PCORI COVID-19 Enhancement Protocol V2: October 31st, 2020

A. Objectives

This work will generate information on the representativeness and generalizability of COVID-19 related clinical trials to real-world target populations and disseminate that information in a publicly available form. This work also extends the visualization tools developed in the earlier stages of the project by adapting them for use when individual-level data from trial and target populations are not available or when obtaining access to the data is cumbersome and time-consuming-as is often the case when quick responses are required. To accomplish this core objective, we will complete two specific aims.

Aim 1: Describe the characteristics of patients participating in COVID-19 related clinical trials with publicly available results. Characterize the eligibility criteria of RCTs as well as the clinical and demographic characteristics of trial participants based on a systematic review of published RCTs related to COVID-19 into 2021.

Aim 2: Adapt our visual tools to show differences between COVID-19 trial participants and real-world target populations. Expand visualizations we have developed to show differences between aggregate data on COVID-19 patients in RCTs and existing and future target populations, as well as how these groups change over time**.**

B. Background

Researchers worldwide are searching for ways to fight COVID-19. While in vitro work, animal subjects research, and observational studies in humans can help identify interventions worthy of further inquiry, the gold standard for assessing treatment efficacy is the randomized controlled trial (RCT).[1] Unfortunately, enrolling participants in RCTs for treating pandemics like COVID-19 is difficult.[2,3] Because RCT participation is often linked to a desire to receive the best possible treatment,[4] those at the highest risk of complications from the disease may be less willing to be randomized when active treatments are available through compassionate use, as in COVID-19.[5,6] Moreover, those with poor access to healthcare and lower socioeconomic status are, historically, underrepresented in randomized controlled trials-and early work has already documented this trend continuing in some COVID-19 trials.[7]

Unfortunately, many treatments with beneficial effects in some individuals have no effect (or even a harmful effect) in others. Even if a treatment is equally beneficial for everyone on the relative scale (i.e. possesses a constant hazard or risk ratio), the number needed to treat will then vary across populations with differing baseline risks of the outcome (and the number needed to treat is pivotal to allocating resources and understanding risk).[8,9] Given that case fatality rates from COVID-19 vary markedly by sex, age, race/ethnicity, and respiratory and cardiovascular comorbidity,[10-12] treatment effect estimates from RCTs may not reflect benefits and harms in real-world populations. Moreover, changes in the characteristics of the infected population may mean that early RCTs fail to generalize to later targets. We propose to improve understanding of the representativeness and generalizability of RCTs assessing treatments for COVID-19 by conducting a literature review of RCTs in COVID-19, identifying current and potential future target populations, and expanding tools developed during our existing award to juxtapose many RCTs with one target and use aggregate data.

B1. Overview of methods for checking generalizability.

Historically, the standard way to check whether a study is generalizable from one population to another is to compare marginal covariate distributions across the two study populations. One might compare, for example, the proportion of trial participants over 65 with the proportion of target population patients over 65, or the proportion of the trial that identifies as Black to the proportion of the target population that identifies as Black. This method is the one most commonly used to assess the representativeness in randomized controlled trials.[13,14]

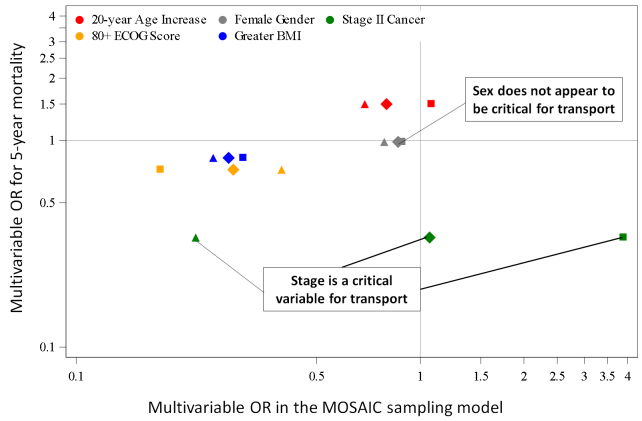

Figure 1: Example of plot already developed for the main grant. Because the gray symbols (representing female gender) are on the Y axis (and independent of the outcome) they are much less likely cause problems when transporting than the other covariates under study, especially the "stage II cancer" covariate.

