STUDY PROTOCOL

REVISED A multi-center, adaptive, randomized, platform trial to evaluate the effect of repurposed medicines in outpatients with early coronavirus disease 2019 (COVID-19) and high-risk for complications: the TOGETHER master trial protocol [version 2; peer review: 1 approved, 1 approved with reservations]

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v2 First published: 05 Aug 2021, 5:117
<https://doi.org/10.12688/gatesopenres.13304.1>
 Latest published: 08 Nov 2021, 5:117
<https://doi.org/10.12688/gatesopenres.13304.2>

Abstract

Background: There remains a need for an effective and affordable outpatient treatment for early COVID-19. Multiple repurposed drugs have shown promise in treating COVID-19. We describe a master protocol that will assess the efficacy of different repurposed drugs as treatments for early COVID-19 among outpatients at a high risk for severe complications.

Methods: The TOGETHER Trial is a multi-center platform adaptive randomized, placebo-controlled, clinical trial. Patients are included if they are at least 18 years of age, have a positive antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and have an indication for high risk of disease severity, including comorbidities, older age, or high body mass index. Eligible patients are randomized with equal chance to an investigational product (IP) or to

Open Peer Review

Approval Status ? ✓

	1	2
version 2	?	✓
(revision)	view	view
08 Nov 2021	↑	↑
version 1	?	?
05 Aug 2021	view	view

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placebo. The primary endpoint is hospitalization defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19. Secondary outcomes include mortality, adverse events, adherence, and viral clearance. Scheduled interim analyses are conducted and reviewed by the Data and Safety Monitoring Committee (DSMC), who make recommendations on continuing or stopping each IP. The platform adaptive design go-no-go decision rules are extended to dynamically incorporate external evidence on COVID-19 interventions from ongoing independent randomized clinical trials.

Discussion: Results from this trial will assist in the identification of therapeutics for the treatment of early diagnosed COVID-19. The novel methodological extension of the platform adaptive design to dynamically incorporate external evidence is one of the first of its kind and may provide highly valuable information for all COVID-19 trials going forward.

Clinicaltrials.gov registration: NCT04727424 (27/01/2021)

Keywords

COVID-19; SARS-CoV-2, repurposed drugs, RCT, adaptive design, early treatment, outpatient care, master protocol

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the [Coronavirus \(COVID-19\)](#) collection.

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Competing interests: No competing interests were disclosed.

Grant information: The TOGETHER Trial is supported by the Bill and Melinda Gates Foundation [INV-019641]. Overall trial infrastructure is also supported by the Rainwater Foundation, with additional funding support from FastGrants for current evaluations of trial interventions. Future evaluations of interventions may be supported by other funding organizations. The funders have no role in the conduct, interpretation, or dissemination of the study findings.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Reis G, Silva EAdSM, Silva DCM *et al.* **A multi-center, adaptive, randomized, platform trial to evaluate the effect of repurposed medicines in outpatients with early coronavirus disease 2019 (COVID-19) and high-risk for complications: the TOGETHER master trial protocol [version 2; peer review: 1 approved, 1 approved with reservations]** Gates Open Research 2021, 5:117 <https://doi.org/10.12688/gatesopenres.13304.2>

First published: 05 Aug 2021, 5:117 <https://doi.org/10.12688/gatesopenres.13304.1>

REVISED Amendments from Version 1

Dear members of the Gates Open Research,

Thank you for the feedback on the TOGETHER Trial master trial protocol manuscript. For each peer reviewer's comments, we provide a response and reference edits in the manuscript, where appropriate. Below is a summary as well of our changes:

In this version of the protocol manuscript we have answered each of the reviewers concerns point by point. We have made changes only to clarify points made by the reviewers. These points generally concerned giving more clarity to trial procedures. We have also aligned this version of the manuscript the protocol submitted for ethical approval and the statistical analysis plan. There were no changes made to the Tables or the Figure in this version of the manuscript. There are no changes to the author list or order of authors and no change to the manuscript title.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Dr. Edward Mills (for the authors)

Any further responses from the reviewers can be found at the end of the article

Introduction

The discovery of effective and affordable treatments for preventing COVID-19 disease progression and subsequent hospitalization in outpatient settings is critical to minimize limited hospital resources, particularly for resource-limited settings¹. As vaccine rollout has been slow in resource-limited countries and new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause concern for their effectiveness, identifying therapeutics that are affordable, widely available and effective against COVID-19 is of prime importance. Repurposing existing medications is an appealing approach as drugs currently used to treat other health conditions have known safety profiles.

There is also a need for more clinical trials in early infected populations. A majority of trials of repurposed drugs are conducted among inpatients with advanced clinical disease, yet the majority of COVID-19 cases are seen in the community setting². Early treatment trials have the added benefit of evaluating drugs with the outcome of disease progression or hospitalization³. The TOGETHER Trial is an example of a global study network to evaluate repurposed drugs in early infected populations.

The TOGETHER Trial is an adaptive, multi-arm platform trial, evaluating multiple concurrent interventions (investigational products [IPs]) versus placebo among outpatients at high risk of developing COVID-19-related complications. The trial is designed to allow for multiple intervention arms to be implemented at any time and data to be merged with data from other external trials. This is a new approach for clinical trials that has occurred as a result of the COVID-19 pandemic and integrates platform adaptive trial designs with data synthesis to facilitate rapid decision-making. The overarching objective of this study is to test the hypothesis that repurposed drugs versus

placebo effectively prevent worsening of COVID-19 requiring hospitalization defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19. This protocol is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines⁴.

Methods

Study overview

The TOGETHER Trial is an adaptive, multi-arm platform trial with equal allocation of interventions and placebo. The setting for the trial is 13 primary care and emergency department outpatient clinics in the Brazilian state of Minas Gerais.

Objectives

The primary objective is to determine if each of the IPs reduces hospitalization defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19. The composite endpoint addresses both hospitalization and a proxy for hospitalization, retention in a COVID-19 emergency setting, as many patients who would be hospitalized were prevented from admission due to hospital over-capacity during peak waves. This region of Brazil implemented hospital-like services in the emergency settings with 50-80 bed settings and provides services including oxygenation, sedation, multi-day stays, and mechanical ventilation.

The secondary objectives are to evaluate, in comparison with placebo, the effect of the IPs on the following parameters: 1) viral clearance, 2) time to clinical improvement, 3) number of days with respiratory symptoms, 4) time to hospitalization for any cause or due to COVID-19 progression, 5) all-cause mortality and time to death from any causes, 6) WHO clinical worsening scale, 7) quality of life scale (PROMIS-10 scale), 8) Telephone Interview for Cognitive Status (TICS) memory assessment scale, 9) days in hospital and on a ventilator, 10) adverse events, 11) adverse reactions to IPs, and 12) adherence with IPs. All secondary outcomes are assessed up to 28 days following randomization.

Ethical considerations

Ethical review for this trial follows the Brazilian standard process of CEP/CONEP approval. The trial protocol is first reviewed by the local ethics review board in Brazil, followed by review at the national level by the National Committee for Ethics in Research (CONEP), since the trial is supported by international funding. CONEP approval number: 41174620.0.1001.5120. Research staff members located at the primary care or emergency department clinic where patients first present with symptoms are responsible for obtaining written informed consent. Prospective participants are read the informed consent form which describes trial procedures, potential risks, measures to protect their personal identity, and which parties will have access to their medical information. Ethics certificates from the CEP/CONEP approval process in Brazil are submitted to the Hamilton Integrated Research Ethics Board (HiREB) at McMaster University, which serves as the Ethics Board of Record, for final review and approval. HiREB project number: 13390.

