PATIENT-IMPORTANT OUTCOMES REPORTED IN CLINICAL STUDIES OF PHARMACOLOGIC TREATMENTS FOR COVID-19: A PROTOCOL OF A META-EPIDEMIOLOGICAL STUDY

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ABSTRACT

Background: The coronavirus disease 19 (covid-19) pandemic has underscored the need to expedite clinical research, which may lead investigators to shift away from measuring patient-important outcomes (PIOs), limiting research applicability. We aim to describe the extent to which randomized controlled trials (RCTs) of covid-19 therapies will determine PIOs. **Methods:** We will perform a meta-epidemiological study of RCTs that included people at risk for, or with suspected, probable, or confirmed covid-19, examining any pharmacological treatment or blood product aimed at prophylaxis or treatment. We will obtain data from all RCTs identified in a recent published network metanalysis (NMA). To categorize the outcomes according to their importance to patients, we will adapt a previously defined hierarchy: a) mortality, b) quality of life/ functional status/symptoms, c) morbidity, and d) surrogate outcomes. Outcomes within the category a) and b) will be considered critically important to patients, and outcomes within the category c) will be regarded as important. We will use descriptive statistics to assess the proportion of studies that report each category of outcomes. We will perform univariable and multivariable analysis to explore associations between trial characteristics and the likelihood of reporting PIOs. **Discussion:** The findings from this meta-epidemiological study will help health care professionals and researchers understand if the current covid-19 trials are effectively assessing and reporting the outcomes that are important to patients. If a deficiency in capturing PIOs is identified, this information may help inform the development of future RCTs in covid-19.

Open Science Framework registration: <https://osf.io/6xgjz/>

Keywords: Patient-important outcome, reporting, treatment, prevention, coronavirus, covid-19.

BACKGROUND

Healthcare systems worldwide have called for the increased involvement of lay people, which has led public and patients to become more active in their own health and health care decisions. Patient-important outcomes (PIO) are gaining wide acceptance in most fields of clinical research with clinicians and researchers advocating for “the patient at the center” of medical decision making (1).

This trend has provoked a shift when recommending interventions. In the past, the magnitude of the effect as “clinically relevant” was considered as the most relevant factor; judgments have replaced this as to whether effects are it is “patient-important” (1). The notion of “patient-important” sheds light on the individual clinical encounter and the importance of patients’ values and preferences. In clinical research, a PIO has been previously defined as: “a characteristic or variable that reflect how a patient feels, functions or survives” (2, 3).

This change in clinical decision-making paradigm represent a shift from a parental model of care in which the clinician decides the relevant outcomes to a patient-centered approach involving patients’ values and preferences (1). This shift becomes especially important when one considers that, despite compelling physiological rationale, interventions’ that impact on surrogate outcomes such as laboratory results often fail to achieve patient-important benefit (4).

Thus, including PIOs become of essential importance when assessing the benefits and harms of a new therapy. However, despite this potential, PIOs are often not the focus of clinical trialists. Because a focus on surrogates results in trials that are faster, cheaper, and require fewer patients, many trialists focus on endpoints that are not in themselves important

(5). Health care providers and administrators perceive time to collect and input data as the greatest barriers to PIO implementation (6). However, given the repeated failure of intervention effects on surrogate outcomes to align with effects important to patients, the result may be implementation of useless or even harmful interventions (7).

In the coronavirus disease 19 (covid-19) pandemic, researchers are rushing to test pharmacological interventions that may decrease the personal and social burden of the disease as well as making producing associated guideline recommendations (8). The need to obtain expedient answers may lead investigators to shift away from PIOs, which can lead to unresolved questions regarding the benefits and harms of the treatments. In an effort to standardize outcome measures in covid-19 studies, the World Health Organization has developed a minimal set of common outcome measures for ongoing and future covid-19 studies (9). With hundreds of current and future covid-19 RCTs ongoing or planned, it is essential to understand the outcomes being evaluated.

METHODS

The protocol for this meta-epidemiological study is registered in Open Science Framework (OSF) (<https://osf.io/6xgjz/>) and the study will be conducted and reported in line with international standards (10, 11). For the development of the present protocol, we used to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (12) (see Additional File 1). This project is associated to a recently published network metanalysis (NMA) that compared the effects of treatments for covid-19 (13).

Data source and eligibility criteria

We will obtain data from all randomized controlled trials (RCTs) identified in a recent published NMA (13) published until September 2020, that a) included people at risk for, or

with suspected, probable, or confirmed covid-19 and b) include any pharmacological treatment or blood products intervention aimed either at prophylaxis or treatment vs placebo, standard care, an alternative intervention and/or no intervention. We will apply no restrictions based on illness severity or setting. We will include studies regardless of their publication status (peer reviewed, in press, or preprint) or language.

