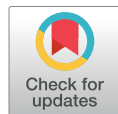




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REVIEW

How pragmatic are randomized trials of remdesivir and favipiravir for in-hospital treatment of COVID-19: a descriptive methodological review of trial design using the PRECIS-2 framework

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Abstract

Objectives: To review the pragmatism of published randomized trials of remdesivir and favipiravir based on the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) framework.

Study Design and Setting: Ten eligible trials were identified from an existing comprehensive living review and were evaluated across the nine PRECIS-2 domains by two independent reviewers.

Results: All 10 trials had mostly pragmatic design characteristics. Four of the domains (i.e., recruitment, setting, organization, and primary analysis) were found to be pragmatic with most trials scoring four or five across the two interventions. In comparison scores for four other design domains (i.e., eligibility, follow-up, flexibility of delivery, and primary outcome) varied across the trials with some design choices being more explanatory.

Conclusion: In our descriptive review of randomized controlled trials for two drugs for patients infected with COVID-19 early in the pandemic, we found that most trials had more pragmatic than explanatory characteristics. Some design choices for some of the trials, however, were not consistent with the urgent goal of informing clinical decision making in an epidemic. PRECIS-2 should be used as a guide by trialists, to help them match their trial design choices to the intended purpose of their trial. © 2022 Elsevier Inc. All rights reserved.

Keywords: COVID-19; Pragmatic trials; PRECIS-2; Remdesivir; Favipiravir; Methodological review

1. Introduction

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 a global pandemic. As of March 2022, their reports indicated that over 462 million people worldwide were infected with over 6 million dead. COVID-19 infections have been linked to several physiological complications ranging from myocardial injury and pulmonary dysfunction to severe end-organ damage with many requiring intensive care admissions and extensive life support measures [1]. In Canada as of February 25th, 4.1% of COVID-19 patients have thus

far required hospitalization with 17.1% of them needing intensive care unit care based on Health Canada estimates. The treatment options for hospitalized patients infected in 2020 were unknown, and even now remain relatively limited [2]. As such methodologically robust and pragmatic randomized controlled trials (RCTs) of effective management options were of critical priority at the onset of the pandemic and still continue to remain important.

Given the urgent need for effective therapeutic agents the usual long process of novel drug development and testing, which can take years, was supplemented by an effort to explore the efficacy of existing antivirals against COVID-19, known as “repurposing” [3,4]. While some repurposed antivirals like lopinavir and the ritonavir have been dismissed in guidelines following negative trials, others like remdesivir, originally developed for the treatment of Ebola virus, and favipiravir, originally developed for the influenza virus, have shown clinical benefit against COVID-19 in some studies [5,6]. Particularly, pooled data

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What is new?

Key findings

- To our knowledge, this is the first study to evaluate the applicability of COVID-19 clinical trials by assessing pragmatism of their design choices in the context of a real-world pandemic using a validated framework, the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2).
- We found that most trials were more pragmatic than explanatory.
- The domains for recruitment, setting, organization, and primary analysis scored highly on the PRECIS-2 scale.
- Some design domains, such as eligibility, follow-up, flexibility of delivery, and primary outcome were relatively more explanatory with idealised, laboratory-like features, reducing the direct applicability and usefulness for decision making of the findings of these trials.

What does this add to what was known?

- Our study showed that in the early phase of an urgent pandemic situation, trialists selected mostly pragmatic design features for their clinical trials.

What is the implication?

- We postulate that the predominance of pragmatic design characteristics may be due to the extreme urgency of conducting trials as quickly as possible during the pandemic.
- Few resources or time were available for constructing any trial infrastructure, in the overstretched hospitals to which patients were admitted, resulting in high degrees of similarity to usual care in most trials for most domains.
- While necessity drove most trials towards mostly pragmatic design choices, some trials made more explanatory choices in some domains suggesting that there may be a return to traditional explanatory design choices as the pandemic sense of urgency and constraint on research capacity recedes.

What should change?

- PRECIS-2 is a tool which encourages trial designers to match their choice of design features to their intention for their trial (direct applicability versus confirmation of mechanism of action).

- We recommend widespread use of PRECIS-2 for design of trials aimed at supporting real world decisions, especially in epidemic and pandemic situations.

have indicated efficacy of remdesivir in preventing the need of mechanical ventilation, and of favipiravir in reducing the length of hospital stay and time to resolution of symptoms, leading to conditional approval for use in certain settings [6]. However, the applicability of these findings outside the trial itself is unclear.