Unfortunately, this method completely ignores something critical when it comes to the final bias in transported effect estimates-the extent to which the variable in question actually modifies treatment effect (which, in turn, depends on its association with the outcome in question).[15] If a variable is a very weak effect measure modifier, a major difference across study populations may not be problematic; on the other hand, small differences in potent effect measure modifiers can cause meaningful bias in treatment effect estimates.

In our previous work for this PCORI award, we developed visualization tools allowing researchers to examine associations betweeen covariates and the study population, as well as the outcome of interest, simultaneously (see **Figure 1**). We believe that a similar approach can be used to understand the potential consequences of systematic gaps between trial and target populations with respect to covariates known to be associated with COVID-19, provided one understands covariate distributions in the trials and can estimate the correlation of the covariates with the outcome.

B2. Gaps in knowledge surrounding COVID-19 representativeness and transportability.

B2a. Difficulty understanding trial enrollment and participation in studies related to COVID-19.

COVID-19 has only been around since the end of 2019. Between the recency of its emergence and the unprecedented scale of the pandemic (at least during the digital age), thus far we have generally been relying on conventional wisdom to understand likely patterns of enrollment and participation when it comes to trials attempting to treat COVID-19 patients or prevent the spread of COVID-19 within and across communities. It is important to assess the extent to which this conventional wisdom holds conducting a large-scale review of the types of patients enrolled onto COVID-19 related clinical trials, as well as to what extent trials actually report key demographic and clinical risk factors.

B2b. Uncertainty regarding the ideal target populations for these studies.

Another major area of uncertainty is how to enumerate and describe the types of patients we are interested in generalizing or transporting the results of the trials to. COVID-19 is an infectious disease and, over time, the most impacted communities are likely to shift due to policy changes, disease mutations, and the behaviors (voluntary or otherwise) of the communities in question. Any attempt to understand the extent to which trial

participants are representative of the larger population should take these temporal shifts into account.

C. Innovation.

In our existing award, we developed visualization tools to describe differences between one trial and several real-world populations to guide the implementation of hybrid comparative effectiveness research studies when individual-level data were available. This enhancement innovates on these tools in three primary ways.

1) We will adapt and scale our existing tools to display differences in patient characteristics across many trials and a given target population and the potential relevance of those differences. These new tools will be readily usable for exploring differences in other substantive areas as well.

2) We will illustrate the usage and performance of these tools when drawing on aggregated (rather than individual level) data. This will expand their use profile, as obtaining individual-level data from a large number of trials and target populations can be time-consuming despite ongoing efforts to increase transparency and availability of trial data.[16] This time simply does not exist in pandemics like the one the world is currently facing.

3) We will track changes in trial and target population composition over calendar time. The types of individuals impacted by the pandemic in the United States has rapidly shifted from business travelers returning from international trips or academic conferences[17] to those with limited access to healthcare in vulnerable communities,[18] and these shifts may continue. As a result, even trials that are generalizable to those infected during the early stages of the pandemic may not be appropriate for estimating benefits and harms during the second or third waves of infection.

D. Study Design or Approach

D1. Overview. The primary objective of this supplement is to generate timely information on the representativeness and generalizability of COVID-19 related clinical trials. This work also extends our visualization tools and adapts them for use when individual-level data from trial and target populations are not available or when obtaining access to the data is cumbersome and time-consuming-as is often the case when quick responses are required.

D3. Data sources and study populations.

Trial data sources:

Trial data sources will be extracted from PubMed, Web of Science, clinicaltrials.gov, and the CDC library of gray literature COVID-19 articles. PubMed results will be limited to the “clinical trial” or “randomized controlled trial” subsection. Web of Science results will require the term “trial” in their title and will restrict to only English articles. The CDC database articles will require the term “trial” in their title, and clinicaltrials.gov will be limited to completed, terminated, interventional (clinical trial) with results. If any additional databases or COVID-19 specific resources emerge during the study periods (e.g. dedicated pre-print arXiv collections), they may also be used. The first pull of articles will come on October 31st, 2020, the second pull on January 31st, 2021, and the third and final pull on April 31st, 2021. We will identify articles using MeSH terms (i.e. COVID trials, COVID RCT, clinical trial) in their title, keywords, or abstract; these mesh terms will be refined as we create the abstraction form.

Target population data sources:

Initial target population data sources will be pulled from COVID-19 databases administered by the Johns Hopkins University Center for System Science and Engineering (JHU CSSE). This data includes an aggregation of each U.S. state level data. It is broken down into aggregated case count, death toll, people tested, and people hospitalized at the county level since January 22, 2020. The JHU CSSE dataset will be combined with the U.S. census data which include demographic characteristics (i.e. race, ethnicity, age, and gender) to characterize potential target populations. Because there may be disparities in impacted populations even at the county level, we will compare the results obtained using this methodology to data obtained directly from the North Carolina Department of Health and Human Services (NCDHHS), which reports race, ethnicity, age, and sex distributions for cases and deaths in the state.

In addition to the statewide and county level populations, we will be pulling potential population published in literature to look at more specific populations that may also have data on key clinical characteristics (i.e. hospitalized patients, patients with comorbidities). These target population data sources will also be extracted from PubMed, Web of Science, clinicaltrials.gov, and the CDC library of gray literature COVID-19 articles. Unlike the trials, they will not be pulled at specific times.

D4. Aim 1: A literature review will be conducted to describe the characteristics of patients enrolled onto COVID-19 clinical trials with publicly available results. We will characterize the eligibility criteria of randomized trials as well as the clinical and demographic characteristics of trial participants based on a systematic review of published randomized trials related to COVID-19.

D4a. Creating a literature review abstraction form:

A systematic literature review will be used to collect data from trial and target population data sources. A search in the PubMed and other data sources will be conducted from early 2020 to 2021 to find published randomized COVID-19 trials that include clinical and demographic characteristics of trial and target participants. To search for relevant literature, we will make a list of key MeSh terms such as COVID trials, COVID RCT, clinical trial, etc. to narrow our literature search. We will also take note of recurring citations within publications of interest. Randomized COVID-19 trials will include a spectrum of trials with different exposures and outcomes. The eligibility criteria for literature review will be 1) a randomized clinical trial and 2) COVID-19 related.

As a start, we expect to be extracting the following (where available) from each trial population and potential target population **(see Table 1)**: title of study, author, region/country of research, information on treatment, control/alternative treatment, outcome, total number of participants, and if provided, information regarding race, ethnicity, sex, smoking history, age, comorbidities, pregnancy, oxygen therapy, and BMI. We will also be identifying other key data points based on feedback from co-investigators.

Table 1: Information to be extracted from the randomized controlled trials and target populations	
Study identifiers	Title, first author, country/countries, publication date, enrollment dates
Key study information	Treatment and control, outcome, prevention vs treatment (hospitalized vs

	general), asymptomatic vs symptomatic, total number of participants
Demographic information	Race and ethnicity, sex, age, pregnancy, socioeconomic indicators
Clinical information	Smoking, comorbidities (incl. COPD, HTN, DM), pregnancy, BMI, O2 therapy

An example of the preliminary information we will be collecting is illustrated below using a trial that has already been published.[19]

Table 1: An example of the preliminary information we will be collecting

Study Identifiers	Title	Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe SARS-CoV-2 infection
	First Author	Borba
	Country/countries	Brazil
	Publication date	April 2020
Key Study information	Treatment and Treatment2	high-dosage CQ vs low-dosage CQ
	Outcome	higher CQ not recommended
	Hospitalized vs general	Hospitalized
	Asymptomatic v symptomatic	Symptomatic
	Total # of participants	81
Demographic information	Race	Black, Mixed, White
	Sex	Male, Female
	Age	Mean, sd (51.1, 13.98)
	Pregnancy	Yes/no
Clinical information	Smoking history	Never, Current, Former
	BMI	Median, IQR 28.1 (26-31.6)
	Oxygen therapy, hypertension, diabetes, alcohol use disorder, heart disease, asthma, chronic kidney disease, rheumatic diseases, liver disease, tuberculosis, HIV/AIDS	Yes/no

D4b. Evaluation of literature review abstraction form with the investigation team

After creating an initial literature review abstraction form and applying it to 10 different articles, we will take our preliminary data to the co-investigators on the project. Their knowledge will help us perform an additional refinement and improvement of the abstraction form before initiating the search proper. After the literature review abstraction form and the search terms are finalized, we will register the review on PROSPERO and begin in earnest.

