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

Title of proposed research
Can observational data answer questions about treatment effects during an emerging infectious disease outbreak? Trial emulation of oral or intravenous corticosteroid for patients admitted to hospital with covid-19
Version: (Date: Day/Month/Year)
3.0, 10 May 2023
Working Group Chair (name, ORCID ID, email, institution, country)
Mark G Pritchard, 0000-0003-1726-8989, mark.pritchard@ndm.ox.ac.uk, University of Oxford, United Kingdom
[1]Working group co-chair (name, ORCID ID, email, institution, country)
Jose Andres Calvache, 0000-0001-9421-3717, jacalvache@unicauca.edu.co, Universidad del Cauca, Colombia

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

[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.

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

Prompt, accurate and relevant data are essential for the effective response to an emergent pathogen. World Health Organization—ISARIC case report forms are designed to allow rapid collection and reporting of data early in an outbreak of a pathogen of public health interest.[1,2] Data collected using these forms for patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) were published in January 2020.[3] International sharing of data led to ISARIC's first collaborative report in March 2020.[4] The report in March 2022 included data on 800 thousand people admitted to hospital with covid-19.[5] Despite collecting data on treatments and outcomes, no estimates of treatment effectiveness have been reported using the multinational ISARIC dataset. Such analyses have been avoided since inadequate control of confounding could lead to biased conclusions. The desire for prompt answers must be balanced against the danger of causing harm with misleading conclusions about treatments. Dexamethasone is an ideal candidate for assessment of the utility of observational treatment data: there are clear clinical trial results and the drug is widely used in intensive care and other acute clinical settings.

The RECOVERY (Randomised Evaluation of Covid-19 Therapy) trial produced the first finding of a beneficial treatment for patients with covid-19. It found that dexamethasone improved survival for patients admitted to hospital with covid-19 who required supplementary oxygen therapy but did not benefit patients not requiring supplementary oxygen. These results were released via press release on 16 June 2020,[6] on a pre-print server on 22 June 2020,[7] and online first in a peer-reviewed journal on 17 July 2020.[8] Further investigation has found that higher doses of steroids are harmful for patients requiring only simple oxygen therapy but the optimal dose for patients requiring ventilatory support is unanswered.[9]

Trial emulation methods have been used to reduce bias in estimates of causal effects from observational data,[10,11] including an analysis of corticosteroid use for patients with covid-19 and severe hypoxia.[12] These methods aim to generate conditional exchangeability between the intervention and control groups by accounting for observed variables that correlate with greater likelihood of intervention. This requires knowledge about the treatment received and covariates before treatment. Most ISARIC case report forms did not give detailed information on treatments. We anticipate only being able to use a subset of the ISARIC cohort. We will initially perform the analysis for an intervention of any corticosteroid treatment at

any dose. If sufficient data are available we will then repeat this for specific doses of dexamethasone.

In this analysis, we will investigate whether a trial emulation analysis using the ISARIC multinational cohort could reproduce the result of the RECOVERY trial (Table). Secondarily, we will explore:

1. how soon into the pandemic this result could have been obtained (with the data as collected and under assumptions of greater data completeness),
2. whether the observational data collected by the ISARIC Clinical Characterisation Group could answer secondary questions about the optimal dose of dexamethasone,
3. whether a timely report of treatment effects from observational data could have beneficially affected clinical practice.

	Protocol for the Ideal Target Trial (Pragmatic)	**Protocol for the Emulated Trial**
Eligibility criteria	Patients admitted to hospital diagnosed with covid-19 without prior exposure to corticosteroid treatment in the previous 28 days.	Patients admitted to hospital who have covid-19 and who were not receiving corticosteroid treatment in the previous 28 days. - Excluded if admitted in a country with fewer than 100 total eligible patients, violation of time zero, missing data.
Recruitment period	2020-2021	ISARIC data
Follow-up duration	- Start: trial initiation - End: the end of hospitalization, death	- Start: trial initiation - End: the end of hospitalization, death
Outcome(s)	28-day in-hospital mortality	28-day in-hospital mortality
Treatments to be compared	1. Corticosteroids 2. Standard treatment without use of corticosteroids	1. Start of at least one dose of corticosteroids 2. No doses of corticosteroids
Causal contrast	Risk difference	Risk difference
Analysis plan	GLR modeling with robust SEs	GLR modeling with propensity score methods, IPW, ML accounting for confounding

Results of this analysis are not expected or intended to change clinical practice. They will instead inform discussions of the utility of collection and analysis of data on treatments in future versions of the ISARIC data collection protocol.

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, including submission for publication in an international peer-reviewed journal. This analysis explicitly aims to compare observational results to those from a published randomized controlled trial, and is not intended to inform patient care or public health policy. 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
Primary objective 1) To use trial emulation methods to estimate the effect of treatment with corticosteroids on 28-day in-hospital mortality for patients admitted to hospital who have covid-19 and who were not receiving corticosteroid treatment in the previous 28 days. **Secondary objectives** 1) Subgroup analyses of primary outcome: a. age and sex b. level of respiratory support at time of decision whether to start corticosteroid treatment* (none, oxygen without invasive mechanical ventilation, invasive mechanical ventilation) c. days since symptom onset at time zero (≤7 days, >7 days) 2) Explore the effect of different approaches, such as machine learning techniques, to controlling for confounding 3) Describe use of corticosteroids for hospitalised patients with covid-19 4) Estimate how soon into the covid-19 pandemic conclusions on the causal effect of corticosteroid on outcomes might have been possible, and the confidence that would have been associated with such estimates. 5) Explore whether questions regarding optimal dosing of corticosteroids can be answered using the multinational ISARIC covid-19 dataset

6) Explore the validity of any conclusions in different countries that did not contribute sufficient data to be included in the analysis.

