Clinical Trials Tumor Name Standardization using Embedding Analysis

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**Affiliations:**

**Abstract**

*Objective:*

*Materials and Methods:*

*Results:*

*Discussion:*

*Conclusion:*

1. **Background and Significance:**The Food and Drug Administration Modernization Act of 1997 (FDAMA) mandated the National Institutes of Health (NIH) to create a publicly available resource to disseminate information on the effectiveness of drugs in federally or privately funded clinical trials (CT) \cite{CT.gov}. This eventually led to the creation of the ClinicalTrials.gov registry, which was publicly launched on February 29, 2000. Since then, the registry has amassed over 482,529 research studies across all 50 states in the US and 223 countries \cite{CT.gov}. Each record within the CT registry is self-reported by the trial sponsor through the web-based data entry platform known as the Protocol Registration and Results System (PRS) {\cite.gov}. The registry requires sponsors to enter basic details regarding the trial, such as purpose, design, patient eligibility criteria, and other critical information about the study [(Zarin et al. 2011)](https://paperpile.com/c/NPPxEM/Hrsy). The CT registry requires by law that data be entered in a tabular format and that an individual with knowledge of study design and data analysis be involved in the submission process to ensure that results are appropriately summarized and the data submission is consistent with the review criteria of the CT registry. Following the submission of a record, the record is reviewed internally by CT registry staff before it is posted publicly on ClinicalTrials.gov.

Even with the established protocols and guidelines in the submission process, the registry data may contain various inconsistencies in the form of extraneous information, typographical errors, missing values, etc. Such discrepancies must be addressed or filtered out before the data can be used for further downstream analysis. In this study, we developed a computational pipeline to standardize the tumor names contained in the "conditions" data file in the CT registry. The conditions data includes the names of the diseases or conditions that are the subject of the trial. Among the various diseases present in the CT registry, we focused on cancers as they are a leading cause of death in the US and the world [(Siegel et al. 2023)](https://paperpile.com/c/NPPxEM/GzPE). Thus, standardizing cancer names in the CT registry , i.e. by mapping each tumor name in the CT registry to their equivalent standardized names in the World Health Organization's tumor classification system or the National Cancer Institute terms (NCIT) will allow us to integrate tumor data from the CT registry with other databases such as Open Targets or Illuminating the Druggable Genome will allow us to deeply understand the landscape of tumors, targets, and drugs.

It must be noted that the CT registry recommends adding relevant Medical Subject Headings (MeSH) terms or terms from another controlled 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 for each of the conditions \cite{CT.gov}. While this recommendation adds a level of standardization to the disease/condition names present in CT registry, the MeSH terms by themselves often fall short of describing the disease or condition accurately. Furthermore, for a given disease/condition there may be multiple associated MeSH terms, thereby leaving it to the user of the data to establish the most appropriate MeSH term for that disease/condition. Additionally, for certain records in the CT registry, there might be no associated MeSH terms provided for a disease/condition name, therefore solely using the MeSH terms for analyzing the diseases or conditions that are the subject of a clinical trial record is not reliable. In table 1, we show examples of CT records with their disease/condition names and associated mesh terms. Table 1 was created by performing a full join on the files “conditions.txt” and “browse\_conditions.txt”, the files were joined on CT ID.