Eligibility criteria

The inclusion criteria are:

1. Patients 18 years and over with the ability to provide free and informed consent.
2. Patients presenting to an outpatient care setting with an acute clinical condition compatible with COVID-19 and symptoms beginning within 07 days from the randomization date.
3. Patients over 18 years and with at least ONE of the following criteria:
 - a) Age ≥ 50 years (does not need any other risk criteria)
 - b) *Diabetes mellitus* requiring oral medication or insulin
 - c) Systemic arterial hypertension requiring at least 1 oral medication for treatment
 - d) Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion)
 - e) Symptomatic lung disease and / or being treated (emphysema, fibrosing diseases)
 - f) Symptomatic asthma patients requiring chronic use of agents to control symptoms
 - g) Obesity, defined as BMI > 30 kg / m² (weight and height information provided by the patient)
 - h) Transplant patients
 - i) Patient with stage IV chronic kidney disease or on dialysis
 - j) Immunosuppressed patients / using corticosteroid therapy (equivalent to a maximum of 10 mg of prednisone per day) and / or immunosuppressive therapy
 - k) Patients with a history of cancer in the last 5 years or undergoing current cancer treatment
 - l) Patients with documented fever at screening ($>38^{\circ}\text{C}$)
 - m) Patients with at least one of the following symptoms: cough, dyspnea, pleuritic chest pain AND/OR myalgias with limited daily activities (to a maximum of 25% of enrollment)
4. Patients with a positive rapid test for SARS-CoV-2 antigen performed at the time of screening or patients with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset.
5. Willingness to use the proposed investigational treatment and follow the research procedures.
6. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use

adequate methods of contraception during the study and through 90 days after the last dose of study medication.

Participants who already have a positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at the time of screening and meet all the inclusion criteria in the survey will not need a new confirmatory test for COVID-19 and can be considered eligible for the randomization.

Patients who meet any of the following criteria are excluded:

1. Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need.
2. Patients with acute respiratory condition due to other causes.
3. Severe terminal illness irrespective of type or etiology.
4. Acute flu showing at least ONE of the criteria below:
 - I. Respiratory Rate > 28 / min
 - II. SaO₂ $< 90\%$ or $< 93\%$ on nasal oxygen therapy at 10 L / min
 - III. PaO₂ / FIO₂ < 300 mmHg
5. Use of the following medications in the last 14 days:

Monoamine Oxide Inhibitors (MAOIs): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazide, moclobemide

Alpha-1 antagonists, Sotalol, Clonidine, Phosphodiesterase 5 inhibitors, Methyldopa, Prazosin, terazosin, Doxazosin)

Use of antiretroviral agents
6. Patients using serotonin reception inhibitors (Donepezil, Sertraline).
7. Pregnant or breastfeeding patients.
8. Surgical procedure or use of contrast planned to occur during treatment or up to 05 days after the last dose of the study medication.
9. Inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol.
10. Known hypersensitivity and / or intolerance to IPs, or taking medications contraindicated by IPs.
11. Inability to follow protocol-related procedures.

Screening

Patients presenting to an outpatient clinic setting with clinical criteria for presumptive diagnosis of COVID-19 who meet the above eligibility criteria are invited to participate in the trial. Nurses, clinicians and health workers will obtain written informed consent from potential trial participants. After obtaining informed consent, research personnel collect demographic information and medical history, and confirm positivity for SARS-CoV-2 using the Abbott Panbio rapid antigen testing for previously undiagnosed patients.

Randomization and allocation

Participants are randomized using a centralized randomization process which uses pre-prepared lists for each participating clinical site. Block sizes of 10 are used. Randomization is stratified by clinical site and participant age (< 50 years / ≥ 50 years). At the time of randomization, clinical site personnel send a text message to the unblinded pharmacist at the coordinating center requesting to randomize a participant. The unblinded pharmacist at the coordinating center replies to the message within 5-10 minutes with the medication letter and randomization number. Allocation of treatment assignment is concealed from all other study personnel.

Different placebos may be used depending on which IPs are included. For example, if IPs are being administered in both pill format and by injection, participants randomized to the placebo group will be randomly assigned to receive a placebo pill or a placebo injection. If IPs of different duration are being used (e.g. 1 day, 3 days, 10 days, 14 days), participants randomized to the placebo group will also be randomized to different placebo regimens (e.g. 1 day, 3 days, 10 days, 14 days).

Blinding

Randomization lists are prepared and kept confidential by an unblinded statistician and treatment packages are prepared by an unblinded pharmacist. With each newly eligible participant, the clinician contacts the unblinded pharmacist by WhatsApp to request a code that corresponds to a blinded treatment package. Data are unblinded at the time of the planned interim analyses and at the end of the trial. The trial is quadruple blinded, with participants, research personnel, sponsors, and designees. The Data and Safety Monitoring Committee (DSMC) do not have access to the patient's allocation during review of the interim analysis data, except in the foreseen situations (i.e., decision to stop a treatment arm, termination of the trial, or safety concerns).

Investigational products

The master protocol format and the adaptive design allows the easy addition of different IPs. Ethics approvals are obtained before adding a new IP. Participants are prescribed the IPs and corresponding placebo as indicated in the protocol. An unblinded pharmacist at each clinical site prepares the IP or placebo as per the randomization sequence. The IPs are shipped and stored in a temperature-controlled manner as per the requirements for each IP. [Table 1](#) shows the previous, current (at the time of writing), and planned IPs of investigation in the TOGETHER Trial.

Data entry and quality checks

Study data are collected on a paper record by the study staff member either in-person at the clinic or by WhatsApp video or voice call with the participant. Data are entered into the IBM electronic case report forms (eCRFs) at each study site. Data quality checks are first performed at the site level, and secondary data checks are performed by central research staff, located at the research coordinating office in the Minas Gerais capital of

Belo Horizonte. Weekly meetings are held by Zoom with all study sites to provide feedback on data quality and completeness and continuous training is provided to each site following any changes to the eCRFs or other study procedural amendment. The CRFs can be found as extended data⁴.

Study outcomes

The primary endpoint is hospitalization defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19.

Secondary outcomes include: 1) viral clearance at days 3 and 7, 2) time to clinical improvement, 3) number of days with respiratory symptoms, 4) time to hospitalization for any cause or due to COVID-19 progression, 5) all-cause mortality and time to death from any causes, 6) WHO clinical worsening scale, 7) quality of life scale (PROMIS-10 scale), 8) Telephone Interview for Cognitive Status (TICS) memory assessment scale at day 28, 9) days in hospital and on a ventilator, 10) adverse events, 11) adverse reactions to IPs, and 12) adherence with IPs. All secondary outcomes are assessed up to 28 days following randomization.

The study activities for capturing these outcomes at each visit is displayed in [Table 2](#) and [Figure 1](#).

Participant follow-up procedures

All participants receive standard treatment for COVID-19 as adopted by the health units to which they are linked, as defined by the medical assistant team. All participants will also receive 24-hour telephone contact number which they can call if they have any questions about the trial, if their condition worsens, or if they experience an adverse event. The first quarter of participants enrolled into each treatment arm will self-collect nasal swab and saliva for RT-PCR on day 3 and day 7 after randomization. Participants are instructed on this home sample collection and on the logistics for sample retrieval from their residence by study personnel.

The majority of patient evaluations are carried out by telephone contact, social media apps (e.g. WhatsApp), video calls or telemedicine. Face-to-face visits are limited as the virus is highly transmissible. Participants will follow the local health authorities' guidelines regarding isolation and quarantine requirements, which are generally 14 days from a positive COVID-19 test. Only the day-14 visit will be conducted face-to-face to enable study personnel to collect the medication kits for drug accountability and treatment compliance.

