such as this COVID-19 map from Hopkins, could show where clinical trials are located, both in aggregate, and by the search criteria entered in by each user:
<https://qz.com/1814380/interactive-map-from-johns-hopkins-shows-coronavirus-in-real-time/>

Google flights is also a good example of how searches could be done:

https://www.google.com/flights?hl=en#flt=/m/0d6lp..2020-03-24*/.m/0d6lp.2020-03-28;c:USD;e:1;ls:1w;sd:0;t:h

Companies like Clara Health provide a good example of study information on a modern web platform, and use of plain language: <https://www.clarahealth.com/>.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Originally, ClinicalTrials.gov was proposed, and established, to create a better way for patients to find clinical trials, based on experiences by cancer patients (and others) who used the NCI Physician Data Query (PDQ) system. It quickly morphed, however, into a clinical trial data repository for sponsors and other "professional" audiences, not patients. The current system only works for very savvy internet users, or people who are familiar with science.

These comments primarily address the original intent: helping patients and their caregivers find relevant clinical trials when they need them. My comments have been informed by decades of clinical trial experience and several other groups, including: Patient Advocates In Research (PAIR), the DIA Clinical Trial Disclosure (CTD) Community, Health Literacy Media (HLM), the Metastatic Breast Cancer Alliance (MBCA), and bctrials.org.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I rarely go to ClinicalTrials.gov due to limited usability, but when I do, it is for both purposes listed above.

Being able to limit eligibility criteria helps eliminate huge lists of irrelevant studies for people. The more detailed we allow people to get, the better their searches become. They also need to be able to save multiple searches.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

- Strongly encourage sponsors, and support them with streamlined submission formats, to use plain language in their current study descriptions and brief summary statements that are posted on ClinicalTrials.gov.
- Include a designation for adaptive design: checkbox, tag, and other forms that can be used to sort/filter and search.

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

- Greater enforcement of the requirement to submit clinical studies.
- Lower burden in the submission process, especially for non-profit/non-governmental/non-academic organizations in the U.S.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

- Create clear instructions and corresponding data standards and fields to register and reports adaptive trials and master protocols as either one study or as sub-studies, at the sponsor's discretion depending on what is needed to preserve trial integrity.
 - o Identify adaptive clinical trials as a separate 'type' with sub-types (similar to EAP)– that are searchable on the ClinicalTrials.gov website.
 - o Example subtypes to master protocol: platform, umbrella, basket, etc.
 - o Link all sub-studies together for easier viewing of the whole trial, similar to EAP.
 - o Indicate if registration as single or multiple studies

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

- Create penalty for sponsors who do not post studies or results in ClinicalTrials.gov. For instance, create a checkbox so that FDA knows whether or not applicable clinical trials are posted. If not, then no approval will be given until that is done as required.

- o It is important to flag individual studies from a sponsor that may have acquired those studies in mergers or acquisitions, so that explanation can be given as results are prepared.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

- Require sites to update their recruitment status more frequently. This information is really important to patients.
 - o Enable alerts for when Phase I/II trials (or other expanded cohorts) transition. Users (patients) should also be able to flag this for notification when study status changes.
 - o Enable alerts when new arms open/close in master protocols as well.
- Create specific formats that better incorporate clinical trials in the social science paradigm.
 - o Allow flexibility to reflect the diverse range of clinical trials and methodologies that go beyond biological studies.
 - Create minimum machine-readable data standards to allow for greater comparability between studies.
 - Include information/resources how to incorporate evidence into decision-making processes.
 - o Shared decision-making evidence exists and can be linked to in resource areas.
 - o Set data standards and describe how they can be used to incorporate evidence into the decision-making process.
 - Make the fields for “additional MeSH terms” and “sponsor-added keywords” available through the API.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Monitored organizations and initiatives focused on improving the clinical trial process, and update ClinicalTrials.gov accordingly. Examples of these groups include:

- FDA guidances, such as adaptive trials (statistical design) & master protocols
- o Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry
- o Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; Draft Guidance for Industry
- EMA– Adaptive Trials guidance

- o CTFG Recommendations of initiation and conduct of complex clinical trials
- CTTI—www.ctti-clinicaltrials.org
- Review more mature coding systems such as SnoMed, Loinc, and RxNorm.

Submission No.: 260

Date: 3/14/2020

Name: Rachael Fones

Name of Organization: IQVIA

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The following unsupported or under-supported, yet achievable, uses for ClinicalTrials.gov (CT.gov), are grouped by three main purposes for which we use the website (described more completely in answer 1c):

For the purpose of informing new trial design and planning:

Analyses we do to understand the landscape, inform inclusion/exclusion (I/E) criteria and endpoints, and identify opportunities for novel designs would be enhanced with:

- Flags on the current trial record that make it obvious if key characteristics like number of primary outcomes, sample size, completion date, etc. have changed from the original entry
- A flag indicating if the study is referenced in an approved drug's label
- The ability to track a drugs development path (i.e. consolidation of all text versions of a drugs generic name into a dictionary).

For the purpose of site/country mix planning:

The evaluation of enrollment rate, country experience, competitive landscape (# of trials already competing for the same patient pool in that country/region), among other key planning analytics are under-supported due to the data's structure and completeness. Inaccurate calculation of enrollment rate requires key variables that are obscured and sometimes inaccurate, which leads to unrealistic expectations for both the time to enroll and then number of sites and/or countries needed to meet trial goals in a timely manner.

There are workarounds and commercial products that help, namely Citeline, however a few changes in CT.gov could be made to the site more valuable for the overall clinical trial ecosystem, improving predictability and efficiency of trials and thus reducing delays and timelines for getting needed therapies to patients sooner. Misinformation and calculations fuel inefficiencies and false expectations for sponsors and NIH grantees alike.

Citeline is good model, supporting the level of granularity of the data export and technical features (Filtering and Dashboard functionality) for such analytics.

What's needed:

The ability to drill down to patient segment (e.g., type of cancer, subtype, mutation); Including i/e criteria in the file export. Citeline, which combs data from CT.gov, provides 70 fields/columns in its export vs. 27. Simply, the more data that is exported in field, the more analyzable and useful.

Specific to calculating enrollment rate:

-Number of sites: While you can hand count from the listing of locations, a field that presents the number of sites would be helpful and may help with the data. If the sponsor lists only 3 sites, yet used 5, the enrollment rate calculation is skewed higher and creates that unrealistic expectation.

-Time to completion of enrollment: This requires backing out time to primary endpoint/treatment outcome to estimate time to completed enrollment, which is not clear or easily determined. Ideally CT.gov would have a primary outcome timeframe collected in a controlled terminology, allowing searchability and analysis (i.e. a structured numeric field and a field for day/month/year) and not left to textual description which varies widely. (e.g., week 52, 52 wks, 365 days)

For the purpose of facilitating patient participation, particularly the ability to find trials for patients:

Searching for trials that are suitable for a particular patient is under-supported. (This is covered more extensively in answer to 1c) Along with many other companies, we developed a 're-skin' of ct.gov to help patients find trials, and deployed that link to sites and patient groups, online communities, etc. While we can present the information in a more patient-friendly manner, the utility is still hampered by the underlying data structure and limited search capability. Other niche companies have gone further and implemented excellent interfaces for sponsors, although their reach and range are limited in comparison to CT.gov.

1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

For trial design and planning purposes:

- Linking to the Drugs@FDA database would be a tremendous step forward. The ability to easily link a study to a drug label would be very beneficial for understanding current standard of care treatment benchmarks. Links would also aid landscape analysis.

- Link to scientific publications and deidentified participant-level trial data, where possible, would aid the analysis of Screen Failure Rates, Drop Out Rates, Adverse Events/Serious Adverse Events, which would be beneficial to development of new therapies, reduce avoidable mistakes, and lead to better designed clinical trials.

For site/country mix planning purposes: Data on country level patient contribution would be useful for evaluation of country level Enrollment Rates.

For facilitating patient participation:

- To assist physicians and health systems: Linking with EMR query solutions would assist health care organizations and treating physicians in identifying suitable trials for patients. One of common complaints we hear from health care organizations that conduct clinical trials is their lack of bandwidth

to comb through every study available in CT.gov, identify studies that best fit their organizations focus and build out the inclusion/exclusion criteria in their local EMR query tools.

The current process where each site builds its own searchable I/E criteria from the free text in CT.gov is prone to interpretation error, in part due to the lack of linkable, specific codes in the protocol (ie. ICD, RxNorm, etc). Individual builds of queries also leads to inefficient and varied implementation across different sites and health systems using the same EMR solution.

Benefit: Giving the EMR query solutions the ability to import each protocol definition in a standard way would reduce the administrative burden at the site, create a more consistent interpretation of the protocol from site to site and allow research staff to spend more time on recruiting patients and less time interpreting and building the inclusion/exclusion criteria to find patients for a study.

- To assist patients and their caregivers:

Provide a quick, clear and reliable source of patient information outside of CT.gov, e.g., in a side bar, that the site could link to enhance the ability for patients to digest the information in the trial description. (E.g., brief condition descriptions like you see on Google search of medical terms or videos for required procedures like biopsies)

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

As one of the largest providers of global clinical trial services, IQVIA assists industry sponsors in all aspects of planning, design, operations and oversight of clinical trials, including working with investigators and the broader patient community to facilitate recruitment and enrollment.

ClinicalTrials.gov is a valuable, foundational resource we utilize, along with numerous other platforms and data streams and analytics to help sponsors make good decisions on their programs, improving efficiency and probability of getting needed medicines to patients sooner. Our specific uses for CT.gov include:

1. Trial planning and protocol design: Informing clinical development strategy and protocol design by:
 - Creating indication landscape assessments, which cover standards of care and benchmarks for design characteristics and highlights opportunities for novel designs.
 - Analyzing the degree to which designs are changed throughout the lifecycle of the study and what the trends across therapy areas and sponsors are by using the archive of changes, which helps avoid repeating design mistakes and improve likelihood that good drugs do not fail due to design or are delayed due to foreseeable protocol amendments.

How well this works: The current functionality allows our planners to get find what they are looking for fairly quickly, if we have baseline idea of what we're looking for.

What could be improved is the use of the site as a tool to explore and learn about trends and unearth insight into particular subsets of diseases (by adding disease subset— e.g., Breast Cancer, Triple Negative, HER2-Negative). While there are paid sources we use that have done this subdividing, it would make

CT.gov more useful to the greater community, and particularly patients to add patient subset dropdowns and include it in the export functionality for easy filtering.

2. Site/Country Mix Planning and Feasibility - Developing informed, realistic operational plans (e.g., # of sites, sites per country to reach enrollment needs) and improving the predictability of trials by:

- Evaluating enrollment rate for disease population (# of patient enrolled per month, per site, per country)
- Considering country experience with that population/similar trials
- Determining the Competitive Landscape (how many trials in that country/area are already seeking similar patients).

How well this works and area for improvement: The current data availability supports Enrollment Rate evaluation on project-level only.

What could be improved: Please see suggestions for elements and formatting under-supported uses in answers to Q1a

3. Facilitating patient participation by supporting matching of interested patients with trials for which they are eligible and assisting investigators in identifying existence (#) of eligible patient in their practice and nearby.

What could be improved: We recognize CT.gov core purpose is as a registry of trials and did not originate as a tool for patient to find trials (or others to help patients find trials). Well known, oft-discussed shortcomings of CT.gov stem from this legacy. In short, CT.gov entries describe 'what patients are right for the trial' not 'what trial is right for the patient'.

CT.gov, however, is the most used, most populated publicly available research registry, downloaded and shared exponentially. Recognizing this, CT.gov is a tremendous resource that, with some changes, could dramatically improve or alleviate some key issues in drug development— and better serve patients who want to participate. Other companies have built interfaces on top of CT.gov data to make it easier for sponsors to make searching easier patients, yet they cannot have the reach of range that this resource has.

Increasing the system's utility will help patients and physicians find study opportunities, and thus help accelerate patient recruitment -- one of the other most time-consuming portions of trials. The single biggest delay in clinical trials is finding and enrolling patients, a challenge that only grows as new therapies are becoming more targeted.

Primary Issue: Key information that could help narrow down trials for which a patient would be eligible is not structured. The search function does have a number of valuable parameters and presentation options, but the inclusion/exclusion criteria and other key elements— such as disease subtypes - are not readily accessible. Search yields a 'gross cut of information' that can only be read one by one.

One solution is to provide standardized criteria or even just exportable fields for each trial's inclusion/exclusion criteria and specific disease subtype, which would help patients and others find suitable trials.