| CT ID | Condition name | MeSH term |  |
| --- | --- | --- | --- |
| NCT05082610 | triple negative breast cancer | neoplasms,triple negative breast neoplasms,carcinoma, non-small-cell lung,breast neoplasms,neoplasms by site,breast diseases,skin diseases,carcinoma, bronchogenic,bronchial neoplasms,lung neoplasms,respiratory tract neoplasms,thoracic neoplasms,lung diseases,respiratory tract diseases |  |
| NCT04254107 | triple negative breast cancer | lymphoma,carcinoma,lymphoma, t-cell, peripheral,lymphoma, large b-cell, diffuse,triple negative breast neoplasms,squamous cell carcinoma of head and neck,stomach neoplasms,neoplasms by histologic type,neoplasms,lymphoproliferative disorders,lymphatic diseases,immunoproliferative disorders,immune system diseases,neoplasms, glandular and epithelial,neoplasms by site,carcinoma, squamous cell,lymphoma, b-cell,lymphoma, non-hodgkin,lymphoma, t-cell,breast neoplasms,breast diseases,skin diseases,head and neck neoplasms,gastrointestinal neoplasms,digestive system neoplasms,digestive system diseases,gastrointestinal diseases,stomach diseases |  |
| NCT01590680 | neuroblastoma | neuroblastoma,pheochromocytoma,paraganglioma,neuroectodermal tumors, primitive, peripheral,neuroectodermal tumors, primitive,neoplasms, neuroepithelial,neuroectodermal tumors,neoplasms, germ cell and embryonal,neoplasms by histologic type,neoplasms,neoplasms, glandular and epithelial,neoplasms, nerve tissue,neuroendocrine tumors |  |
| NCT04081701 | medulloblastoma | adenoma,meningioma,medulloblastoma,paraganglioma,pituitary neoplasms,esthesioneuroblastoma, olfactory,central nervous system neoplasms,hemangioblastoma,neoplasms, glandular and epithelial,neoplasms by histologic type,neoplasms,pituitary diseases,hypothalamic diseases,brain diseases,central nervous system diseases,nervous system diseases,endocrine system diseases,neoplasms, nerve tissue,neoplasms, vascular tissue,meningeal neoplasms,nervous system neoplasms,neoplasms by site,glioma,neoplasms, neuroepithelial,neuroectodermal tumors,neoplasms, germ cell and embryonal,neuroectodermal tumors, primitive,neuroendocrine tumors,endocrine gland neoplasms,hypothalamic neoplasms,supratentorial neoplasms,brain neoplasms,neuroblastoma,neuroectodermal tumors, primitive, peripheral,olfactory nerve diseases,cranial nerve diseases,hemangioma, capillary,hemangioma |  |
| NCT04294784 | gastroesophageal cancer | NA |  |
| NCT02669914 | gastroesophageal cancer | lung neoplasms,carcinoma, non-small-cell lung,colorectal neoplasms,pancreatic neoplasms,ovarian neoplasms,brain neoplasms,kidney neoplasms,carcinoma, renal cell,breast neoplasms,respiratory tract neoplasms,thoracic neoplasms,neoplasms by site,neoplasms,lung diseases,respiratory tract diseases,carcinoma, bronchogenic,bronchial neoplasms,intestinal neoplasms,gastrointestinal neoplasms,digestive system neoplasms,digestive system diseases,gastrointestinal diseases,colonic diseases,intestinal diseases,rectal diseases,endocrine gland neoplasms,pancreatic diseases,endocrine system diseases,ovarian diseases,adnexal diseases,genital diseases, female,female urogenital diseases,female urogenital diseases and pregnancy complications,urogenital diseases,genital neoplasms, female,urogenital neoplasms,genital diseases,gonadal disorders,central nervous system neoplasms,nervous system neoplasms,brain diseases,central nervous system diseases,nervous system diseases,urologic neoplasms,kidney diseases,urologic diseases,male urogenital diseases,adenocarcinoma,carcinoma,neoplasms, glandular and epithelial,neoplasms by histologic type,breast diseases,skin diseases |  |

Table 1: Conditions data with MeSH Terms

In Table 1, for the condition triple negative breast cancer with CT ID: NCT05082610, the most appropriate MeSH terms is “triple negative breast neoplasms”, however, there are other associated MeSH terms such as “carcinoma, non-small-cell lung” and “respiratory tract diseases” which do not describe the condition of triple negative breast cancer. Since there is no metric in the CT registry by which we can computationally determine the most appropriate MeSH terms for a given condition. Furthermore, the MeSH terms are not identical between studies where the condition names are the same, which adds to the inconsistencies between records with same condition names. Consider studies with CT ID: NCT05082610 and NCT04254107, in both the studies the condition names are “triple negative breast cancer”, however, the MeSH terms are not identical. For instance, in the study with CT ID: 04254107 contains various MeSH terms associated with lymphomas such as “lymphoma, b-cell” , “large b-cell”, “lymphoma, large b-cell, diffuse”, “lymphoma, t-cell, peripheral” etc, these terms are not contained in the study with CT ID: NCT05082610. We can also see in study NCT04294784 , for the condition “gastroesophageal cancer” , there are no MeSH terms , however, for the same condition with a different CT ID NCT02669914 has multiple associated MeSH terms. Due to these inconsistencies, and a lack of metric to determine the most accurate MeSH term for a given condition, we can determine that using the MeSH terms to describe the conditions is not reliable. Therefore, we decided to use the conditions filed in the CT registry to extract the disease/conditions that are the subject of a CT. This study focuses on extracting tumors from the conditions field in the CT registry and standardizing them by matching them to their closest matching terms in the WHO tumor classification system or NCIT.