In 1967 two French statisticians, Daniel Schwartz and Joseph Lellouch proposed that a randomized trial could be designed either to provide direct evidence for a choice between alternative interventions in the “usual care” or “real-world” setting (which they named as the pragmatic intention), or to test a hypothesis about the mechanism of an intervention under highly controlled or ideal conditions (explanatory intention) [7]. Trials with pragmatic intention and design assess the effectiveness of interventions under parameters like those of the situation in which it will be applied, characterized by few exclusions for settings, staff and participants, use of clinically important outcome measures, and practical organization of intervention delivery [7]. The results of such trials are more likely to apply outside the trial and hence more useful in practice for decisions [7]. They asserted that too often trials aimed at a pragmatic purpose test interventions under idealized conditions, so that the intervention may fail to achieve the same results when implemented in the more usual conditions, misleading decision makers [7].

While the quality of COVID-19 related clinical research has been shown to vary, the focus of reviews has so far been on sources of bias and internal validity, and no previous study has assessed the pragmatism of these trials and the external validity of their results [8–10]. This is particularly important because within the context of a growing pandemic, when the world needs rapid RCTs that could provide rigorous evidence to inform care decisions, trials with more explanatory design choices may be less directly useful as they may be less applicable to the usual care settings where these interventions are applied to a wide array of patients.

The “Pragmatic Explanatory Continuum Indicator Summary” (PRECIS-2) is a validated framework that can be used to evaluate the design features of a clinical trial for applicability [11,12]. We conducted a methodological review of published RCTs involving the two repurposed antivirals remdesivir and favipiravir, that have shown net clinical benefit in previous pooled-analyses, using the domains of the

Table 1. Characteristics of included studies and summary of design limitations based on the PRECIS-2 framework for (a) remdesivir, (b) favipiravir

Study identifier	Study design	Setting	Delivery	Primary outcome	Limitations
A					
Goldman et al., (2020) [13]	Open label, RCT, N = 397 n = 200 for 5 days n = 197 for 10 days	55 hospitals, international trial	Intravenous remdesivir 200 mg on day 1, 100 mg daily on days 2–10 or 100 mg for 4 days	Clinical status at day 14 (on a 1–7 ordinal scale)	Eligibility: Inclusion criteria -Patients receiving another treatment within 24 hours were excluded Follow-up: -Extensive blood samples and biochemical tests were performed -Patient followed extensively for 14 days -Monitored adverse events up to 30 days after last dose
Spinner et al., (2020) [14]	Open label, RCT, N = 584 n = 197 for 10-day course of remdesivir n = 199 for 5-day course of remdesivir n = 200 for standard care	105 hospitals, international trial	Intravenous remdesivir 200 mg on day 1, 100 mg daily on days 2–10 or 100 mg for 4 days Standard care	Clinical status on day 11 (on a 1–7 ordinal scale)	Eligibility: -Inclusion criteria: Patient with SPO ₂ greater than 94% excluded -Patients receiving concurrent medications were excluded Follow-up: -Extensive blood samples and biochemical tests were performed -Pharmacokinetic assessments
Wang et al., (2021) [15]	Double blind, RCT N = 237 n = 158 for remdesivir n = 79 for placebo	10 hospitals, all based in Hubei, China	Intravenous remdesivir 200 mg day 1/100 mg up to day 2–10, or intravenous saline for 10 days	Time to clinical improvement within 28 days (on a 1–6 ordinal scale)	Eligibility: Inclusion criteria: -Adults only Follow-up: -Nasopharyngeal swabs were collected -Faecal and anal swabs collected for RNA quantification
Beigel et al., (2020) [16]	double blind, RCT, N = 1,062 n = 541 for Remdesivir n = 521 for placebo	60 hospitals, international trial	Intravenous remdesivir 200 mg day 1/100 mg up to day 2–10, or placebo for 10 days	Clinical recovery (on a 1–8 ordinal scale)	Eligibility: -Adults only Flexibility (delivery): -Prevented off-label drug usage Follow-up: -Measured viral shedding which is not pragmatic
WHO solidarity trial	Open label, RCT N = 11,330 n = 2750 for remdesivir n = 954 for hydroxychloroquine, n = 1,411 for lopinavir n = 1,412 for interferon n = 651 for interferon + lopinavir n = 4088 for no drug	405 hospitals, international trial	Intravenous remdesivir 200 mg on day 1, 100 mg daily on days 2–10 Standard care	Mortality while hospitalized	Eligibility: -Adults only -Excluded patients who were taking other study medications

(Continued)

