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
The utility and limitations of clinical trials and cohort studies to determine treatment efficacy during a disease outbreak.
Version: (Date: Day/Month/Year)
19FEB2021
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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**

[1] Either chair and/or co-chair are based in an institution in an LMIC. If you would like to be connected with an eligible co-chair please let us know at ncov@isaric.org.

Introduction

The COVID pandemic has exemplified a common problem in emerging infectious disease outbreaks. There are no proven therapies at the beginning at an outbreak, but there is significant pressure to provide patients with treatments that may improve outcomes. Since gathering of the highest quality data - through clinical trials - has historically lagged behind the epidemiological curve, decisions to treat are often based on extrapolation of preclinical data and inferring cause and effect from associations in observational data.
In this manuscript, we demonstrate the utility, and the limitations of observational data to determine drug safety and efficacy, by exploration of an international observational dataset and by comparing observationally collected data in the ISARIC international cohort, with the outcomes of the RECOVERY trial for corticosteroids.

Participatory Approach

This is the standard ISARIC collaborative analysis approach. Please amend if you would like to suggest any changes.

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
1) Describe use of corticosteroids for hospitalised patients with COVID-19 2) Compare the association of corticosteroids with mortality, among patients in observational studies, with effects of corticosteroids as measured in RCTs. Where discrepancies exist, explore potential underlying reasons of variation in outcomes, including bias. 3) Compare assessment of safety of corticosteroids in patients using observational data with RCT data. Where discrepancies exist, explore explain potential underlying reason sources of variation in outcomes, including bias. 4) Compare similar observational and RCT analyses for other agents (such as, but not limited to hydroxychloroquine and remdesivir) should feasible approaches be identified using corticosteroids as an example.
Proposed Target Population
Observational data will be included if: • Patients are hospitalised • Patients have clinically suspected or laboratory confirmed SARS-CoV-2 infection

- It is known that the patient did, or did not receive corticosteroids
- All age groups will be included
- Pregnant and post-partum women will be included.

Observational data will be excluded if:

- The primary outcome (discharge or death by Day 28 following hospitalization*) is not known.

  * where day of hospitalization is a proxy for day of randomization in a clinical trial.

Clinical Questions/Descriptive Analyses

Exploration of completeness of observational data

- proportion of patients receiving corticosteroids for whom the drug, route of administration, duration of therapy and and dose and total dose was known, converted to a common equivalent corticosteroid dose
- proportion of patients for whom pre-admission use of corticosteroids was known.
- proportion of patients for whom admission to ICU/HDU was known
- proportion of patients for whom details of oxygen therapy (NP, HFNO, mask, NIV, IMV) and inotrope/vasopressor support is known.
- proportion of patients for whom administration of oxygen therapy was known
- proportion of patients for whom a drug adverse event was identified.

Exploration of dexamethasone use in hospitalised patients

- proportion of patients receiving dexamethasone based on hypoxemia (Spa02) and PaO2/FiO2 ratio where this is available.
- proportion of patients receiving corticosteroids based on level of respiratory support (on arrival)
- proportion of patients receiving corticosteroids based on level of respiratory support (at anytime during admission)
- proportion of patients receiving corticosteroids stratified by days after symptoms onset
- proportion of patients who received corticosteroids stratified by comorbidities.
- proportion of patients who received corticosteroid stratified by country
- proportion of patients who received corticosteroid therapy
  - by age
  - by gender
  - by ethnicity
  - by comorbidity (asthma, COPD, diabetic, other immune and rheumatologic)
- proportion of patients who were prescribed corticosteroids before and after publication of the RECOVERY findings.
- Statistical analysis of variation of drug administration across treatment groups.

Side by side comparison of outcomes for observational vs RCT data with assessment of biases to explain discrepancies.

Planned Statistical Analyses, Methodology and Representation

Outcomes of interest:

- all-cause mortality within 28 day s of hospitalization/randomization (hazard ratio from Cox regression) and at 6 months
    - for subsets based on level of respiratory support at hospitalization (no oxygen therapy, supplementary low flow oxygen, High flow nasal cannula, NIV, IMV, ECMO)
    - adjusted by age.
- time until discharge
- In the proportion not using IMV or ECMO at time of hospitalization, subsequent use of IMV or ECMO following hospitalization, or death.
- Requirement and duration of ventilation (in survivors).
- Requirement and duration of renal HD or HF.

Causal inference methods

- Unadjusted comparison of baseline characteristics and outcomes of patients who received, and did not receive dexamethasone
    - Method: chi-square or Fisher exact for categorical, Student T or Mann-Witney U for continuous.
        - case studies on selection bias
        - case studies on immortal time bias
        - discussion regarding propensity to treat
        - case study of simpson's paradox (perhaps using anticoagulation)
- Case-control approach
- Logistic regression models
    - tiered approach to inclusion/exclusion of variables
- Cox proportional Hazards Regression
    - with dexamethasone as a time-varying covariate
- Marginal structural model

Handling of Missing Data

Preliminary analysis would be performed to ascertain a detailed overview of the extent of missingness in the data. This should enable the identification of variables which lack sufficient data to allow for any useful analysis to performed on them. Type of missingness shall be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. Variables with greater than 30% missingness will be excluded from analysis. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE).

Other Information

The outputs of this work will include submission for publication in a peer-reviewed journal.

References

Please list any relevant references.

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