A number of procedures are implemented to maximize participant retention. An informative video recorded by the principal investigator and take-home flyer encourages patients to adhere to study procedures and complete the trial. Participants are also sent occasional notification reminders on WhatsApp encouraging trial participation and follow-up appointments by WhatsApp are conducted in an effort to minimize travel days to the clinic.

Table 1. Interventional Products (IPs) of evaluation in the TOGETHER trial (previous and current).

Investigational Product (IP)	Dose	Dosing schedule	Route of administration
Hydroxychloroquine*	400mg	Two tablets on Day 1, then 1 tablet for 9 days	Oral
Lopinavir/ritonavir*	200/50mg	Four tablets twice a day on Day 1, then two tablets twice a day for 9 days	Oral
Fluvoxamine Maleate	100mg	One tablet every 12 hours for 10 days	Oral
Ivermectin	400 mcg/kg up to 90kg weight	3–6, 6mg tablets (weight dependent) every 24 hours for 3 days	Oral
Metformin Extended Release	750mg	One tablet every 12 hours for 10 days	Oral
Doxazosin	2mg	Progressive dosing conditioned on SBP <120 mmHg; 0.5 tablet Day 1–2, 1 tablet Day 3–4, 2 tablets Day 5–7, 3 tablets Day 8–10, 4 tablets Day 11–14	Oral
Pegylated Interferon Lambda	180 mcg in 0.45 mL	One injection at randomization	Sub-cutaneous injection in lower abdomen

*Reis G, Moreira Silva E, Medeiros Silva DC, Thabane L, Singh G, Park JJH, Forrest JI, Harari O, Quirino Dos Santos CV, Guimaraes de Almeida APF *et al*: **Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial**. *JAMA Netw Open* 2021, **4**(4):e216468.

By Brazilian regulations, we provide medical care to all patients throughout their participation (2 months). For longer term events, the trial insurance covers any study related adverse event for a period of three years post-randomization.

Trial committees

A Steering Committee and an independent DSMC have been established. The Steering Committee oversees the study to ensure scientific integrity and routinely assess emerging evidence to recommend interventions of interest for the trial. The Data and Safety Monitoring Committee oversees the safety of the research participants and reviews the results of each interim analysis and final analysis and makes recommendations on stopping or continuing each IP. Events of special interest flagged by the Data and Safety Monitoring Committee are followed-up by study physicians.

Members of the Data and Safety Monitoring Committee include: Dr James Orbinski of York University (Canada), Dr Sonal Singh of University of Massachusetts (USA), and Dr. Jonas Haggstrom of Cytel Inc. (Sweden). Dr. Kristian Thorlund of McMaster University (Canada) serves as the non-voting chair of the Data and Safety Monitoring Committee.

Sample size

The trial is a platform adaptive trial design with three planned interim analyses at approximately 25%, 50%, and 75% of the total required sample size. The initial sample size calculation is based on the test for the hypothesis that each of the IPs will be better than placebo in reducing hospitalization defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19. (defined above). The sample size of 681 patients per arm was chosen for each experimental group to achieve 80% power with 0.05 two-sided Type 1 error for a pairwise comparison against the control to detect minimum treatment efficacy defined by 37.5% relative risk reduction (RRR) of preventing hospitalization assuming a control event rate (CER) of 15%.

Sample size re-assessment will be performed, subject to the DSMC's approval, if after the third interim analysis the control event rate appears to be considerably lower to the one the original sample size calculation was based on, irrespective of the observed RRR. In that event, we will rerun the simulation based on the new sample size calculated and with the first three interim analyses taking place as originally planned, to confirm that no type I error rate inflation is occurring. Should the

Table 2. Schedule of study activities.

	Screening Visit (D-0)	Baseline and Randomization (1) D-0	Day 1	Day 2 ⁽⁴⁾	Day 3 ⁽⁴⁾ ± 1 day	Day 4 ⁽⁴⁾	Day 5 ⁽⁴⁾	Day 7 ⁽⁴⁾ ± 1 day	Day 10 ± 2 days	Day 14 ⁽⁴⁾ ± 2 days	Day 28 ⁽⁴⁾ ± 3 days	Day 60 ^(4,8,9) or Early Termination ± 5 days
Informed Consent	X											
SARS-CoV-2 Rapid Test	X ⁽¹⁾											
Eligibility Criteria Review	X ⁽²⁾											
Pregnancy Test	X ⁽³⁾											
Demographics	X ⁽⁶⁾											
Co-morbidities and Risk Factors	X											
Medical History	X											
WHO Clinical Worsening Scale	X		X	X	X	X	X	X	X	X	X	X
Exposure to Index Case Information		X										
Substance Abuse		X										
PROMIS Global Health Scale		X ⁽⁶⁾								X ⁽⁶⁾	X ⁽⁶⁾	X ⁽⁶⁾
ECG		X										
Height and Weight		X										
Nasopharyngeal Swab		X		X	X			X				
Randomization		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Investigational Treatment Administration			X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾	X ⁽⁷⁾		
Hospitalization / Emergency Room Visits			X	X	X	X	X	X	X	X	X	X
Respiratory Symptoms			X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Adverse Drug Reactions			X	X	X	X	X	X	X	X	X	X
Vaccination Status										X	X	X
TICS scale - Memory Evaluation											X	

Legend

- Screening and baseline visit: must be carried out at the same time when attending the outpatient setting. Rapid antigen test for COVID-19 at the screening visit. Day 1 visit should also be conducted on the same day as the screening and baseline visit. After completing the screening visit procedures at the baseline visit and present all inclusion / exclusion criteria, participants should be immediately randomized. The first dose of IP must be administered on the same day of randomization (immediately after randomizing). The study medication will be administered as prescribed. Patients must be observed for 30 minutes after the medication administration.
 - Patients can be included in the trial if they have a COVID-19 diagnosis at baseline visit and have less than 7 days of flu-like symptoms.
 - Only women of childbearing potential and / or potential to become pregnant. Women of childbearing potential must necessarily use contraception during the first 15 days of the trial.
 - Visits through telephone contact, video call, telemedicine are calculated from the randomization date.
 - After signing the Informed Consent Form.
 - Questionnaires must be completed BEFORE any procedures of the proposed visit. Only a person not related to the research can help the patient during the questionnaire. In telephone visits, the patient must respond directly, at the time of contact.
 - Maintain the administration of the IP according to schedule. Discontinue it if adverse events prevent the IP from continuing.
 - Assessment of late complications associated with COVID-19.
 - Unscheduled visits may also be conducted as needed. The clinical outcome data collected at the unscheduled visit should be entered at the next scheduled visit. The treatment period is up to 14 days.
- COVID-19=coronavirus disease 2019, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2, WHO=World Health Organisation, ECG=electrocardiogram, TICS=Telephone Interview for Cognitive Status.

Figure 1. Research flowchart. 1. Treatment: Investigational Products (IP) IP 1, IP 2, IP 3 in parallel groups for the planned period. Discontinue if significant symptoms or adverse reactions. 2. Screening and randomization (baseline visit) must be performed on the same visit. Ensure that the patient is randomized when at medical care facility. Patient with confirmed SARS-CoV-2 positive test and less than 7 days of symptom onset can be considered for randomization. 3. Subsequent visits: D3, D7, D10, D14, D28, D60 will be carried out by primarily by telephone and/or social media App. Extra visits for safety purposes can be made at any time. Visits D14 and D28 are considered outcome visits as per protocol. D60 is considered post-study visit for monitoring late complications, including mortality, related to COVID-19 and eventual evaluation of late adverse reactions to research drugs and will be carried out by telephone. There is no provision for face-to-face visits in this research in view of the regulatory recommendations issued by the public health authority in the context of the pandemic. 4. Daily contact by phone (not marked above) will be made between Days 1 to 7. Phone contact after D7 will be performed as per protocol. COVID-19=coronavirus disease 2019, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

efficacy criterion at the final analysis be modified to ensure that, any further change to the original design will be documented and reported.