Data extraction and coding

We will use a standardized data extraction form to collect the data from included studies. Pairs of reviewers will extract data and classify the outcomes independently and in duplicate. Disagreements between reviewers will be resolved through discussion and consensus. If necessary, a third reviewer will be consulted.

The following details will be extracted:

- Type of publication (peer-reviewed vs. preprint)
- Patient characteristics (age, gender, disease severity, and comorbidities)
- Covid-19 diagnosis method (nucleic tests vs. clinical criteria)
- Publication characteristics (country, type of funding, trial phase, sample size, design, whether the study protocol had been previously published)
- Interventions' characteristics (doses, routes and duration of administration)
- Outcomes (standard mean or standard mean difference for continuous outcomes, and odds ratio or relative risk for dichotomous outcomes).

We will extract information for all outcomes (primary and other), along with their corresponding definition. We will categorize the outcomes according to their importance to patients adopting a previously established hierarchy (14-16), which was adjusted to include, but not limited to, relevant outcomes in COVID-19, as follows:

a) Mortality	<ul style="list-style-type: none"> • all-cause mortality • disease-specific mortality
b) Quality of life / Functional status / Symptoms	<ul style="list-style-type: none"> • mental health • physical health • prevalence of fever • clearance time of fever • prevalence of dyspnea, • clearance recovery time score of clinical symptoms • pneumonia severity index
c) Morbidity	<ul style="list-style-type: none"> • respiratory support (e.g., respiratory failure occurred, need for respiratory support, mechanical ventilation required, duration of mechanical ventilation, frequency of requirement for mechanical ventilation, ventilator free days, need for non-invasive mechanical ventilation, including noninvasive ventilation (NIV) and high flow nasal cannula (HFNC), prevalence of mechanical ventilation) • cardiovascular major morbid events (e.g. stroke, myocardial infarction) • other major morbid events (e.g., intensive care unit (ICU) admission, shock occurrence, prevalence and time of progressing to severe or critical types, renal replacement therapy, vasopressor support) • incidence/prevalence of severe acute respiratory distress syndrome (ARDS) coronavirus 2 disease (e.g., recovery

	prevalence) and other chronic diseases (e.g., COPD exacerbation, new onset of diabetes) <ul style="list-style-type: none"> • hospitalization, medical and surgical procedures (e.g., length of hospital stay, time to achieve a normal respiratory rate, rate of survival,) • organ failure (in addition to pulmonary) • adverse events or side effects (any)
d) Surrogate outcomes	<ul style="list-style-type: none"> • viral load, virus antibody level, oxygen saturation, arterial blood-gas analysis, lymphocyte count, PaO₂/FiO₂, C-reactive protein (CRP) level, time for CRP return to baseline, time to negative conversion of severe acute respiratory syndrome coronavirus 2, lesions progression within 24–48 h in pulmonary imaging

Outcomes within the category a) and b) will be considered critically important to patients, and outcomes within the category c) will be regarded as important (14). Outcomes within category d) will be regarded as not patient-important. We will identify the “most patient-important outcome” of each study as the outcome that pertains to the highest level of the hierarchy (16). For the primary outcome (as reported by the authors) and the most patient-important outcome, we will determine if it is one of benefit or harm and will extract the relative and the absolute effect estimates used to report the outcome results. Data of the risk of bias assessment will be also obtained from the original NMA (13).

Data synthesis

We will use descriptive statistics to summarize the study characteristics. We will use frequencies and percentages to describe the proportion of studies that report:

- Each individual outcome in each study.
- Each outcome category (a to d).
- A PIO (category a or b or c) as the primary outcome of the study.
- The most PIO as the primary outcome of the study.