Table 1. Continued

Study identifier	Study design	Setting	Delivery	Primary outcome	Limitations
B					
Chen et al., (2020) [17]	Open label, RCT N = 240 n = 120 for favipiravir n = 120 to receive Arbidol	3 hospitals, all in China	conventional therapy plus Arbidol (200 mg*3/day) or favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for 10 days	clinical recovery rate at day 7	Eligibility: -Covid-19 was confirmed by clinical suspicion, not PCR test Follow up: -Very specific follow-up protocol. Requires CT scans etc. -Requires extensive viral testing on specific days. Outcome: -Clinical recovery on basis of improvement in vital signs
Doi et al., (2020) [18]	Open label, RCT N = 89 n = 44 for early treatment n = 45 for late treatment	25 hospitals, all in Japan	Favipiravir was dosed at 1,800 mg twice orally at least 4 hours apart on the first day, followed by 800 mg BID, for a total of up to 19 doses over 10 days	Negative RT-PCR for SARS-CoV-2	Eligibility: -Exclusion criteria were broad: e.g., i. immunosuppressive conditions ii. receipt of systemic antiviral agent against SARS-CoV-2 within 28 day Follow up: -Negative RT-PCR for SARS-CoV-2 daily or once every 2 days Outcome: -Negative RT-PCR for SARS-CoV-2
Lou et al., (2021) [19]	Open label, RCT N = 30 n = 10 for baloxavir marboxil n = 10 for favipiravir n = 10 for control group	1 hospital trial	Placebo Oral 80 mg baloxavir marboxil on day 1, 4, 7 Oral 1,600 or 2200 mg favipiravir on day 1, 600 mg three times day everyday	Negative RT-PCR for SARS-CoV-2	Eligibility: -Patients weighing less than 40 kg excluded Follow-up: -Collected concentrations of drug in blood -Collected viral loads Outcome: - Negative RT-PCR for SARS-CoV-2
Udwadia et al., (2021) [20]	Open label, RCT N = 150 n = 75 for favipiravir n = 75 for control group	7 hospitals, all in India	oral favipiravir (day 1: 1,800 mg BID and days 2–14: 800 mg BID) vs standard care	Oral shedding of SARS-CoV-2	Eligibility: Exclusion criteria: patients older than 75 excluded, concurrent medication use, other exclusion criteria vast Follow up: -Measured viral clearance and performed nasopharyngeal swabs daily for days 2–28 Outcome: -Oral shedding of SARS-CoV-2
Zhao et al., (2021) [21]	Open label, RCT N = 26 n = 14 for favipiravir and tocilizumab	4 hospitals, all in China	oral favipiravir day 1 1,600 mg, 600 mg BID afterward tocilizumab	Remission of lung lesions	Eligibility: -Inclusion criteria: elevated IL-6

(Continued)

Table 1. Continued

Study identifier	Study design	Setting	Delivery	Primary outcome	Limitations
	<i>n</i> = 7 for favipiravir <i>n</i> = 7 for tocilizumab		according to rheumatoid arthritis guidelines		-Exclusion criteria: presence of TB bacteria, scientist can exclude at will Flexibility (delivery) -Had a specific protocol for fever Follow-up: -Flow cytometry and CT scans day 1 and 14 Outcome: -Remission of lung lesions, not very pragmatic to patient, although relevant

Abbreviations: RT PCR, reverse transcriptase polymerase chain reaction; RCT, randomized controlled trial.

PRECIS-2 framework [6,11,12]. The objective of this descriptive review is to provide insight into the pragmatism of their design choices and to discuss the match between the design of these trials and the urgent need for evidence with direct applicability to the usual contexts of care in a pandemic.

2. Methods

2.1. Literature search and study selection

We selected papers reporting randomized trials of remdesivir and favipiravir from the search results of a methodologically rigorous living systematic review on drug treatments for COVID-19, as of the April 2021 update [6]. This comprehensive review includes over 25 literature databases with no restrictions on language of publication or publication status [6]. We particularly selected this review due to its comprehensive scope and its “living” nature which allowed for continuous updates and extracted all

published and preprint reports pertaining to remdesivir and favipiravir that were available in full-text for our study.