Interim evaluations

Interim efficacy analyses are scheduled. Assuming a uniform prior assigned to the different event rates, a total sample size of 681 patients per arm, a CER of 15%, and a RRR equals to 37.5%, an interim analysis will be performed after observing approximately 25%, 50% and 75% of the maximum number of patient outcomes, as well as at the trial completion. The posterior efficacy threshold to stop for superiority is 97.6% and the futility threshold is 20%, 40% and 60% at the respective interim analyses. Intervention arms(s) showing a posterior probability of efficacy crossing either boundary, will be stopped for either reason. These superiority and futility thresholds were determined based on 200,000 simulation runs wherein different values of the RRR were considered (0%, 20%, and 37.5%). A description of this interim analysis in an event-based Bayesian adaptive trial and accompanying illustrating example can be found in the appendix of this document.

When other data from other relevant studies become available, we will use Empirical Bayes meta-analysis⁵ to borrow information from the treatment effects or safety signals emerging from these

studies. This is effectively a random effect Bayesian model that results in simultaneous shrinkage of the treatment effect or safety estimates reported in the various studies toward the meta-analysis estimate, while still providing standalone estimates. Schoenfeld *et al.* have shown⁶ that this approach is, in some ways, equivalent to the power prior approach of Chen and Ibrahim⁷, whereby historical studies are assigned fractional weight(s) whose magnitudes correspond to the consistency of their data with that of the study they are thought to inform. The analyses incorporating external evidence will be presented to the DSMC as secondary findings to consider but will not alone trigger a recommendation for a trial adaptation.

Statistical analyses

A detailed description of the TOGETHER Trial statistical analysis plan can be found in the extended data⁴.

In brief, the efficacy of each intervention will be analyzed in terms of its posterior efficacy with respect to placebo, using the Bayesian paradigm, while calibrating the decision boundaries to meet the type I error rate requirements. We will adopt an intention-to-treat principle to analyze all results. For descriptive statistics, multiple imputation will be employed where baseline covariates with up to 20% missing values among age, sex, race, BMI, time since disease onset and comorbidities, using the Multiple Imputation by Chained Equations (MICE)

algorithm. However, adjustment to covariates - and subsequent pooled - analysis in the outcome model will only include covariates whose distribution appears to be imbalanced across the treatment arms.

We will validate the proportional hazards assumption by visually inspecting Kaplan-Meier and log-negative-log of survival plots and fit Cox model for time-to-event outcomes. Secondary outcomes, such as viral clearance will be modelled using a longitudinal logistic model with a subject random effect, using the PCR test result over time as our dependent variable.

Subgroup analyses

We will perform subgroup analyses to assess the consistency of effects in four patient subgroups:

- Age: ≥ 50 years or < 50 years
- Sex: Male or female
- Comorbidity in screening
 - o Diabetes mellitus (yes or no);
 - o Cardiovascular disease (yes or no);
 - o Lung disease (yes or no);
 - o Immunosuppressed patients / use of corticosteroid therapy (yes or no);
 - o Other special categories (solid organ transplantation, end-stage kidney disease).

We hypothesize that younger patients will benefit more than older patients, women will benefit more than men, patients with an earlier diagnosis will benefit more than those with a later diagnosis, and patients without the clinical co-morbidities described above will benefit more than those with these co-morbidities. All the subgroup hypotheses are based on data emerging from other countries, indicating the differential impact of COVID-19 by age, sex and the existence of clinical comorbidities at baseline conditions.

Data from the IBM eCRFs are securely sent by File Transfer Protocol (FTP) to the statistical team in SAS format. SAS v9.4 is used to convert raw data into an analytic dataset applying CDISC standards. Analyses are conducted using R v4.0.3. Results will be reported following the CONSORT guidelines.

Role of the funding source

The funder of this trial had no role in study design, data collection, decision to publish, or preparation of the manuscript.

Dissemination of study findings

The final trial dataset will be accessible by written request to the study principal investigators (G Reis or EJ Mills). There are no contractual agreements to limit access to final trial data. All data collected by the TOGETHER Trial will be shared with the International COVID-19 Data Alliance. Access to these data through the ICODA Workbench will follow the standard operating procedures developed by the ICODA working group.

Findings will be disseminated in several ways. All investigations of IPs vs. placebo will be submitted to an appropriate,

peer-reviewed scientific journal. Lay summaries of findings will be made available on the TOGETHER Trial website (togethertrial.com). The investigative team is also connected to the WHO COVID-19 guidelines committee, where trial findings will help inform global clinical guidance.

Study status

The TOGETHER Trial has randomized more than 3700 patients to date. The trial has previously evaluated the effect of hydroxy-chloroquine or lopinavir/ritonavir on risk of hospitalization⁸. Investigations evaluating metformin, ivermectin, and flvoxamine have been completed and manuscripts are under-development. Investigations are continuing for doxazosin and pegylated interferon lambda. The IPs of investigation in the TOGETHER Trial and their study status at the time of writing is further described in Table 1.

Discussion

Our TOGETHER trial is innovative in a number of ways. First, from a clinical perspective, we are examining the use of drugs that would be widely available and accessible if proven effective and safe for the treatment of COVID-19. Second, our trial uses a new methodological approach adaptable to both internal accumulating data, as is common in platform trials, as well as incorporating external trial evidence that may be unplanned at the time of initial study launch.

Currently, there are no effective approved therapeutic interventions approved for the early treatment of SARS-CoV-2⁹⁻¹¹. Proposed therapies for SARS-CoV-2 are based on previous clinical experience directed against SARS-CoV-1 and Middle East respiratory syndrome (MERS)¹². These therapeutic modalities consisted of viral methyl transferase inhibitors, protease inhibitors, interferon, inhibitors of viral ribonucleic acid (RNA) synthesis as well as anti-inflammatory drugs. For the treatment of COVID-19, there has been much promise and excitement for repurposing drugs that have similar targets described for SARS-CoV-1 and MERS¹³. The current use of repurposed drugs for COVID-19 treatment offers several key advantages as these medicines have been proven safe, their pharmacokinetics are well understood, and optimal dosages are standardized. Although hydroxychloroquine is ineffective for the treatment of COVID-19 among hospitalized adults¹⁴, other repurposed drugs have already shown promise against COVID-19 disease at the later stages of disease. Both dexamethasone and tocilizumab appear to significantly increase survival according to findings from the UK RECOVERY trials¹⁵. Furthermore, other new molecules such as remdesivir and monoclonal antibodies have had inconsistent findings^{16,17}. Unfortunately, well-designed studies on asymptomatic or mild, or pediatric cases of COVID-19 are lacking. Neither hydroxychloroquine nor lopinavir-ritonavir showed any significant benefit for decreasing COVID-19-associated hospitalization or other secondary clinical outcomes in early symptomatic COVID-19 patients⁸. In a preliminary study of adult outpatients with early COVID-19, patients treated with flvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days¹⁸. In another recent trial of favipiravir, an RNA-dependent RNA polymerase inhibitor, also did not show any statistically significant benefit in term of mortality in the general group of patients with mild to moderate COVID-19¹⁹.

It was suggested that the use of antivirals in symptomatic patients is too late and would explain their low efficacy in the clinical setting. A number of clinical trials (NCT04426695, NCT04425629, NCT04479631) have now been initiated to assess safety, tolerability, and efficacy of SARS-CoV-2 neutralizing monoclonal antibodies (nMAbs) using either a prophylactic or therapeutic approach^{20–22}. In addition, potent human monoclonal antibodies against SARS-CoV-2 have been isolated from COVID-19 convalescent patients which could provide another layer of therapeutic options against the disease²³. Thus, by blocking acute virus replication, early nMab intervention would potentially induce a better clinical outcome against COVID-19.

Our study has several limitations. The greatest limitation of our study is that the administrative stages of conducting a trial, from protocol development and ethics review to obtaining study drug and creating electronic case report forms are all reliant on the local infrastructure and norms of study conduct in those settings. Our adaptive elements of the trial complicate what is understood by some agencies and push-back from approval bodies has previously delayed enrolment. The rapid change in the scientific interest or confidence in interventions means that an application submitted to a funding agency or ethics committee, may, by the time it is reviewed, have changed dramatically. In addition, the generalizability of this trial is limited to patients who do not have severe terminal illness irrespective of type or etiology. Strengths of our study include the adaptive nature of the study to change arms by dropping or adding arms as the data, both internal and external. Our design permits outside data, from either trial we already collaborate with or trials with emerging data we learn of as we are conducting our trial. Similarly, outside evidence in the form of completed trials, may provide sufficiently compelling evidence to change the direction of our trial or change outcomes and interpretation of trial findings.

Our design is adaptive and also Bayesian in its learning structure and analysis. We refer to this as a learning structure as emerging data from our own trial will, almost certainly be influenced from data we were unaware of at the study outset. We are already learning of similar trials examining similar interventions (in at least one arm) where the population inclusion criteria and the outcomes can be harmonized with our dataset. Similarly, we may find out about completed trials that have convincing evidence that mandates a change in our trial. For example, if a large study with a similar population and outcome

found overwhelming evidence of a treatment effect (whether that is harm, futility, or benefit), we may examine our data to confirm that the direction of treatment effect is similar. This may take the form of matching the population using a strategy such as propensity scoring or combining in a meta-analysis.

Results from this trial will help identify repurposed therapeutics for COVID-19 that can easily be scaled in low- and middle-income settings. The novel methodological extension of the platform adaptive design to dynamically incorporate external evidence will be the first of its kind and may prove highly valuable for all COVID-19 trials and trials for other indications going forward.

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: A multi-center, adaptive, randomized, platform trial to evaluate the effect of repurposed medicines in outpatients with early coronavirus disease 2019 (COVID-19) and high-risk for complications: the TOGETHER master trial. <https://doi.org/10.17605/OSF.IO/EG37X>⁴.

This project contains the following extended data:

- ConsentForm_1.docx
- Signed_TOGETHER_MP_SAP.pdf (statistical analysis plan)
- TOGETHER_CRF_V2.2_05May2021.pdf
- SPIRIT_Fillable-checklist-Together-Trial.pdf

Reporting guidelines

Open Science Framework: SPIRIT checklist for 'A multi-center, adaptive, randomized, platform trial to evaluate the effect of repurposed medicines in outpatients with early coronavirus disease 2019 (COVID-19) and high-risk for complications: the TOGETHER master trial protocol'. <https://doi.org/10.17605/OSF.IO/EG37X>⁴.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ? ✓

Version 2

Reviewer Report 22 November 2021

<https://doi.org/10.21956/gatesopenres.14690.r31383>

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Christian Gluud

Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Anders Granholm

Department of Intensive Care, Rigshospitalet, Copenhagen, Denmark

We thank Edward Mills for his many positive reactions to our comments to the protocol and design article and the statistical analysis plan of the platform TOGETHER trial for COVID-19 patients by Reis and colleagues (Reis *et al.*, 2021¹). Moreover, we thank them for the many implemented amendments in the manuscript. All Mills' actions have substantially diminished our few reservations towards the manuscript. However, we are still a bit reluctant to give our full-blown thumbs-up due to the following:

1. We have been unable to identify the link to an updated statistical analysis plan. The links only seem to lead to the 2.0 version of the statistical analysis plan from June 22, 2021. Are we making any errors here?
2. We would have preferred more scientific detail and stringency regarding some of the statistical issues raised by us, including missing data handling, possible MCMC analyses, and incorporation of external data – even if this is not the primary plan. We can follow the decisions taken in the replies but suggest that these decisions become discussed more, describing the advantages and disadvantages of the decisions.
3. Kristian Thorlund, still having 'several hats on', seems only to lose his voting rights in the Data and Safety Monitoring Committee and is still appointed chair of the committee. We do not find this move sufficient to remove our worries as well as the worries any other outsiders may have. We are not suggesting that this will cause problems but seen from the outside it does not look sufficient for the committee to be called independent; what we think it should be (Ellenberg *et al.*, 2019²). If Kristian Thorlund is removed from the committee and gets a function as statistical advisor to the committee, then properly the team behind the trial as well as people from the outside the trial will both achieve what they want, an independently functioning committee that may obtain crucial statistical advice in

case it is needed.

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Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 08 November 2021

<https://doi.org/10.21956/gatesopenres.14690.r31384>

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Andrew Conway Morris

Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

All my prior comments have been addressed to my satisfaction, thank you.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular diagnostics, pneumonia diagnostics, critical care, neutrophil biology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 08 September 2021

<https://doi.org/10.21956/gatesopenres.14546.r31073>

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Andrew Conway Morris

Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

Thank you for asking me to review this manuscript which describes the protocol for a multi-agent platform trial of repurposed medications in the management of patients with early COVID-19. COVID has had a devastating effect on the world over the past 18 months, and although there is a growing armamentarium of pharmacological interventions, there remains potential for further improvements. In resource-limited settings, some of the therapies with proven benefit may not be available, and given the frequent use of repurposed medications in the management of patients with COVID-19 a trial of such interventions is highly warranted.

My comments are as follows

1. Consideration should be given to aligning the outcomes chosen to those identified in core-outcome sets to allow comparability with other trials (e.g. Tong *et al.*, 2021¹, or Marshall *et al.*, 2020²). This need not preclude the use of the outcomes identified by the protocol authors.
2. Inclusion criteria – cancer within last 55 years seems a prolonged period of time, most patients who have recovered from cancer and have been relapse free for at least 5 years could be considered immunologically normal in the absence of defined secondary immunocompromise (e.g. secondary hypoglobulinaemia).
3. Rapid antigen tests are relatively insensitive and may well miss patients who have a more moderate viral load, could consideration be given to PCR testing patients who are rapid antigen negative and enrolling if this returns positive if recruiting site resources allow?
4. The exclusion for ‘acute flu’ is unclear – does this refer to influenza (which is presumably excluded by being not COVID-19) or is it exclusion of patients with more severe acute presenting COVID-19 requiring likely immediate hospitalisation?
5. The definition of moderate to severe liver disease is unclear, sticking to Childs-Pugh C alone (or a lower C-P cut-off) would make this more objective.
6. Severe degenerative neurological disease or psychiatric disease are again vague – quantification of functional impairment, or in case of psychiatric disease requirement for psychiatric hospitalisation, or indication of specific diagnoses may make these more objective.
7. The inclusion of placebos is worthy of commendation – this has not been used in previous multi-platform trials, and the use of variable placebos in line with the agents being included is a novel and innovative approach to this issue and is to be commended.
8. It is unclear how the trial drugs included have been selected or what process is in place for

review and selection. Although several drugs included are those with established in-vitro antiviral activity (e.g. hydroxychloroquine, Lopinivir/ritnovir) both these have been subjected to large RCT assessment without any evidence of benefit, all-be-it in either more severe patients or in prophylaxis. Review of the existing literature, criteria for selection and rationale for each agent selected should be included. Rationale for the dose and dosing interval selected should also be included. The protocol authors rightly indicate that their trial is adaptable and will be informed by external trial results, but in the proposed initial medication this is not immediately apparent.