D4c. Conducting the literature review.

The first pull of articles will come on October 31st, 2020, the second pull on January 1st, 2021, and the third and final pull on April 31st, 2020. During each phase, we will pull the full set of articles from each database meeting our search terms, then deduplicate articles based on authors and title. These articles will then be split among the reviewers on the research team, and the first sheet in the Excel document used to compile the results will be filled out, as will the Word document listing the various ways each study reported distributions of non-binary variables like age, smoking, or BMI. Actual abstraction of distributions be done once the first sheet has been completed. We will also track rejected articles so that we can analyze the proportion of articles rejected as non-trials.

After this abstraction, we will (for each phase of studies) summarize and synthesize common trends and themes of reported demographics and clinical characteristics for trial populations and analyze and interpret trends in the trial populations with respect to commonly reported demographics and clinical characteristics.

D4d. Deliverables and impact.

Output from this aim will include 1) the actual abstraction form, 2)publicly available Excel and Word documents shared on GitHub providing a concise description of the collected data, including data dictionary and protocol, 2) a manuscript documenting our methods and explaining significant findings based on the literature review, and 3) an abstract for submission to several different academic conferences (at minimum, the Society for Epidemiologic Research, the International Society for Pharmacoepidemiology, and ID Week).

D5. Aim 2: We will adapt visual tools to show differences between COVID-19 trials participants and real-world target populations. We will expand visualizations we have developed to show differences between aggregate data on COVID-19 patients in trials and existing and future target populations, as well as how these groups change over time. This process will proceed in several different stages.

D5a1. Drafting figures with toy data.

We will begin by creating “toy” simulated data for both trial and target populations, including simulated time trends in both the target population and the type of patients that are willing to enroll. These “toy” trial and target populations will be representative with respect to some variables and non-representative with respect to others. Moreover, data on some covariates will be set to “missing” in some of the trials to mimic a lack of data on effect modifying covariates in real-world data.

After creating these synthetic cohorts, we will experiment with the best ways to adapt to the visual tools we already created during this PCORI award using SAS graphics. After developing a first draft of these figures

with the core study team, these visual tools will be circulated to the other team members to gather feedback on both style and substance. This feedback will be incorporated into the second generation of figures.

D5a2. Generating the figures with real data.

Once the figures are acceptable in the context of the toy data, we will move on to apply them to the organized data sets created during Step D4c. In this step, we expect to require several additional steps of refinement and adaptation. Once we have finalized the look of the figures, we will draw on the Excel database created in Step 4C to create different visualizations for each potential target population and each potential category of treatment (prophylactic treatment, treatment in hospitalized patients, treatment in symptomatic individuals, etc.). These figures will receive an additional round of review by the study team.

D5b. Deliverables and impact.

Output from this aim will include 1) publicly available SAS and R code on the GitHub to generate the figures from our Excel databases, including clear documentation, 2) an abstract for submission to several different academic conferences (at minimum, the Society for Epidemiologic Research, the International Society for Pharmacoepidemiology, and ID Week), and 3) a manuscript documenting our methods and explaining their utility alongside sample code for submission to a major academic journal.

We believe that the results of this specific aim will be very useful for those interested in studying the generalizability and representativeness of large numbers of trials simultaneously, as well as those specifically interested in infectious disease trials and COVID-19. By adding to the tools available to researchers and those conducting systematic reviewers, we hope to enable and encourage future work involving systematic reviews of trial representativeness and generalizability to explicitly consider multiple different target population, the association of the covariates in question with the outcome, and trends in the trial population over time.

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For detailed instructions, refer to the Application Guidelines for the PFA. Do not exceed 10 pages.

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