2.2. Pragmatic-explanatory continuum indicator summary assessment

The PRECIS-2 tool includes nine different domains that pertain to different design features of a clinical trial: (1) eligibility; (2) recruitment; (3) setting; (4) organization; (5) delivery flexibility; (6) adherence flexibility; (7) follow-up; (8) primary outcome; and (9) primary analysis [11]. Each domain is scored from one (very explanatory) to five (very pragmatic) [11]. For training purposes, three trials not related to the current topic were randomly selected, evaluated by the two reviewers (T.S. and I.Q.), and discussed and agreed on with an expert (M.Z.). All retrieved trials in this case were assessed domain by domain and rated independently by two reviewers (T.S. and I.Q.) based on the PRECIS-2 framework. As such, studies were

Table 2. Final PRECIS-2 scores for all reviewed COVID-19 trials for both remdesivir and favipiravir

Study	PRECIS-2 Category								
	Eligibility	Recruitment	Setting	Organization	Flexibility (delivery)	Flexibility (adherence)	Follow-up	Primary outcome	Primary analysis
Remdesivir									
Goldman et al., (2020) [13]	4	5	5	5	5	N/A	3	5	5
Spinner et al., (2020) [14]	3	5	5	5	5	N/A	3	5	5
Wang et al., (2021) [15]	4	5	4	5	5	N/A	1	5	5
Beigel et al., (2020) [16]	4	5	5	5	4	N/A	3	5	5
WHO solidarity trial	3	5	5	5	5	N/A	5	5	5
Favipiravir									
Chen et al., (2020) [17]	3	5	4	5	5	N/A	2	4	5
Doi et al., (2020) [18]	2	5	4	5	5	N/A	2	3	5
Lou et al., (2021) [19]	3	5	3	5	5	N/A	1	3	5
Udwadia et al., (2021) [20]	3	5	4	5	5	N/A	2	3	5
Zhao et al., (2021) [21]	2	5	4	5	3	N/A	3	2	5

initially analyzed individually by the two independent raters followed by discussion to reach consensus on scores for each domain. Trials were classified as having a mostly pragmatic design if the majority (5 or more) of their design domains scored four or five. If a design characteristic did not apply to a particular trial or if there was insufficient information available, the rating was left blank. Disagreements between the two reviewers were resolved in discussion with MZ where needed.

3. Results and discussion

Ten eligible primary reports of RCTs were identified, five of remdesivir and five of favipiravir (Table 1) [3,13–21]. Hospitalized patients were specifically recruited in all cases. While there is a clear disparity in size, with most trials being very small and only two trials exceeding 1,000 patients, our goal in this paper is to focus on other design choices.

All 10 trials had mostly pragmatic design characteristics with each trial scoring a four or five on at least 5 out of the 8 applicable PRECIS-2 design domains (Table 2). One of the domains (i.e., flexibility of adherence) in this case was found to be inapplicable as all trials involved only hospitalized patients and hence no issue of medication adherence was expected for patients after consent had been given. Four of the domains (i.e., recruitment, setting, organization, and primary analysis) were found to be pragmatic with the majority of the trials receiving a score of four or five. In comparison, scores for four other design domains (i.e., eligibility, follow-up, flexibility of delivery, and primary outcome) varied across the trials.

For trials of both the drugs, the setting and organization of delivery from a design standpoint were very similar to usual care as these trials were mostly conducted in community hospitals and care was provided by local health care teams. Majority of the trials were multicentre. Additionally, given the pandemic situation, the recruitment process was compatible with resources available in the usual care setting. Since the recommendations from these trials are geared toward the management of admitted patients with COVID-19, we consider these results pragmatic for this context.

All the remdesivir trials included outcomes directly important to patients as their primary end points with the majority utilizing an ordinal scale with clinically relevant categories such as mortality, hospitalization, requirement of oxygen support and so on. Additionally, the majority of the remdesivir trials were also pragmatic with respect to the primary analysis domain as they analyzed results using the intention-to-treat principle. The primary outcomes in the favipiravir trials tended toward the explanatory side with some of the trials utilizing outcomes that may not be as directly patient relevant. For instance, the study on favipiravir by Zhao et al. used cumulative lung lesion

remission rate, determined through changes on computed tomography scans, as the primary outcome [21].

With respect to eligibility the selection of the population was deemed more explanatory overall for favipiravir trials with scores of 2 or 3, while the remdesivir trials were relatively more pragmatic with scores of 3 or 4. While some of the trials included a broad spectrum of patients, most trials involved certain exclusion criteria that excluded patients who would be expected to receive the treatment in the usual care setting once the intervention was more widely implemented. This resulted in patients with certain comorbidities being excluded from certain trials, for example those with asthma or chronic obstructive pulmonary disease as seen in the trial by Udawadia et al., hence reducing the generalizability of the findings [20]. Another example of restrictions included the selection of participants based on age criteria. For instance, the study on remdesivir by Wang et al. only enrolled adult patients older than the age of 18 year; however, remdesivir is currently approved for COVID-19 patients older than the age of 12 year [15]. Overall the implication of having narrower participant selection criteria is that it reduces the external validity of the results.