1. **Materials and Methods:**

***2.0 Data Availability :***The data used in this paper is obtained from the Clinical Trials registry (<https://clinicaltrials.gov/>). The data can be publicly accessed via the Clinical Trials API or from the Aggregate Analysis of ClinicalTrials.gov-Clinical Trials Transformative Initiative (AACT-CTTI) website (<https://aact.ctti-clinicaltrials.org/download>). ​​The ACCT-CTTI website is updated daily with contents from ClinicalTrials.gov and a static database is made available at the start of each month. The static database contains information about all the studies registered in ClinicalTrials.gov. We downloaded a copy of the database from the ACCT-CTTI website on August 31, 2023.

***2.1 Data Extraction Pipeline***

The clinical trials database contains information about every aspect of the study such as outcomes, drugs used, conditions (diseases) studied, design of experiments, sponsors of the studies etc in individual text files. Each text file contains the National Clinical Trial Identification Number (NCTID) which allows one to relate information contained in one text file to another. The NCTID serves as a foreign key for the clinical trial database. For the purpose of this study, we select only the conditions and interventions text files, which contain information regarding diseases and drugs used in a Clinical Trial respectively. The conditions file contains the following fields “id”, “nct\_id”, “name”, and “downcase\_name”. The “id” field represents the identification number for that record within the conditions file whereas the “nct\_id” is the foreign key that helps connect this record to related information contained in other files in the database. The “name” and “downcase\_name” fields contain names of the diseases studied in a specific clinical trial study , the only difference is that the “downcase\_name” contains the disease name in uncapitalized format. The disease names do not have classification such as tumors, viral diseases, sexually transmitted diseases, blood borne diseases etc. Thus the data needs to be filtered to identify tumors. Furthermore, for our analysis in this paper we only considered diseases that had a corresponding intervention belonging to the categories of “*Drug*”, “*Biological*”, “*Combination Product*”, “*Genetic*” in the interventions text file. The rationale behind limiting our diseases to these intervention types was to ensure that there is a corresponding targeted or chemotherapy, immunotherapy-based treatment option for the tumors from the clinical trials database. The intervention files list the “id”, “nct\_Id”, “intervention type”, “name”, and “description” for every study registered in the clinical trials database. There are 11 distinct “intervention types”: "*Drug","Biological","Radiation","Device","Behavioral", "Other","Genetic","Procedure" ,"Combination Product" ,"Dietary Supplement",* and *"Diagnostic Test*".

*2.2 Data Anomalies and Processing Pipeline*

*2.3 Adult and Pediatric Tumor Annotation of Disease Data*

*2.4 Standardardization Pipelines*

*2.4.1 Extract WHO and NCIT tumors*

*2.4.2 Compute pairwise edit distance between CT tumors and WHO and NCIT Tumors*

*2.4.2.1 Nearest match for edit distance*

*2.4.2.2 Affinity Propagation Clustering based on edit distance and standardization to WHO Terms*

*2.4.3 Extract tumor name embeddings from ADA 2.0 and V-3 Large Text Embeddings*

*2.4.3.1 Nearest match for ADA 2.0 and V-3 Large*

*2.4.3.2 Clustering with KMeans and Standardization to WHO Terms for ADA2.0 and V-3 Large Embeddings*

*2.4.3.3 Clustering with Affinity Propagation Clustering and Standardization to WHO Terms for ADA2.0 and V-3 Large Embeddings*

1. **Results:**
2. **Discussion:**
3. **Conclusion:**