9. The previously published results of the HCQ, ritnovir/lopinavir (JAMA Network 2021) appear to show, with a different end-point (hospitalisation only) no benefit, it is unclear why they are included in this protocol as they are not being judged against the same endpoint as published here?
10. The power calculation assumes at 15% event rate, however the authors previous iteration of this study comparing HCQ, ritnovir/lopinavir and placebo (JAMA network open, 2021) had an event rate of 5% for hospitalisation. Do the authors have any data to indicate that the control group event rate of hospitalisation and prolonged ER stay is likely to be 3x higher than hospitalisation alone? The 37.5% relative risk reduction, corresponding to a 5.6% absolute risk reduction does seem fairly generous, and it would be helpful to know how that value had been selected (prior data, minimum clinically beneficial response?)

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular diagnostics, pneumonia diagnostics, critical care, neutrophil biology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Oct 2021

Edward Mills, McMaster University, Hamilton, Canada

1. Consideration should be given to aligning the outcomes chosen to those identified in core-outcome sets to allow comparability with other trials (e.g. Tong *et al.*, 2021¹, or Marshall *et al.*, 2020²). This need not preclude the use of the outcomes identified by the protocol authors.

Response: We have clarified the primary and secondary outcomes. As our trial is ongoing and has already enrolled over 3,000 participants we are unable to revise our outcomes at this time[SS1] .

2. Inclusion criteria – cancer within last 55 years seems a prolonged period of time, most patients who have recovered from cancer and have been relapse free for at least 5 years could be considered immunologically normal in the absence of defined secondary immunocompromise (e.g. secondary hypoglobulinaemia).

Response: We have corrected this typo. It should be 5 years, not 55 years.

3. Rapid antigen tests are relatively insensitive and may well miss patients who have a more moderate viral load, could consideration be given to PCR testing patients who are rapid antigen negative and enrolling if this returns positive if recruiting site resources allow?

Response: Due to availability of local resources in Brazil, we are unable to use PCR testing. We will use PCR testing when available[SS2] .

4. The exclusion for 'acute flu' is unclear – does this refer to influenza (which is presumably excluded by being not COVID-19) or is it exclusion of patients with more severe acute presenting COVID-19 requiring likely immediate hospitalisation?

Response: We have deleted this exclusion criteria as we agree that it is redundant with inclusion criteria 2.

5. The definition of moderate to severe liver disease is unclear, sticking to Childs-Pugh C alone (or a lower C-P cut-off) would make this more objective.

Response: As suggested by reviewer #1, we have removed this criteria and replaced it with the following: *severe terminal illness irrespective of type or etiology.*

6. Severe degenerative neurological disease or psychiatric disease are again vague – quantification of functional impairment, or in case of psychiatric disease requirement for psychiatric hospitalisation, or indication of specific diagnoses may make these more objective.

Response: As suggested by reviewer #1, we have removed this criteria and replaced it with the following: *severe terminal illness irrespective of type or etiology*.

7. The inclusion of placebos is worthy of commendation – this has not been used in previous multi-platform trials, and the use of variable placebos in line with the agents being included is a novel and innovative approach to this issue and is to be commended.

Response: Thank you for the positive feedback.

8. The previously published results of the HCQ, ritonavir/lopinavir (JAMA Network 2021) appear to show, with a different end-point (hospitalization only) no benefit, it is unclear why they are included in this protocol as they are not being judged against the same endpoint as published here?

Response: The composite endpoint addresses both hospitalization and a proxy for hospitalization, retention in a COVID-19 emergency setting, as many patients who would be hospitalized were prevented from admission due to hospital over-capacity during peak waves. This region of Brazil implemented hospital-like services in the emergency settings with 50-80 bed settings and providing services including oxygenation, sedation, multi-day stays, and mechanical ventilation. We have added the above text to the manuscript.

9. The power calculation assumes at 15% event rate, however the authors previous iteration of this study comparing HCQ, ritonavir/lopinavir and placebo (JAMA network open, 2021) had an event rate of 5% for hospitalization. Do the authors have any data to indicate that the control group event rate of hospitalization and prolonged ER stay is likely to be 3x higher than hospitalization alone? The 37.5% relative risk reduction, corresponding to a 5.6% absolute risk reduction does seem fairly generous, and it would be helpful to know how that value had been selected (prior data, minimum clinically beneficial response?)

Response: Thank you, assuming an excessively high CER has been detrimental to our purposes in the past. However, the event type we use these days has been shown to have a much higher CER (see our response to comment #4 of reviewer #1).

Competing Interests: No competing interests to declare

Reviewer Report 06 September 2021

<https://doi.org/10.21956/gatesopenres.14546.r31072>

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Christian Gluud

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Anders Granholm

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The study protocol by Reis and colleagues entitled the TOGETHER master trial protocol as well as the detailed statistical analysis plan (SAP) for the TOGETHER trial, and have been reviewed by us and discussed between us.

The authors have done a masterful job in many aspects. They are addressing a very prominent global health problem, namely outpatients with early coronavirus disease 2019 (COVID-19) and high risks of complications. They are assessing large numbers of interventions (to be decided) that may have a potential to benefit the course of disease and prevent complications. The authors are doing so in an international collaboration employing an adaptive platform trial structure with decentralized randomization by study pharmacists using centralized pre-generated randomization with variable block sizes. The randomization is stratified by clinical site and participant age (less than 50 years or more). The protocol promises placebo controls, an important advancement compared to many other current platform trials. The adaptive platform trial conducts novel analysis plans for the accumulating data combined with external trial evidence. The team of authors covers many experienced trialists, methodologists, and statisticians, which heralds high chances of success in conducting this complex adaptive platform trial. This is really a clinical research project that significantly may help to guide future treatments for such outpatients.

We have also some comments and points that we think should be addressed more in the protocol and/or SAP to become clearer as well as some points where this platform trial could consider adapting some of our suggestions. These comments and points are as follows:

Investigational products:

Considering the pressures for getting access to just something that could work against COVID-19 infection (e.g., chloroquine; ivermectin; bleach; etc.), we suggest the screening for interventions for this trial could maybe become a bit better described and organised? Why not center such screening around living systematic reviews of interventions for hospitalised patients with COVID-19 as well as for outpatients with COVID-19 (both less affected and as affected as the present cohort of participants)? As the patients going to be entered into the TOGETHER trial have been less well examined, ideas for interventions for this type of patients will likely come from other patient groups or similar patients but with less or more disease severity.

Sample size estimation:

We think the issue of sample size estimation needs reconsideration, discussion, and possible adaptation. The start intervention effect of a relative risk reduction (RRR) of 37.5% seems unrealistically high for most interventions directed at this condition and outcome. There will be risks of both stumbling over larger effects (type I errors) or smaller effects (type II errors) when the trial has low accrued sample size and these may lead to erroneous decisions and conclusions. As we are speaking often of repurposed drugs as experimental interventions, why not use the meta-analytic intervention effects to guide decisions of choice of RRR, often in the range of RRR of 5% to 15%? You seem to suggest this in 4.3.2 of your SAP, but it has not been adapted?

You address sample size re-estimation in 4.3.1 of the SAP, but we are bewildered as the methodology is not described in any detail and the heading states that this only deals with Brazil? We suggest these central aspects need detailed description in the SAP as well as clear mention and description in the article proper.

The control event proportion (CEP) chosen as 15% also seems too high. In your own publication of results from the TOGETHER trial, the placebo group had a CEP of 4.8% (Reis *et al.*, 2021¹); despite the small number of patients and associated uncertainty, the planned sample sizes may thus be too small for this proportion. Adaptation of realistic CEP for future sample size estimations will increase the demands for participants, but the problem in the world is not difficulties finding COVID-19 infected people. The type II error chosen is on the low side being only 80%. Would 85% not be more correct considering your own results in Appendix 1 of your SAP and the prominence this trial will likely achieve?

Exclusion criteria of participants:

Considering that you are dealing with outpatients where time constraints limit the possibilities for conducting in depth differential diagnostic activities, would it not be simpler and just as effective to condense or delete the following exclusion criteria:

- 4. Why have this at all?
- 5, 10, 11, 13, 14, 15, 16, which could be condensed into something like: severe terminal illness irrespective of type or etiology.

The substantial number of exclusion criteria limit the external validity to the full population of patients that may get treated with the assessed interventions somewhat, and exclusion of patients with several comorbidities may explain the lower than expected CEP. This may warrant further discussion in the manuscript.

Sites:

In the abstract, the authors write that the trial is currently ongoing in Brazil **and** Africa, but throughout the manuscript and SAP, only Brazil is mentioned. A paragraph clearly explaining the current number of sites, countries and total number of participants enrolled would be a valuable addition to the manuscript.

Randomisation strategy:

The authors describe the use of equal randomisation to all arms (control and interventional arms),

using stratified (for site and age < 50 years) block randomisation. First, the authors write that "blocking criteria (e.g. age and co-morbidities)" are texted to the unblinded pharmacist in control of allocation; this could be clarified. Which comorbidities? Why are the "blocking criteria" listed here different from the stratification variables? Further, the authors may elaborate a bit more on the planned change of block sizes if the number of arms in the trial is altered. Second, all experimental arms appear to be compared individually to the control. In this case, an increased control group allocation compared to the experimental group allocation ratios ratio may increase overall power in the trial, as previously discussed by several of the authors (Park *et al.*, 2020²). The authors may want to justify or clarify their choice. Further, while the decision to not use response-adaptive randomisation is fine, it could also be justified.

Blinding:

We think it is a decisive strength that this trial intends to be sufficiently blinded. How this blinding is carried out in real life should be sufficiently described. In your JAMA Network Open article was the placebo matching, and to what? Did the control patients receive three placebos matching the three vera? This needs clearer description.

Trial outcomes:

According to 4.3.4 at page 23 of the SAP, you intend to conduct a follow up interview at day 60. Why not use this data to assess more 'long-term' mortality as well?

Data Monitoring and Safety Committee:

Why is this committee not independent? Professor Thorlund is Vice President of the contract research organisation (CRO, i.e CYTEL), employee of the CRO, professor at the sponsoring university, author of the TOGETHER protocol, and member of the DMSC for the trial. Dr Haggstrom also seems connected to the CRO? And why is this committee not blinded?

Statistical analysis:

1. Missing data handling: the authors plan to use multiple imputation for baseline covariates with up to 20% missing values, with no imputation of outcome variables. This description is very sparse and could be expanded. Which imputation method will be used? How many imputations will be performed? Which variables will be included in the imputation models?
2. Prior choices: the authors plan to solely use flat priors. This is a convenient and reasonable choice, but it is often recommended to 1) justify prior choices and 2) consider sensitivity analysis using different priors (Sung *et al.*, 2005³). Could the authors comment on this?
3. The authors plan to use Markov chain Monte Carlo methods, but do not specify how chain convergence/model fit is going to be assessed. This is generally recommended (Sung *et al.*, 2005³) and should be added to the SAP.
4. The authors write: "We will use Bayesian inference for dichotomous outcomes, adjusting for covariates when necessary." More details seem necessary - while adjustment for relevant, pre-specified covariates is generally recommended in clinical trials (to increase power and

handle potentially important baseline imbalances), the adjustment strategy should ideally be pre-specified. Which co-variables will the author adjust for? When will it be considered "necessary"? Will the authors adjust for the stratification variables, as is generally recommended in stratified trials (Kahan and Morris, 2012⁴)? Ideally, the full model should be specified a priori.

5. The authors plan to incorporate external data using an empirical Bayes individual-participant data meta-analysis. This strategy appears sound - however, the authors write that this will be done **if** individual-participant data becomes available. Most trials (for data sharing/privacy reasons) do not share individual-participant data openly, and when done, this is usually after a substantial delay. Are the authors planning to contact relevant trials to obtain individual-participant data or is there another strategy for this in place? If not, it seems relatively unlikely that this will be possible, and then a bit less sophisticated but possibly practically more feasible strategy could be the inclusion of meta-analysed trial-level data in the analysis. Could the authors comment on this?
6. The individual-participant data meta-analysis is sparsely described, and further details would add substantial value. The authors write that they will use pseudo-informal variable selection, partially based on expert knowledge and on forward selection. This description is very vague and leaves a lot of room for "researcher degrees of freedom". Could the approach be described in greater detail? Which experts will be asked? How will the forward selection be performed? In general, the use of forward selection could also be discussed, as stepwise selection approaches are often recommended against (Smith, 2018⁵) due to the relatively high risk of incorrect selections.

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 20 Oct 2021

Edward Mills, McMaster University, Hamilton, Canada

Investigational products:

1. Considering the pressures for getting access to just something that could work against COVID-19 infection (e.g., chloroquine; ivermectin; bleach; etc.), we suggest the screening for interventions for this trial could maybe become a bit better described and organised? Why not center such screening around living systematic reviews of interventions for hospitalized patients with COVID-19 as well as for outpatients with COVID-19 (both less affected and as affected as the present cohort of participants)? As the patients going to be entered into the TOGETHER trial have been less well examined, ideas for interventions for this type of patients will likely come from other patient groups or similar patients but with less or more disease severity.

Response: Thank you for the comment. Investigational products tested for the TOGETHER Trial were carefully chosen by an international collaboration of pharmacological experts, clinicians, previous RCT's and an extensive literature search across multiple databases.

Sample size estimation:

2. We think the issue of sample size estimation needs reconsideration, discussion, and possible adaptation. The start intervention effect of a relative risk reduction (RRR) of 37.5% seems unrealistically high for most interventions directed at this condition and outcome. There will be risks of both stumbling over larger effects (type I errors) or smaller effects (type II errors) when the trial has low accrued sample size and these may lead to erroneous decisions and conclusions. As we are speaking often of repurposed drugs as experimental interventions, why not use the meta-analytic intervention effects to guide decisions of choice of RRR, often in the range of RRR of 5% to 15%? You seem to suggest this in 4.3.2 of your SAP, but it has not been adapted?

Response: Thank you for your great question. There is a balance to be found here between our quest to finding effective treatments, the magnitude of the effects, and the resources required to determine the efficacy of said treatment. A 5-15% RRR treatment is both limited

in its efficacy and hugely taxing in terms of the number of patients it would require, deeming it not worthy of investment. Our judgement was that around 30% RRR would represent a good working point.

3. You address sample size re-estimation in 4.3.1 of the SAP, but we are bewildered as the methodology is not described in any detail and the heading states that this only deals with Brazil? We suggest these central aspects need detailed description in the SAP as well as clear mention and description in the article proper.

Response: Thank you. We have now added the following text: "Sample size re-assessment will be performed, subject to the DSMC's approval, if after the third interim analysis the control event rate appears to be considerably lower to the one the original sample size calculation was based on, irrespective of the observed RRR. In that event, we will rerun the simulation based on the new sample size calculated and with the first three interim analyses taking place as originally planned, to confirm that no type I error rate inflation is occurring. Should the efficacy criterion at the final analysis be modified to ensure that, any further change to the original design will be documented and reported."

4. The control event proportion (CEP) chosen as 15% also seems too high. In your own publication of results from the TOGETHER trial, the placebo group had a CEP of 4.8% (Reis *et al.*, 2021¹); despite the small number of patients and associated uncertainty, the planned sample sizes may thus be too small for this proportion. Adaptation of realistic CEP for future sample size estimations will increase the demands for participants, but the problem in the world is not difficulties finding COVID-19 infected people. The type II error chosen is on the low side being only 80%. Would 85% not be more correct considering your own results in Appendix 1 of your SAP and the prominence this trial will likely achieve?

Response: Thank you for your question. This is the same issue addressed in our last response. We will comment that we have learned our lesson from the early TOGETHER trial, and evidently, the CER in the latest iteration of the trial has been almost spot on the expected 15%.

Exclusion criteria of participants:

5. Considering that you are dealing with outpatients where time constraints limit the possibilities for conducting in depth differential diagnostic activities, would it not be simpler and just as effective to condense or delete the following exclusion criteria:

- 4. Why have this at all?
- 5, 10, 11, 13, 14, 15, 16, which could be condensed into something like: severe terminal illness irrespective of type or etiology.

The substantial number of exclusion criteria limit the external validity to the full population of patients that may get treated with the assessed interventions somewhat, and exclusion of patients with several comorbidities may explain the lower than expected CEP. This may warrant further discussion in the manuscript.

Response: We agree with your suggestions and we have removed the exclusion criteria as suggested, and we have condensed them into a new exclusion criteria *severe terminal illness irrespective of type or etiology* as suggested. We have also add the following sentence to our discussion: *In addition, the generalizability of this trial is limited to patients who do not have severe terminal illness irrespective of type or etiology.*

Sites:

6. In the abstract, the authors write that the trial is currently ongoing in Brazil **and** Africa, but throughout the manuscript and SAP, only Brazil is mentioned. A paragraph clearly explaining the current number of sites, countries and total number of participants enrolled would be a valuable addition to the manuscript.

Response: The reference to Africa has been removed from the manuscript as that information was out of date. We have updated the 'Study status' section of our manuscript to include the current numbers of patients screened and randomized as well as interventions investigated.

Randomisation strategy:

7. The authors describe the use of equal randomisation to all arms (control and interventional arms), using stratified (for site and age < 50 years) block randomisation. First, the authors write that "blocking criteria (e.g. age and co-morbidities)" are texted to the unblinded pharmacist in control of allocation; this could be clarified. Which comorbidities? Why are the "blocking criteria" listed here different from the stratification variables? Further, the authors may elaborate a bit more on the planned change of block sizes if the number of arms in the trial is altered.

Response: We have clarified that we are only stratifying by clinical site and age. We have reorganized the randomization strategy section so that it is easier to follow.

8. Second, all experimental arms appear to be compared individually to the control. In this case, an increased control group allocation compared to the experimental group allocation ratios ratio may increase overall power in the trial, as previously discussed by several of the authors (Park *et al.*, 2020²). The authors may want to justify or clarify their choice. Further, while the decision to not use response-adaptive randomisation is fine, it could also be justified.

Response: Thank you for a great point raised. Indeed, response adaptive randomization could increase the power of the trial, if the goal is finding the most effective treatment among multiple active treatment. However, here we are interested in finding all effective treatments, therefore all test performed will involve control comparisons. Because the arms are not 100% overlapping, we need to confirm that each of them is compared to sufficiently many controls. To warrant that without planning on non-concurrent control borrowing, we have to apply 1:1 randomization ratio.

Trial outcomes:

9. According to 4.3.4 at page 23 of the SAP, you intend to conduct a follow up interview at day 60. Why not use this data to assess more 'long-term' mortality as well?

Response: We have revised the SAP to also look at long-term mortality[SS1] .

Data Monitoring and Safety Committee:

10. Why is this committee not independent? Professor Thorlund is Vice President of the contract research organisation (CRO, i.e CYTEL), employee of the CRO, professor at the sponsoring university, author of the TOGETHER protocol, and member of the DSMC for the trial. Dr Haggstrom also seems connected to the CRO? And why is this committee not blinded?

Response: We have corrected the membership of our DSMC and clarified that Professor Thorlund serves as the non-voting chair of the DSMC.

Statistical analysis:

11. Missing data handling: the authors plan to use multiple imputation for baseline covariates with up to 20% missing values, with no imputation of outcome variables. This description is very sparse and could be expanded. Which imputation method will be used? How many imputations will be performed? Which variables will be included in the imputation models?

Response: Thank you for your question. The following text was added to the SAP: "For descriptive statistics, multiple imputation will be employed where baseline covariates with up to 20% missing values among age, sex, race, BMI, time since disease onset and comorbidities, using the Multiple Imputation by Chained Equations (MICE) algorithm (van Buuren & Groothuis-Oudshoorn, 2011). However, adjustment to covariates - and subsequent pooled - analysis in the outcome model will only include covariates whose distribution appears to be imbalanced across the treatment arms."

12. Prior choices: the authors plan to solely use flat priors. This is a convenient and reasonable choice, but it is often recommended to 1) justify prior choices and 2) consider sensitivity analysis using different priors (Sung *et al.*, 2005³). Could the authors comment on this?

Response: Thank you for this thoughtful comment. While we agree with the general premise, we expect fairly large samples and number of events, therefore the chosen prior is unlikely to have much impact, and the convenience of using uniform priors is also likely to be received better by Bayes-skeptics. In fact, our results (e.g., point estimates and credible intervals) agree with standard frequentist analysis almost perfectly.

13. The authors plan to use Markov chain Monte Carlo methods we, but do not specify how

chain convergence/model fit is going to be assessed. This is generally recommended (Sung *et al.*, 2005³) and should be added to the SAP.

Response: To make it clear, Markov Chain Monte Carlo sampling will only ever be used in the rare event that adjusted analysis is required, in which case we will be using Stan, i.e., Hamiltonian Monte Carlo. We have added the comment and reference to the SAP.

14. The authors write: "We will use Bayesian inference for dichotomous outcomes, adjusting for covariates when necessary." More details seem necessary - while adjustment for relevant, pre-specified covariates is generally recommended in clinical trials (to increase power and handle potentially important baseline imbalances), the adjustment strategy should ideally be pre-specified. Which co-variables will the author adjust for? When will it be considered "necessary"? Will the authors adjust for the stratification variables, as is generally recommended in stratified trials (Kahan and Morris, 2012⁴)? Ideally, the full model should be specified a priori.

Response: Thank you for this important comment. This issue has now been addressed in the response (and the corresponding added text) to comment number 12.

15. The authors plan to incorporate external data using an empirical Bayes individual-participant data meta-analysis. This strategy appears sound - however, the authors write that this will be done **if** individual-participant data becomes available. Most trials (for data sharing/privacy reasons) do not share individual-participant data openly, and when done, this is usually after a substantial delay. Are the authors planning to contact relevant trials to obtain individual-participant data or is there another strategy for this in place? If not, it seems relatively unlikely that this will be possible, and then a bit less sophisticated but possibly practically more feasible strategy could be the inclusion of meta-analysed trial-level data in the analysis. Could the authors comment on this?

Response: Thank you. This is highly unlikely indeed. The cited paper makes no mention of IPD, and the inclusion of it in the text was erroneous. In any case, this will serve as merely a complementary analysis and not a primary one.

16. The individual-participant data meta-analysis is sparsely described, and further details would add substantial value. The authors write that they will use pseudo-informal variable selection, partially based on expert knowledge and on forward selection. This description is very vague and leaves a lot of room for "researcher degrees of freedom". Could the approach be described in greater detail? Which experts will be asked? How will the forward selection be performed? In general, the use of forward selection could also be discussed, as stepwise selection approaches are often recommended against (Smith, 2018⁵) due to the relatively high risk of incorrect selections.

Response: See our response to comment #16.

Competing Interests: No competing interests to declare