* In a randomized trial, this would be the time of randomization. For the trial emulation we use a time-zero on which a patient is eligible for admission to the trial and we know whether or not they started taking a corticosteroid.

Proposed Target Population

Target trial population
Inclusion criteria

- Patients in hospital who have covid-19
- Patients of any age and sex

Exclusion criteria

- Use of oral or intravenous corticosteroids in the 28 days prior to time zero.*

Note that an interventional study would exclude participants with a contraindication to the study treatment but we do not require that as an exclusion criterion in this analysis. Instead, we include any contraindications as confounders to be used to calculate the propensity score. This propensity score will then be used to create a pseudopopulation that emulates the trial (see methodology section).

Trial emulation
Exclusion criteria

- Admitted in a country with fewer than 100 total eligible patients for the emulated trial, as this may make propensity score less reliable
- Hospital admission and diagnosis of covid-19 are both more than 28 days prior to time zero as data collection for these patients is expected to be different from the main cohort.
- Exclusions due to missing data (see below).

* In a randomized trial, this would be the time of randomization. For the trial emulation we use a time-zero on which a patient is eligible for admission to the trial and we know whether or not they started taking a corticosteroid.

Clinical Questions/Descriptive Analyses

Descriptive analyses
For all patients included in the analysis,

- plot recorded use of corticosteroid over time
- repeat plots over time for each planned subgroup
- tabulate presence of data completeness for each confounder
- Summarise data against exposure arm and outcome

Planned Statistical Analyses, Methodology and Representation

Patients may be eligible for the emulated trial on more than one day in the dataset. We will create a record for each eligible patient-day including the most recently available data on confounders. For each record, day zero will be defined as the day on which the patient was eligible to join the emulated trial.

Treatment comparison
Our emulated treatment comparison is at least one dose of oral or intravenous corticosteroid *vs* no doses of oral or intravenous corticosteroid.

Emulation of randomization
We will calculate a propensity score for the probability of receiving treatment using logistic regression models with confounders selected according to the disjunctive cause criterion (any pre-exposure covariate believed to cause the exposure, the outcome or both).[13] The change in practice that followed publication of the RECOVERY trial means that we expect a highly non-linear association between treatment and calendar time, and that this relationship will have an interaction with level of respiratory support, and we will explore the optimal way of modelling this. For a secondary analysis we will explore machine-learning methods for generating a propensity score.

We create a pseudopopulation for the trial by weighting each record by the inverse probability of treatment. We stabilize these weights by using the overall probability of treatment as the numerator. To avoid extreme results, we set the 1% largest weights to the 99th percentile.

Censoring
Patients will be censored when they are lost to follow-up (for example by discharge to another hospital site where data are not being collected), at the most recent date of data collection, or on non-adherence to allocated treatment (i.e. receipt of corticosteroid by patients following the no-steroid arm).

Discharge home or to social care is a competing risk and patients who reach this outcome are censored at day 29. For all other censoring events, we calculate the risk of censoring using a logistic regression model and create an inverse probability of censoring weighting to create an uncensored pseudopopulation. We stabilize these weights by using the overall probability of censoring as the numerator. To avoid extreme results, we set the 1% largest weights to the 99th percentile.

List of confounders at the time of eligibility for the analysis

Variables included in the propensity score for treatment
Calendar time Age Sex Country Time since admission to hospital Time since covid-19 diagnosis Nosocomial diagnosis (y/n) Pregnancy Asthma Chronic obstructive airways disease Hypertension Total number of comorbidities† Most recent respiratory rate Most recent peripheral oxygen saturation in room air Most recent Glasgow coma scale (15 vs <15) Most recent urea Most recent C reactive protein Most recent lymphocyte count Most recent oxygen therapy (none, oxygen without invasive mechanical ventilation, invasive mechanical ventilation) 4C Mortality Score[14] ISARIC 4C Deterioration Score[15]
* From the list chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease (estimated glomerular filtration rate ≤30 mL/min/1.73 m^2), mild to severe liver disease, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus (diet, tablet, or insulin controlled), HIV or AIDS, malignancy, clinician-defined obesity[14,15] † The value recorded on or the latest before time zero.

Emulated trial analysis

Using the pseudopopulation in which confounders are equally distributed between those who did and did not receive corticosteroid and in which the effect of censoring is controlled, we use a pooled logistic regression to compare 28-day mortality in those who do and do not receive steroid.

For each planned subgroup analysis, we assess the subgroup-specific outcome and the difference between this outcome and that for the whole study cohort.

We will display a weighted Kaplan—Meier analysis to compare 28-day mortality in those who do and do not receive steroid in the whole study cohort and in each subgroup.

To determine how quickly this result could have been achieved, we repeat the main analysis with data cut-offs at the end of each calendar month of the pandemic. We assume that repeat testing would not have been a concern and examine the result that would have been achieved from a trial emulation each month.

We will explore how many patients in the dataset have corticosteroid doses reported, and how much these vary. If significant numbers have different doses reported, we will repeat the trial emulation with different doses as different treatment arms. (As sufficient data are unlikely to be available we will provide a more detailed plan for this analysis once we have explored the doses available.)

Handling of Missing Data

We exclude all patients with missing age, sex, country, corticosteroid use or corticosteroid start date. Missing / unreported comorbidities are initially assumed to be absent. Reported confusion or altered mental state are both taken as Glasgow coma score <15. Values for covariates stated above to be used as 'most recent' use the last non-missing value on or prior to the date being considered. Other missing data will be imputed using Multiple Imputation by Chained Equations. When using machine learning methods to calculate propensity scores, method-specific approaches to handling missing data will be explored. We will conduct sensitivity analyses to explore the consequences of different methods of handling missing data.

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