Bivariate analyses (odds ratios and their associated 95% confidence intervals) will be performed to explore associations between trial characteristics and likelihood of reporting PIOs. To test possible predictors, we will perform multivariable analyses, using logistic regression, with PIO (yes/no) reported as the dependent variable where it will be positive if a trial included PIOs as the primary outcome in its report. We plan to conduct more than one multivariable analysis because the dependent variable can be different according to the most patient important outcome (category a or b or c). The independent predictors will include: 1) type of funding (industry supported vs non-industry supported); 2) number of patients (every additional 100 patients); 3) severity of disease (mild/moderate or mixed vs severe, in not prophylactic RCTs); 4) follow-up duration (for every additional 30 days); 5) type of publication (regular vs. preprint); 6) risk of bias (high vs low); 7) prophylaxis trials vs treatment trials; and 8) pharmacological interventions vs blood products. The rationale for choosing these predictors is 1) patient-important outcome reporting may be more frequent in non-industry supported studies; 2) smaller trials may be less likely to report patient-important outcomes because they are not powered for these outcomes; 3) trials enrolling patients with severe disease, may be more likely to report patient-important outcomes; 4) trials with shorter follow-up duration may be less likely to report patient-important outcomes because mortality and morbidity events possibly require longer time to occur; 5) publication in an indexed journal after peer review are expected to report more patient-important outcomes; 6) studies that report patient-important outcome may display an overall lower risk of bias; 7) prophylaxis trials may be less likely to report patient-important outcomes; and 8) pharmacological intervention trials may be more likely to report patient-important outcomes.

We will classify the studies as high or low risk of bias using the same threshold reported by Siemieniuk et al (13). A study will be classified with an overall high risk of bias if one or more domains were rated as some concerns- probably high risk of bias- or as high risk of bias; and as overall low risk of bias if all domains were rated as some concerns-probably low risk of bias- or low risk of bias. This systematic review is nested in a previously published NMA, which will be updated. According to Peduzzi et al. (17)., the minimum required sample size should be based on the rule of 10 event per independent variable. Since in the published NMA, 39 out of 41 trials evaluated PIOs and the planned number of predictors is 8, we will include all trials that meet the inclusion and exclusion criteria. We estimated that we need at least 80 trials that measured PIOs. However, we need to add 5% (n=4) trials that will not evaluate a PIO and 20% (n=16) that will not evaluate the 8 predictors at the same time. This meant that we need to include 100 trials. Considering that trials are usually underpowered to detect predetermined significant differences in their primary outcomes, we considered primary outcomes in our main analysis and conducted sensitivity analysis using both primary and secondary outcomes.

DISCUSSION

To our knowledge, this protocol describes the first meta-epidemiological study that specifically examines the frequency of PIOs reporting in RCTs in covid-19. Previous studies have described the frequency of PIOs in systematic reviews that included RCTs in diabetes (5) and critically ill patients (18). Umbrella reviews have also explored the frequency of PIOs included in systematic reviews of therapeutic interventions for different conditions (19), in the full texts and abstracts of Cochrane and non-Cochrane reviews (14), and in a systematic review that explored whether the outcomes reported in the summary of finding tables (SoF) of Cochrane systematic reviews included PIOs (20).

This meta-epidemiological study will describe the proportion of studies that reported individual outcomes and their categories, or patient-important outcome as the primary outcome of the study, and the most patient-important outcome as the primary outcome of the study.

Our target users are health care professionals, as well as researchers, decision makers and other stakeholders. We plan to present our results at national and international meetings.

Limitations to the meta-epidemiological study may include the diversity of outcomes from different clinical trials that may limit our capacity to classify these outcomes in our proposed category.

The findings from this meta-epidemiological study will help health care professionals and researchers understand if the current COVID-19 trials are effectively assessing and reporting the outcomes that are actually relevant to patients. This study will also identify gaps in outcomes reporting which might be useful for further research and priority setting and it will support decision making and the planning of future clinical trials.

LIST OF ABBREVIATIONS

ARDS= Acute respiratory distress syndrome

Covid-19= Coronavirus disease 2019

COPD= Chronic obstructive pulmonary disease

CRP= C-reactive protein

ICU= Intensive care unit

NMA= network metanalysis

NIV= noninvasive ventilation

HFNC= high flow nasal cannula

PaO₂/FiO₂= ratio of arterial oxygen partial pressure to fractional inspired oxygen

PIO= Patient-important outcome

RCT= Randomized Clinical Trials

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets created and analyzed during this survey will be available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

Funding

The authors received no specific funding for this work.

Authors' contributions

JJY-N conceptualized the study. JJY-N, MAJ-M, JFM-E, JB, and ARV designed this protocol and drafted the article. All authors actively reviewed this manuscript and provided substantial feedback. All authors read and approved the final version of the manuscript. JJY-N is the guarantor of the review.

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Additional File 1. PRISMA-P Checklist.

Section/topic	#	Checklist item	Information reported		Line number(s)			
			Yes	No				
ADMINISTRATIVE INFORMATION								
Title								
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1			
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3			
Authors								
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1,2			
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	13			
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	NA			
Support								
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	13			
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA			
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA			
INTRODUCTION								
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	5,6			

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	5,6
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐	☒	NA
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐	☒	NA
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	8,9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	8,9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	8,9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☒	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	☐	☒	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	10, 11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA