ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium)

A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious disease

Analysis Plan for ISARIC International COVID-19 Patients

Please complete the following sections:

Title of proposed research
Rate of implementation at sites participating in a platform trial compared to sites without a platform trial: An observational study of critically ill COVID-19 patients
Version: (Date: Day/Month/Year)
Version 1: 04/03/2024
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Final draft SAPs will be circulated to all ISARIC partners for their input with an invitation to participate. ISARIC can help to set up collaborator meetings; form a working group; support communications; and accessing data. Please note that the details of all approved applications will be made publicly available on the ISARIC website. Please complete all sections of this form fully and return to **ncov@isaric.org**

Introduction

The COVID-19 pandemic accelerated the acceptance of platform trials to efficiently and effectively answer various research questions (1). The success of platform trials during the COVID-19 pandemic is largely attributed to the ability to add new treatment arms, the shorter time to observe outcomes, the unprecedented levels of coordinated collaborative efforts, and the influx of additional resources to overcome many challenges that have deterred their implementation in the past (1, 2). Platform trials bring complexity in trial implementation and planning and require sufficient incentives for sponsors to initiate the designing of a platform trial (3). Consequently, the expansion of platform trials to other therapeutic areas is severely limited by available funding (2).

Although platform trials have proven efficiencies regarding time and costs for determining optimal therapies (2), the return on investment of platform trials has yet to be established. The overall cost of trials is a complex, multilayered issue, but the return on investment of trials largely amounts to how quickly and effectively the trial generates evidence and the findings are implemented into practice (4). Increasing the value of investment in clinical trials means reducing the cost per patient recruited (5) and speeding up the overall process of getting the best therapies to patients (6) without compromising high-quality trial evidence (2). Determining effective treatments more quickly and with fewer resources would be desirable to researchers, regulators, and patients to ensure that costs, time, and patient numbers are minimized, and the optimal therapies, doses, and treatment durations are promptly embedded in practice. Understanding how evidence generated from platform trials translates into practice, therefore, can illuminate the mechanisms underpinning trial efficiencies, identify opportunities to enhance implementation efforts, and ensure patients receive the best care.

This study aims to determine differences in implementation (or de-implementation) rates of effective, harmful, or futile COVID-19 therapies for critically ill patients among sites participating in a platform trial compared to sites not participating in a platform trial. We will meet the aim in the context of a COVID-19 pandemic platform trial, REMAP-CAP, because the COVID-19 pandemic provided a unique research environment for which timely research translation was vital (1). REMAP-CAP is a global adaptive platform trial for adult patients with community-acquired pneumonia (CAP) and patients with suspected or proven COVID-19 infection in the intensive care unit (ICU).

The COVID-19 Clinical Database, hosted by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), will be used to access individual patient data on COVID-19 patients in the intensive care unit between January 2020 to December 2022. Additional data collected in the Critical Care Asia and Africa (CCAA) database, comprising 16 clinical registries, will be linked to the COVID-19 Clinical Database. A list of participating sites will be collected from the REMAP-CAP project team to identify patients in the dataset admitted to an ICU participating in the REMAP-CAP trial.

Changes in practice (i.e., the proportion of patients receiving the therapy) following the publication of trial results will be observed at sites participating in REMAP-CAP and sites not participating in REMAP-CAP. The proportion of COVID-19 patients receiving various therapies will be determined by dividing the number of patients receiving therapies of interest and the total patients treated at individual ICU sites per month over the study period. We will also explore regional differences in implementation rates. Interrupted time series logistic regression will be used to explore differences between REMAP-CAP sites and sites not participating in REMAP-CAP in the implementation rate of effective therapies and de-implementation rate of harmful and futile therapies after domain publications. We hypothesize the implementation rate of effective COVID-19 therapies and de-implementation rate of harmful and futile COVID-19 therapies was higher among sites participating in REMAP-CAP than sites not participating in the REMAP-CAP trial.

Participatory Approach

All contributors to the ISARIC database are invited to participate in this analysis through review and input on the statistical analysis plan and resulting publication. The outputs of this work will be disseminated as widely as possible to inform patient care and public health policy, this will include submission for publication in an international, peer-reviewed journal. ISARIC aims to include the names of all those who contribute data in the cited authorship of this publication, subject to the submission of contact details and confirmation of acceptance of the final manuscript within the required timelines, per ICMJE policies and the ISARIC publication policy.

Research Plan

Summary of Research Objectives
This observational study aims to determine the implementation (or de-implementation) rates of effective, harmful, and futile COVID-19 therapies for critically ill patients among sites participating in the REMAP-CAP trial compared to sites not participating in the REMAP-CAP trial.
Proposed Target Population
Adult patients admitted to the ICU between January 2020 and December 2022 with clinical suspicion or laboratory confirmation of severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) infection (as defined by the World Health Organization [WHO]) (7, 8) and admission to the hospital for acute illness due to COVID-19 will be included. Patients must also have available information on age, sex, and site to be included in the analysis. Patients admitted to an ICU participating in the REMAP-CAP trial will be identified using the site code.

Clinical Questions/Descriptive Analyses

1. What are the proportions of critically ill COVID-19 patients receiving effect, futile, and harmful therapies by site between January 2020 and December 2022?
2. What are the differences in implementation rates—the rate of use of effective, harmful, and futile therapies—following REMAP-CAP domain publication between REMAP-CAP sites and sites not participating in REMAP-CAP?
    a. What are the regional differences in implementation rates?
3. What are the differences in the time to implementation of effective and de-implementation of harmful and futile therapies following REMAP-CAP domain publication between REMAP-CAP sites and sites not participating in REMAP-CAP?
    a. What are the regional differences in time to implementation and de-implementation?

Planned Statistical Analyses, Methodology and Representation

The primary outcome is the evolution of proportions of COVID-19 patients receiving various treatments at sites participating in REMAP-CAP and sites not participating in REMAP-CAP. We will explore effective, futile, and harmful therapies, such as corticosteroids, tocilizumab, sarilumab, convalescent plasma, antiviral, and antiplatelet therapies. The proportion of COVID-19 patients receiving various therapies will be determined by dividing the number of patients receiving therapies of interest and the total patients treated at individual ICU sites per month over the study period. We will aim to determine eligibility for an intervention where data are available.

Additional data collected in the CCAA database will be linked to the COVID-19 Clinical Database via the subject identifier. A list of participating sites will be collected from the REMAP-CAP project team to identify patients in the dataset admitted to an ICU participating in the REMAP-CAP trial. Changes in practice following the release of trial results (i.e., the proportion of patients receiving the treatment) will be observed at sites participating in REMAP-CAP and sites not participating in REMAP-CAP.

Publications associated with relevant therapies will be accessed to determine whether treatments were effective, futile, or harmful for COVID-19 patients.

Reporting will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (9).

Interrupted time series logistic regression will be used to explore differences in implementation rates of effective therapies and de-implementation rates of harmful and futile therapies following domain publication among sites participating in REMAP-CAP compared to sites not participating in REMAP-CAP. We will also explore dates of regulatory approval and guideline development, where possible. As existing knowledge of how the publication impacts the implementation rate is limited, selecting the most appropriate impact model is difficult and will require exploratory analysis of the data.

Descriptive analysis will be undertaken to identify trend, seasonality, data representativeness, data missingness, and outliers. We will also investigate site characteristics, such as participation in other trials and research studies, that may expound early intervention adoption and adherence to guidelines regardless of REMAP-CAP participation. Autocorrelation and partial autocorrelation will be explored. Furthermore, there is neither a formula to calculate the minimum sample size nor consistent recommendations to ascertain the minimum number of time points needed. Once the data are available, we will determine the appropriate number of time points based on the sample size. Analyses will be conducted in the latest version of R.

Handling of Missing Data

Study size will be determined by the subset of hospitalized COVID-19 patients who were admitted to the ICU over the study period. To manage site workloads and high proportion missing data, not all interventions were collected for each site. For some patients, information on receipt of certain treatments may not be available. In this case, the proportions of COVID-19 patients receiving various treatments may use only those with available information collected in the pre-specified question in CRF.

Other Information

Preliminary results will be presented at the ISPOR 2024 Conference in Atlanta, Georgia in May. I also plan to present the results at ISARIC in-person in July 2024, if possible. We aim to publish the results in a high-impact journal as soon as results are available.

References

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