With respect to flexibility of delivery we found that most trials allowed flexibility with cointerventions. One trial (Zhao et al.) provided specific dosing instructions, for the management of fever [21]. Some trials did restrict the use of other experimental interventions or off-label drugs. Most trials did not report extra measures to improve clinician compliance. A stricter protocol for delivery reduces clinician autonomy, making the trial less easily applicable to usual care settings where the clinicians change treatment according to their personal approach, as the condition of the patient changes.

The scores also varied with respect to the follow-up domain. The remdesivir studies generally scored higher on this domain compared to the favipiravir studies. Out of the five remdesivir trials, one study (WHO Solidarity trial) was deemed to be ‘very pragmatic’ with a score of 5, assessing only mortality at 28 days. Wang et al. was more explanatory on this domain with a score of 1 as this study used frequent fecal swabs for RNA quantification and hence more extensive data collection which is not seen in care protocols for COVID-19 patients [15]. Although this was not their primary outcome, the increased frequency of follow-up associated with it may have made additional clinical monitoring and interventions more likely. The three remaining remdesivir trials scored 3 on the follow-up domain. The favipiravir trials were more explanatory with three of the trials scoring a 2, one trial scoring a 1, and one trial scoring a 3. For instance, Lou et al. measured viral load frequently which would not be done in the usual care setting [19].

Overall while there have been studies reviewing the design elements of COVID-19 trials with a focus on risk of bias, our review is the first to provide a methodological evaluation of the pragmatism and applicability of early

COVID-19 trials conducted during the initial stage of the pandemic based on the established PRECIS-2 framework. In this case our research also relied on an existing comprehensive, living systematic review. The quality of some living evidence summaries on COVID-19 have been previously evaluated and have been found to have significantly high sensitivity for the identification of publications in preprint or peer-reviewed journals [22]. As such these platforms are a viable screening alternative to searching every individual source. However we acknowledge that our review has a narrow scope as we only focused on repurposed antiviral agents and specifically only those that have shown net benefit in pooled analyses of literature. Consequently, only a small number of trials were included and hence the conclusions drawn regarding study design characteristics are not necessarily reflective of all early COVID-19 trials. Additionally, given that the living evidence summary that we based our primary screen on was last updated in April 2021, our review only covers studies that were conducted during the initial phase of the pandemic. As such, the levels of pragmatism observed in studies from this phase may not be reflective of studies performed later in the pandemic.

4. Conclusion

In our review of RCTs of remdesivir and favipiravir among patients with severe infection early in the pandemic, we were encouraged to find that most trials for remdesivir, and to a lesser extent, favipiravir, had more pragmatic than explanatory characteristics even though they did not explicitly declare a pragmatic intention. We believe this default to pragmatic design parameters was driven by the need to conduct trials with extreme urgency, and few spare resources or time for constructing any trial infrastructure, in the overstretched hospitals to which patients were initially admitted. Every hospital became a community hospital under these emergent conditions, and most trials were conducted under usual care conditions. This increased the usefulness of these trials for decision-making, but we fear that this pragmatic tendency may disappear in trials not conducted under these conditions. Sadly, we anticipate this trend toward pragmatic design choices to fade under less urgent conditions.

Some design choices for some of the trials were explanatory with constrained, laboratory-like characteristics, to limit variations other than those directly due to the intervention itself. While not every design characteristic can or always should be pragmatic, even where the intention is pragmatic, in an emergent, rapidly growing pandemic, the world needed RCTs aimed at providing evidence which could immediately and directly inform usual care decisions. More explanatory design choices, scoring lower on the PRECIS-2 scale would have undermined the direct usefulness of the findings of these trials.

While no-one wishes for such a situation the artificially constrained conditions suitable for explanatory approaches were near impossible to construct in the early emergency, resulting in trial designs with more applicable findings. PRECIS-2 encourages potential trialists to see that the findings of their randomized trials, even if integrated into usual care and conducted with few resources under stressful conditions, are just as rigorous and more likely to be applicable than if they delayed in order to build up the constraining design features traditionally but incorrectly regarded as essential to conducting a valid trial. The PRECIS-2 tool could serve as a guide for trialists, helping them match actual trial design choices to the intended purpose of their trial.

CRedit authorship contribution statement

M.Z. designed the study; T.S, I.Q, and M.Z conducted research; T.S. and I.Q. analyzed the data; T.S, I.Q, and M.Z. wrote the manuscript; All the authors read and approved the final manuscript.

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