Additionally, the utility of CT.gov for patients would be enhanced if it included more information that patients would like/need to know. Antidote's Bridge tool provides a good example based on some 17 fields researched identified as of importance to patients.

Overall, we note that CT.gov is superior to other trial registries. The API is great and allows companies to 'play' with data and use. Regarding API, we suggest giving developers advanced notice when making changes to the structure. There are many, many systems linked to CT.gov and no notice equates to errors and inaccurate or incomplete to patients, physicians, sponsors, etc.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

For trial design planning:

Primarily, we rely on a wide range of studies to understand a given indication of interest, a review of which allows us to generalize and spot interesting studies which are likely to be used as a reference for informing clinical development strategies. At this point, we would start to look at a small number of studies in much more detail. At present, we would use the functionality available in CiteLine for this work due to the absence of aggregation/benchmarking info on CT.gov.

For site mix/operational planning:

We use a wide range and filter by Indication, Patient Segment, Phase, Start Date, Sponsor Type and Intervention Type (Interventional, Non-interventional and Open Label Extension trials). Per above, the current functionality does not support direct filtering for Patient Segment and Intervention Type.

For facilitating patient participation:

From a patient point-of-view, it would help to consider what a patient might be looking for and allowing for limiting or filtering by whether the trial is for an investigational product or for an approved product looking at new use, or to further understanding of existing treatments. A cancer patient looking for access to promising therapies would be well-served by such a filter, and someone wanting to participate for altruistic purposes may want to contribute to better understanding of approved drugs. Filtering or limiting could be accomplished by indicating, for example, if the trial for a new line of treatment, a new mode of administration for an approved drug, a drug approved for other conditions, new drug but similar to existing drug in use, a novel drug, etc.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

Timely update of the study status and other applicable study information, in terms of minimizing the data lag.

As stated elsewhere, common terminology for primary outcome timeframe would be useful.

It would also be useful to the wider community to be aware of reasons for major changes to a trial's endpoints (in nature or quantity) or sample size.

- 3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).**
- 3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.**

For the key design characteristics (i.e. size, endpoints, endpoint timings, sites, countries etc.) standardization should be possible without creating any drag on the side of sponsors or individual investigators. Use of common terminologies would only enhance the usage by the wider research community, patients and care providers, and the sponsors themselves. Of particular use would be clarity on the hierarchy of MeSH terminology, such that similar trials could be grouped more efficiently.

Implementation of Machine Learning and Natural Language Processing algorithm is likely to be helpful in preserving the flexibility and categorizing the free text information. While NLM will want to be mindful of adding to the number mandatory fields to be completed by all institutions registering a trial, there are some key opportunities with minimal burden outlined in our submission. For example, the use of 'tick boxes' for some patient-related items may be a low-effort, valuable add.

Aligning standards to improve utility - As programs such as Meaningful Use, MIPS and MACRA have continued to evolve, so to have the NLM standards. CT.gov should look to align with the evolving NLM standards that currently support the quality initiatives within programs such as MIPS.

The government and healthcare industry have invested heavily in the standards and requirements for EMR vendors to have the ability to import electronic quality measure and registry specifications and then generate executable logic against the EHRs database to meet reporting requirements. Since the programmable logic used for quality measures and registries is not different than how a clinical trial protocol is defined, NLM should consider whether adopting the QDM (Quality Data Model) to define clinical trial protocols would be feasible for those registering trials. It holds the promise of allowing EHR vendors (that have already completed the development to support QDM) to import the clinical trial protocols and deliver the executable logic to all of their healthcare organizations. This type of solution would virtually eliminate the need for healthcare organizations to spend significant efforts manually interpreting and building the clinical trial protocols and allow them to spend more time interpreting the results and determining the best clinical trials for their healthcare organization.

- 3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.**

In addition to the detail in 3a, synchronizing the data structure between CT.gov and EudraCT might be beneficial.

As referenced above, there is an opportunity to make the MeSH terms associated with each trial more useful for grouping trials. Also, given the increased usage of Real-World Data in conjunction with trials,

the interaction with ICD-10 and other health-system coding could be explored, or broader adoption of elements of the Quality Data Model, to reflect and connect better with clinical care and thus patients.

Submission No.: 261

Date: 3/14/2020

Name: Mark Ediger

Name of Organization: [Not provided]

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

The search functionality is great, but is essentially black-box. Synonyms generated behind the scenes should have rationale / user should know the UMLS backing for the engine. Most of the main data aggregators (Citeline, etc) have more user input into why each synonym was included. This could include real-time text completion of the user's search input to help guide common searches or a thesaurus guide.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

Public data sources of potential use:

Clinical Study Request - <https://clinicalstudydatarequest.com/Default.aspx>

Project Data Sphere - <https://projectdatasphere.org/projectdatasphere/html/access>

Vivli - <https://search.vivli.org/>

Yoda - https://yoda.yale.edu/trials-search?field_clintrials_gov_nct_number_title=

NCTN - <https://nctn-data-archive.nci.nih.gov/view-trials>

NINDS Study Archive - <https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets>

NIDDK Studies - <https://repository.niddk.nih.gov/search/study/>

Biologic Specimen and Data Repository Information Coordinating Center
<https://biolincc.ncbi.nih.gov/search/>

ImmPort - www.immport.org

NIDA studies -
https://datashare.nida.nih.gov/data?field_clintri_study_division_target_id>All&field_clintri_keywords_target_id>All&page=

NICHD studies - <https://dash.nichd.nih.gov/studyExplorer>

These datasets provide a powerful complement to clinical trials metadata from ClinicalTrials.gov, and the results as well. Granular patient information is not included in ClinicalTrials.gov, but this level of data can be used to decipher additional subgroup analyses within trial datasets.

1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

Search Detail functionality - this search function uses some semantic synonyms during the search and as such is very useful for synonym generation while performing a search on a lesser-known indication or cytogenetic subtype. We use the search detail function to generate additional related synonyms for indications and to confirm external research done on an indication subtype.

API - We use the API to generate exportable lists of studies meeting certain criteria. Our lists are occasionally larger than the API generally allows, and so search chunks have to be serially added to an export. It would greatly expedite search and review if the API limits could be expanded.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Our primary use usually entails identifying a more limited set of studies, but one which we hope is conservative in capturing all targeted studies. We would rather include & export a non-relevant study than miss one in a search process. The most useful criteria for us are Completion Status and various criteria related to study design (masking status, interventional vs observational, etc). Completion status tends to be quite frustrating to work with, likely at the limitation of the submitting entity. Any supplemental information that can be gathered around completion status, last update, likelihood of study delay, etc is extremely useful. Additionally, there are often study design components buried in the Detailed Description or elsewhere which are important (i.e., a true Ph I / II or dose escalation / dose expansion should be able to be labeled as such, similar for a 3+3 dose expansion design, etc). Some study designs are common enough to have their own category.

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

Efforts should be made to guide submitted information into a standard format; 'Other' values can be used if the submitter is willing to enter a reasoning for why.

A submitter should be able to upload data to a specific standard of their choosing, and then identify the standard in use.

Similar incentives to 2e could be in use for submitters who accurately use standards when uploading.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

Better coupling of MeSH terms to their associated trial attributes

Possibility of ICD-9 / 10 coding

Study interventions - better coded to WhoDrug standards

Submission No.: 262

Date: 3/14/2020

Name: Matthew Donovan

Name of Organization: DSFederal

- 1. Website Functionality. NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).**
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

1. Currently, the existing search capability of the application allows for keyword and limited field searches but does not provide patient-specific in-depth searches. More granularity, specificity, and patient-centricity could be added to the ClinicalTrials.gov website in order to best meet patient and user needs using natural language processing (NLP) and free-text data structuring and mapping platforms. These could be used to identify symptomatology, lab values, and personal history which could be considered for a given trial's requirements, such as inclusion/exclusion criteria, and which can then subsequently be utilized within search capabilities. The intention behind these enhanced capabilities is not just to show what trials potential patients are viewing, but also determine why potential patients are searching for any given trials, building a cycle of greater patient engagement, greater data capture, and greater improvement toward the repository as a whole. Such a redesign of ClinicalTrials.gov would motivate potential patients to inform healthcare providers of ongoing or prospective clinical trials, encouraging trial participation and engagement from both parties.

2. The utilization of ClinicalTrials.gov could be expanded via social networking to disseminate clinical trial knowledge and enhance patient recruitment. This process can be done via web and mobile platforms and can register large numbers of unique visitors using low-cost social media outreach means.

- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

After a drug has been approved, it would be useful to link all pre-approval studies for that drug to the approval materials on the FDA website Drugs@FDA (<https://www.accessdata.fda.gov/scripts/cder/daf/>). It might also be useful to provide a link from each trial to the website of the clinical trial sponsor, so that the reader might put each of these clinical trials into the context of the investigational plan (to the extent provided) given on the sponsor's website.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

The DSFederal team is comprised of partners that use ClinicalTrials.gov in different ways.

Firma Clinical is a patient-centric Clinical Research Organization (CRO) whose primary use of the website is heterogeneous and their work involves a broad range of therapeutic areas. They use clinicaltrials.gov to identify all ongoing studies in a particular therapeutic area at a particular stage of clinical

development. They also use the website to identify all clinical studies in a given indication by one pharmaceutical / biotechnology company.

Real Life Sciences (RLS), is a company that pairs clinical scientists with software researchers to solve unstructured data management and analytics challenges within life sciences. RLS uses the ClinicalTrials.gov API for macro-level overviews of studies to understand high-level information across a large number of trials. RLS finds that obtaining specific, granular-level data is difficult, due to a limited number of fields which often require further, manual steps to extract. These deficits within this granular-level feature can be solved using technologies described above and provided by the DSFederal team.

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

The DSFederal team's primary use of ClinicalTrials.gov relies on both a variety of studies as well as a narrow, focused set of studies. The team has worked with both large organizations and clinical operations entities who require macro-level overviews of data from ClinicalTrials.gov, such as the number of trials, trial locations, values of given fields, missing fields, and more. Additionally, we have worked with specific program/study teams with very specific needs to look up specific endpoints and inclusion/exclusion criteria for evaluation purposes.

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

ClinicalTrials.gov has a great opportunity to become a larger data sharing platform using new technologies able to be provided and implemented by the DSFederal team. The European Medicines Agency (EMA), Health Canada, and the NIH are all organizations that are currently making strides in data sharing initiatives and publishing study results. Similarly, ClinicalTrials.gov is a natural platform to do the same-- such as the upload of anonymized CSRs, Clinical Summaries, and more. We hope to be able to explore the possibility of building tighter integrations to streamline sharing processes and enhance interoperability.

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

1.The DSFederal team could deploy and integrate a module which organizes, structures and classifies self-reported data containing Social, Physical, Emotional, Cognitive and Role Activity impairments, symptomatology, and complaints. This module could be exposed as an API that can be integrated to help define and refine patient subpopulations based on their real-world concerns and event data. Data-driven “themes” captured by the module framework could then be used to enable customized outreach and messaging to participants.

2. Content management systems such as Drupal can enhance how information is presented and viewed on the website by providing the ability to easily create static content. Users could easily log in to easily create and update content which can be immediately published to the public, or moderated using content access rules to ensure the proper approval has been received when publishing content. In addition to content, form creation and management could be handled easily with the ability to extend and customize form functionality, if needed. Popular content management systems such as Drupal can also improve security by providing hardening of user sessions, separation of business logic and presentation, and CSRF token protection.

3. Integration with powerful front end javascript frameworks (NodeJS, React) and/or map API's (Google Maps, arcGIS, Tableau) is another area of improvement and could provide more detailed and useful geographical information related to clinical studies than what already exists on ClinicalTrials.gov.

2d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

The PRS Users' Guide, the ClinicalTrials.gov Protocol Review Criteria and the ClinicalTrials.gov Results Review Criteria are all useful support materials for the website in its current state.

2e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

Providing more refined, customized, and relevant communication to participants can heighten chances of sustained adoption, engagement, information submission, and patient retention within the ClinicalTrials.gov repository.

The DSFederal team can provide a range of highly focused software driven services and interactive applications to ClinicalTrials.gov centered around optimizing recruitment, retention and overall engagement. These tools and services can be deployed as integrated or embedded software or data applications and/or as managed services. Recruitment analytics for example, can provide the following:

1. Population Targeting: Define and refine patient populations that best fit the recruitment criteria for given clinical trials and develop geographic insights to prioritize outreach locations and channels.

2. Message Prioritization: Quantifiable insights into the core concerns of untapped or underserved patient populations, both physical (based on geographic location) and virtual (via online social media channels and forums), such that ClinicalTrials.gov users can target messaging and outreach approaches accordingly.

3. **Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

ClinicalTrials.gov as it stands now is massive and needs to become more patient-specific. However, the DSFederal team also understand that over-implementation of protocol granularity and data categorization and standardization can lead to a rigid and unsearchable system. We have two approaches to retaining the balance between upholding data standards and search engine flexibility:

1. Keeping the key word search option that is already in the present website.
2. Adding overarching standardized search methodologies via data mapping and structuring to provide a “contextual search.”

The DSFederal team can provide opportunities for ClinicalTrials.gov users to not only make use of verbatim, key word searches, but to also search more categorically-- by symptom, by trial criteria, by ailment, etc., while also allowing for greater contextual relevance as per patient reports.

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

DSFederal team partner, RLS, constantly maintains and updates a granular and “multi-thematic” patient-data schema. A collection of curated data standards and taxonomies such as National Uniform Claim Committee (NUCC), Clinical Data Interchange Standards Consortium (CDISC), World Health Organization International Classification of Functioning, Disability, and Health (WHO-ICF), Medical Dictionary for Regulated Activities (MedDRA), RX-NORM and HL7 are used to map and categorize outputs generated by custom Natural Language Processing (NLP) pipelines. These pipelines comprise both supervised and unsupervised machine learning approaches, include extensively trained dependency and syntactic parsers and part-of-speech (POS) taggers, and are used to populate the patient-data schema with structured data.

This patient-data schema is then used to create single, consolidated, and often one-of-a-kind patient databases that include a diversity of clinical, economic and functional longitudinal data. Regardless of the type of patient data collected through the ClinicalTrials.gov website, either structured or unstructured data sources (e.g. tabulated datasets in SAS or free-text survey responses stored in JSON), they can be consolidated into a uniform source and format, eliminating many of the manual processes typically required to achieve this. While it is recognized that not all data can, will, or should be structured and consolidated using NLP, this capability is fundamental to efficiently, repeatedly and reliably integrating multiple sources of multi-format data (e.g. free-text fields). NLP-based structuring and analytics would greatly minimize the manual effort required to create clean and highly reusable data.

Attachment: DSFederal Capabilities 2020.pdf



We are in business for one reason... To make the world a better place.

Founded in 2007, DSFederal is a 160-person woman-owned small business (WOSB) headquartered in Rockville, Maryland. We combine world-class technical expertise with a broad understanding of our clients' missions and a passion for making the world a better place. Our research, IT, business process improvement and training solutions help our clients to improve health and safety for people around the world. Through leading-edge capabilities in data analytics, training, mobile development and process improvement, DSFederal "connects the dots" between data, organizations, outcomes and individuals.

12 Years in Business

Over 45 Projects

Across 25 Agencies

160+ Employees

Information Technology

By fostering an open communication environment, we bring innovative solutions to complex system development challenges.

- Agile software development
- Data Analytics, harmonization, and visualization
- Data Engineering
- Systems/Cloud Integration
- Web Content Management (Drupal)

Scientific Research Solutions

We support critical health and biodefense research efforts. Our clients rely on DSFederal to advance their goal of improving human health and saving lives.

- Health Data Analysis
- HIV/AIDS research
- Biological Data/Big Data
- Global research support

Program Management

Our data driven program management capabilities help clients to uncover efficiencies, offering clear value and delivering solutions that solve productivity problems.

- Business Process Improvement
- Workflow Management
- Organizational Policy and Strategy
- Grants lifecycle management

Training and Technical Assistance

Leverage the extensive evaluation, research design and analysis capabilities of our staff to administer successful technical assistance that garners high levels of feedback.

- Assessment of Health and Public Health Programs
- Strategic Planning
- Research on Health Models and Practices
- Data Quality Assessments
- Site Visits

Contract Vehicles

- GSA IT-70 (SIN 132-51)
- GSA Health IT (132-56)
- GSA Professional Services Schedule (SIN 847-7)
- GSA 8(a) STARS II (Constellations I and II)
- GSA HCaTS (Pool 2)
- GSA Alliant 2 Small Business (Pending Award)
- USAMRIID IDIQ
- HRSA Technical Assistance IDIQ
- Program Support Center (PSC) IDIQ
- CMS SPARC (JV)
- CIO-SP3
- VA-T4 (Sub)

Awards

- 2019 – Montgomery County Business Hall of Fame
- 2018 – Hua-guan Award
– The World's Top Chinese Businesswomen
- 2017 – Montgomery County Chamber of Commerce Small Business Leader of the Year (CEO Sophia Parker)
- 2017 – Washington Business Journal Top Small Technology Company
- 2017 – Washington Business Journal “Women Who Mean Business”
- 2017 – Capital Region Minority Supplier Development Council Top 100 MBE
- 2017 – Top 100 MBE
- 2016 – SBA Top Woman-Owned Small Business

Credentials

- Economically Disadvantaged Women-Owned Small Business (EDWOSB)
- ISO 9001:2015
- CMMI Level 3 for Development and Services
- Secret Facility Clearance



World-class capabilities, mission focus and a passion for making the world a better place: We connect the dots between data, organizations and people.

Client Testimonials

"The individuals that DSFederal employed to work on behalf of NIFA were of extremely high talent, and highly motivated to successfully exceed requirements of the work as described. The quality of work products and outputs was uniformly high and routinely improves content pieces in terms of plain language, accessibility and 508-compliance. The contributions of DSFederal staff can be tied directly to significant improvements to the overall quality and currency of a broad and deep curation of dynamic content that populates the NIFA web site".

- USDA Official CPAR Assessme C mme s

"Given what I know today about the contractor's ability to perform in accordance with this contract or order's most significant requirements, I would recommend them for similar requirements in the future".

- DA Official CPAR Assessme C mme s

"The Contractor's performance exceeded the requirements of the contract by ensuring 100% on-time transition from DAI to GFEBS accounting systems in April 2018. During this time, the contractor provided the Division and DHA with knowledgeable support to effectively transition over \$30M in contracts to the new financial system".

- De e se Hea h Age cy Official CPAR Assessme C mme s

Federal Civilian

HHS – National Institute of Health (NIH)
HHS – Health Resources and Services Administration (HRSA)
HHS – Food and Drug Administration (FDA)
HHS – Centers for Disease Control and Prevention (CDC)
HHS – The Office of the National Coordinator for Health Information Technology (ONC)
HHS – Assistant Secretary for Preparedness and Response (ASPR)
HHS - Centers for Medicare & Medicaid Services (CMS)
United States Department of Agriculture (USDA)
National Aeronautics and Space Agency (NASA)
Consumer Product Safety Commission (CPSC)
Homeland Security – Federal Emergency Management Agency (FEMA)

Federal Defense

Department of Army
United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Defense Health Agency (DHA)
Defense Human Resource Activity (DHRA)
Army Research Laboratory (ARL)

Interested in working with us?

Please contact:

Sophia Parker

via email at sophia.parker@DSFederal.com or
by phone at (240) 669-2263



Submission No.: 263

Date: 3/14/2020

Name: Lisa Chotkowski

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.**

I want to see a description of the drugs in the trial, what their targets are, what they're already FDA approved for, abstracts, summaries or results of studies including pre-human studies, plus recent literature about any theories or promising uses for the drugs.

I like Onclive, Pubmed, ScienceDirect, drug manufacturer inserts, NCCN guidelines but there are many, many more.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I am an ovarian cancer patient. I like all the filters that already exist but new ones are needed.

I want to be able to help my oncologist plan my treatments with the intent of not excluding myself from clinical trials in the future. Exclusion criteria data needs to be stored more specifically. For instance, if I'm looking for an immunotherapy trial but my oncologist is suggesting that I go on treatment with an immunotherapy drug for treatment before I enroll in a trial. I need to enter each immunotherapy drug name in the other terms text box. Then I have to look at the exclusion criteria in every trial. If I find that prior treatment with any PD-L1 drug is excluded, there is no easy way to find any trials that don't have the PD-L1 exclusion. Entering PD-L1 in the other terms text box will return all immunotherapy trials as PD-L1 is a common word throughout the entire description of each immunotherapy trial, whether in the exclusion section or other sections. The filter should provide text searches on only exclusion data & also another search for only inclusion criteria.

There needs to be more ways to save trials that have already been reviewed as 100 saved trials is not enough. I don't want to see trials that I've already saved, only newer ones. However, I do want to see saved trials if they have changes to their status, start or completion dates or arms have been closed. I'd like to get email notifications for any new or changed trials that I'm interested in based on saved searches. Many websites including real estate (realtor.com) or car sales (carfax.com) have that feature.

Where are the clinical trial results?....poor enforcement of that critical data!

We need clinical trial contact information for the locations. As a patient, calling the Principle Investigator Contact Info listed in the trial usually leads to a dead end!!!

Somehow institutions that are responsible for the clinical trial information should be penalized or incentivized to keep data accurate & up-to-date. My oncologists don't use it because of the inaccuracy

of the data and patients don't want to be bothered because after many hours of research, promising trials turn out to be dead ends!

1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

I search for clinical trials within the US, sometimes focusing regionally. I want to know the clinical trials based on promising drug information that I've read in literature. My initial search will usually be based on a drug name. If I don't search by drug name, I don't like when the drug name in the trial is a cryptic (non-FDA approved name)...there needs to be a cross-reference to the medical name to make trials cohesive. There also needs to be links to recent literature about the latest promising developments of the drug, what the drug targets are & any existing FDA approved indications. My doctor will use off-label drugs so I also search trials inclusive of all solid cancer types.

These searches often return a very large volume of data. After reviewing each clinical trial, I want to be able to save most of the clinical trials. The save limit of 100 is too small. I want to be able to save the trials by categories. Some categories I need are by drug, phase of trial, if there's a placebo arm, & the exclusion criteria. I don't mind saving these trials in Chrome's Bookmark manager, categorizing them in different bookmarks, however, I want future searches to be able to recognize my saves so I'm only reviewing new or changed trials. This is a huge problem that causes patients to avoid keeping up-to-date on the trials & I'm sure clinical doctors don't want to be bothered with it either.

Submission No.: 264

Date: Submitted post-deadline

Name: Anonymous

Name of Organization: N/A

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
 - 1a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.**

An export of the found hits in RIS format would be good to be able to manage the studies in EndNote similar to hits from PubMed.

- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

Example of searches: Search for all studies for specific indications, search for specific interventions/active substances/products

The search works very well. The synonym search is good, the search options (Boolean operators, prioritization with brackets, field selection) are good. The search in the fields "Condition or disease", "Intervention/treatment" is absolutely necessary. A search only in the study title and a search across all fields is also good.

ClinicalTrials is used to search for ongoing and completed studies for various indications, intervention types and medical devices.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

most often all studies are searched for

sometimes limited to a certain period of time

sometimes restriction to study type/study design (e.g. RCT)

(1) A broad spectrum of studies to provide an overview of currently ongoing or already completed studies on specific types of intervention, medical devices or generally the treatment of a specific indication. The restrictive criteria may vary depending on the search.

- 3. Data Standards.** NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

3b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.

MeSH terms for indexing the study entries and a RIS download to import hits directly into EndNote would be helpful.

Submission No.: 265

Date: Submitted post-deadline

Name: Scott Thompson

Name of Organization: Scott C. Thompson, ELS, Independent Medical Writer

2. Information Submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

2c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

Please include plain language summaries (PLSs) for all clinical trials listed on ClinicalTrials.gov, akin to the new requirement for PLSs for Cochrane Reviews within the redesigned PubMed Health (<https://consumers.cochrane.org/PubMedHealth>).

Submission No.: 266

Date: Submitted post-deadline

Name: Lisa Chotkowski

Name of Organization: [Not provided]

- 1. Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).
- 1c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.**

I have already submitted this form last week but I'd like to clarify my ideas as I previously completed it in haste.

I am an ovarian cancer patient & I search for clinical trials for future treatment and also to align my current treatments so that I don't lose eligibility to clinical trials of interest.

Typically, my search is very broad, usually searching the entire US. My tumor has markers inherent to breast and endometrial cancer so I usually don't filter for a specific cancer when I'm searching for trials. My searches are usually filtered for a particular drug. Unfortunately, the results listing is usually very long and will take hours, if not days, to peruse. The existing filtering criteria usually returns a limited & manageable listing of trials if I was targeting my diagnosed cancer for a specific drug in a regional location. However, there needs to be design changes for more broad searches that return many rows of trials and also enhance filtering for drug biomarkers & treatment history & planning.

See my proposals in section 1d for design changes.

- 1d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.**

These are my proposed changes for your existing Clinicaltrials.gov website.

1. Reject column - a new column where a box can be checked & value stored so that future searches returning the same already reviewed & rejected trials can be avoided for redundant review by the user. It should be designed similar to the existing Saved column. The maximum number of rejected rows should be unlimited or many more than 100!
2. Saved column - the existing process should be increased so the maximum number of saved trials is unlimited or many more than 100!
3. The NCT (CT Identifier) needs to be shown for each trial on the list page. This helps a user remember a trial that may be the original source of interest when viewing a list of trials that have similar attributes.
4. Email notification - User's search criteria needs to be saved and daily or weekly emails sent identifying new or changed trials that meet the search criteria.

5. Viewing individual trials page:

- Links to other websites should be added that have more information about the drugs being tested or interim or summary results of the trial stats published elsewhere.
- Links to all of the CT locations website pages that have the correct contact information for clinical trial enrollment, needs to be added. Most principle investigator contact information displayed is usually a dead-end for patient inquiry.
- Cross-reference links to past or current phases of the same clinical trial should be added. For instance, Ovarian Cancer has many Ariel trials for Rucaparib. The ability to view each of those trials without opening up a new tab & doing a new search would save time.
- Submission of detailed trial information should be standardized & enforced. Much inclusion criteria in the Inclusion Criteria Section inappropriately includes exclusion criteria. For basket trials, finding the specific info pertaining to your tumor type is daunting. See the Inclusion Criteria section in this trial for an example: NCT02554812. Most of the inclusion criteria should be in the Exclusion Criteria Section or at least repeated in the Exclusion Section.

6. Search filter changes:

- Exclusion criteria needs to have a separate search box instead of having a shared text box (Other Terms) that's currently matched to any info from any section of clinical trial information. This should be a reverse process where if the exclusion search text is matched to text in the exclusion section of a trial, the trial will be EXCLUDED from displaying in the results list page. As a patient, if I'm not eligible for a trial, why would I want the trial displayed in my list of results as is the process today?
- Inclusion criteria should also have a separate search box. It should search only the Inclusion Criteria section of a trial. If a match is found, then the trial should be INCLUDED in the results.
- Searches with filters for the already Saved clinical trials should be an option. This would allow selecting only a subset of trials originally interested in for download & printing.
- Add a filter to exclude clinical trials already checked as Rejected. This will reduce trials listed that will be ignored anyway.

7. Nice to have:

- Add a report that lists the different Exclusion Criteria info for a group of clinical trials. Ideally, exclusion info would need to be stored differently to eliminate redundancy & size of report. The currently entered & stored free-form text should be modified to a drop-down box submission. This report would help patients get familiar with the conditions that prevent eligibility & have the appropriate info needed to filter clinical trials more efficiently.
- Add a report that lists the different Inclusion Criteria info for a group of clinical trials. Ideally, inclusion info would need to be stored differently to eliminate redundancy & size of report. The currently entered & stored free-form text should be modified to a drop-down box submission. This report would help patients easily identify all of the biomarkers that are being targeted by the drugs being tested in a select group of trials.

Submission No.: 267

Date: Submitted post-deadline

Name: [Not provided]

Name of Organization: Cochrane

Attachment: RFI conchrane.docx

ClinicalTrials.gov Modernization RFI

This document is intended to capture Cochrane's coordinated response to NLM's request for information on the modernization of ClinicalTrials.gov

Background: <https://grants.nih.gov/grants/guide/notice-files/NOT-LM-20-003.html>

Response form: https://nlmenterprise.co1.qualtrics.com/jfe/form/SV_e2rLEUAx99myump

Information Requested

NLM is requesting public comment to guide efforts to enhance and better support the users of ClinicalTrials.gov, particularly within the topic areas outlined below. Response to this RFI is voluntary, and respondents are free to address any or all topics listed below, and other relevant topics, for NLM and NIH consideration:

1. **Website Functionality.** NLM seeks broad input on the ClinicalTrials.gov website, including its application programming interface (API).

a. List specific examples of unsupported, new uses of the ClinicalTrials.gov website; include names and references for any systems that serve as good models for those uses.

Within Cochrane we are establishing a trial surveillance workflow where newly registered and newly published trials are identified, PICO annotated according to Cochrane's PICO ontology and, using machine learning, given a likelihood score as the study's relevance to a particular Cochrane review group and/or Cochrane review. It would be really useful if ClinicalTrials.gov newly registered randomised controlled trials used the same/similar PICO elements. This might not be possible for all fields but if terms from controlled vocabularies could be used for as many as possible would have the advantage of making ClinicalTrials.gov more discoverable.

b. Describe resources for possible linking from ClinicalTrials.gov (e.g., publications, systematic reviews, de-identified individual participant data, general health information) and explain why these resources are useful.

1. Link to trials included in Cochrane Reviews. The included study within a Cochrane review will have undergone a quality assessment to assess the study's risk of bias, the results of which can be seen in the Cochrane review. This linking could therefore help provide people with more information about the trial.
2. Link records related to drugs to the Drug Information Portal (which links to CT.gov as well: <https://druginfo.nlm.nih.gov/drugportal/>)
3. Allow pharmaceutical industry to attach standardised documents to the trial (PDFs of Clinical Study Reports, IPD datasets on <https://vivli.org/>).

c. Provide specific examples of how you currently use the ClinicalTrials.gov website, including existing features that work well and potential improvements.

In Cochrane, we currently use ClinicalTrials.gov in two main ways: 1) It is one of the sources we search ‘centrally’ for reports of RCTs for Cochrane’s Central Register of Controlled Trials (CENTRAL). This process involves harvesting ClinicalTrials.gov records via the API. The records are then screened by a Crowd (via [Cochrane Crowd](#)) for eligibility for inclusion within CENTRAL. 2) The other main use case is searching undertaken by Cochrane Information Specialists for trials relevant to Cochrane systematic reviews. Here the ClinicalTrials.gov interface is queried with search terms and the results are exported, usually in xml format for import into the Cochrane Register of Studies (Cochrane’s reference management software).

Overall the platform works very well and is a critical resource in terms of identifying new, ongoing and unpublished trials.

We have noted a few areas that could potentially be improved:

Quality assurance and information clarity and transparency items:

1. We have noticed that records sometimes contain conflicting information regarding study design in the study design description area: for example, NCT04143165. Here the trial is described as both “single group assignment” as well as “randomised”. Other examples include where the inputter has selected both “case control” and “randomised” (NCT04166578). One possible technical solution would be to prevent the inputter from being able to select two conflicting designs, or to add this to the automated validation checks that happen.
2. Another issue is conflicting information across fields (NCT04192331, NCT04166578, NCT04151862, NCT04193345, NCT04193761). One common error seems to be a confusion between random selection and random assignment. It could be that some of these inconsistencies could be prevented with more support/guidance for inputters at the input stage (though we acknowledge this task is likely often by the PIs or trialists themselves).
3. It would be useful if a couple of other fields of information could be changed from free text fields e.g. the Investigators field, and the Outcomes Measures fields. The Investigators field often contains the name of the lead or senior author on the published results and is therefore really useful as it helps us to link related reports. At the moment this field is fairly inconsistently populated on ClinicalTrials.gov so we don’t use the information as much as we would if it was a more standardised field. Also, specifically relating to the investigator field, it would be good to be able to view the PI in the results listing - this currently is not an option in the show/hide columns function. Outcomes field – consider parsing out the field into different pieces of information related to outcomes (the expert PICO tool might be a good model to follow here): high-level classification, more detailed outcome description, instrument used. Some inputters have done a nice job though: NCT03254875.
4. Inconsistent use of title case for titles. Data inputted sometimes has the indefinite articles capitalised. Suggest that sentence case would make the data neater.
5. Publications provided by trialists (“More information > Publications”) are sometimes not related to the trial record. (Make clear this is not a literature list).

6. Automatic flagging of “outcome switching” (or do not allow outcomes to be changed after record has been accepted). Currently this needs to be figured out manually by checking the history of changes

7. Highlight external links provided by trialists (this is currently a relatively hidden feature).

8. The status of the trial used to be more prominent on the trial record. It is now reflected in the colour-coded line at the top of the timings panel. Could the status be made more prominent again?

Export:

9. Include the detailed description in xml export

10. Allow automatic bulk export of PMIDs attached to record (PubMed records automatically indexed via NCT-number).

Search functionality:

11. Word truncation would be welcomed

12. It would be good if the Advanced search would allow longer search strings

13. There is useful MeSH in the records but it would be good if the terms were updated in line with the annual MeSH reload

14. It would be useful to have a filter for date posted

15. A possible bug/glitch: If a search is performed for studies first posted between two dates e.g. 01/01/2018 and 01/01/2020, a certain number of results are returned. When the search is modified to include trials that were last updated during the same period, the number of results returned is always fewer indicating that perhaps the wrong boolean operator is being used here (it should be an OR not an AND).

d. Describe if your primary use of ClinicalTrials.gov relies on (1) a wide range of studies, such as different study types, intervention types, or geographical locations or (2) a more limited range of studies that may help identify studies of interest more efficiently. Explain why and, if it applies, any limiting criteria that are useful to you.

Cochrane's primary uses of ClinicalTrials.gov relies on the effective identification of interventional studies (predominantly randomised controlled trials) for a wide range of healthcare conditions. However, we are also increasingly interested in other study designs to support other review types, such as studies that aim to assess diagnostic tests (these studies can be both interventional or observational). It would be useful if it was possible to filter by study aim with diagnostic being one possible filter option.

2. Information submission. NLM seeks broad input on initiatives, systems, or tools for supporting assessment of internal consistency and improving the accuracy and timeliness of information submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).

a. Identify steps in the ClinicalTrials.gov registration and results information submission processes that would most benefit from improvements.

As regards the registration process, it's unclear whether records become public before they have been quality approved. For example, some records have been given a range of study designs which is not possible. It might be helpful to have a way for users to see that a record has not yet been quality approved, and possibly to offer the option to filter by that status.

b. Describe opportunities to better align the PRS submission process with your organization's processes, such as interoperability with institutional review board or clinical trial management software applications or tools.

N/A

c. Describe any novel or emerging methods that may be useful for enhancing information quality and content submitted to the PRS and displayed on the ClinicalTrials.gov website.

N/A

d. Suggest what submission-related informational materials you currently find useful and what other materials would make the submission and quality control process easier for you.

Reduce the number of free text fields. Whilst the information inputted into ClinicalTrials.gov is already well structured, there are certain fields that could be more standardised, helping both the inputter avoid typos and other input errors and improve overall consistency across registrations and aid discoverability. Also, more guidance might be necessary to help inputters understand some of the controlled vocabulary terms better. An example is the (mis)use of the term single-group assignment. This appears to be confused with single institution or single location study, rather than a single arm trial which is what I think single-group assignment means.

e. Suggest ways to provide credit, incentivize, or recognize the efforts of individuals and organizations in submitting complete, accurate, and timely registration and results information submission.

The responsible organisation could be rewarded with named recognition on a panel on the site's homepage once the trial results are posted (especially if they do within a year of the trial's primary end date) but also perhaps enable organisations to download their trials status which would show how many are ongoing, how many completed but have not yet uploaded results and how many have completed and uploaded results. Organisations' would be able to show funders etc their track record (and funders should be able to view an organisation's and/or a specific PI's trials track record).

3. Data Standards. NLM seeks broad input on existing standards that may support submission, management, and use of information content (e.g., controlled terminologies for inclusion and exclusion criteria).

a. Provide input on ways to balance the use of standards while also retaining needed flexibility to ensure submitted information accurately reflects the format specified in the study protocol and analysis plan.

This is in part described in question 1. Cochrane has developed an ontology for describing Cochrane Reviews as well as randomised controlled trials and other evidence assets. The PICO ontology uses a number of controlled vocabularies for each of the PICO elements in the construction of a Cochrane vocabulary. This is in an attempt to improve the way in which users of Cochrane evidence can identify and navigate relevant evidence and could be used to make trials and studies more discoverable on ct.gov, as well as facilitating linking of trials, publications, and related systematic reviews, datasets, and other assets.

b. List names of and references to specific standards and explain how they may be useful in improving data quality, enabling reuse of data to reduce reporting burden, or improving consistency and management of data on ClinicalTrials.gov.