STUDY PROTOCOL

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 1; peer review: 2 approved with reservations]

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Reviewer Status

Invited Reviewers

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05 Aug 2021

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report

report

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is hospitalization due to clinical worsening of COVID-19 or emergency room required observation for more than 6 hours up to 28 days after randomization. Key secondary endpoints include viral clearance, clinical improvement, hospitalization for any cause, mortality for any cause, and safety and tolerability of each IP. 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 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 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

This article is included in the Coronavirus (COVID-19) collection.
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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 settings. 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. Early treatment trials have the added benefit of evaluating drugs with the outcome of disease progression or hospitalization. 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 or emergency room observation for greater than 6 hours among high-risk adults at 28 days post-randomization. This protocol is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

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 10 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:

1) Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) within 28 days of randomization;
2) Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.

The secondary objectives are to evaluate, in comparison with placebo, the effect of the IPs on the following parameters:

- All-cause, respiratory, and cardiovascular death
- Viral clearance and viral load on day 3 and 7 after randomization (conducted the first 150 randomized participants)
- Number of days with respiratory symptoms since randomization
- Time between the start of treatment until the need for hospitalization/urgent care due to the progression of COVID-19
- Rate of all-cause and COVID-specific hospitalizations
- Time between the start of treatment and the need for hospitalization for any reason
- Quality of life scale and symptoms (PROMIS-10 scale and WHO scale)
- Telephone Interview for Cognitive Status (TICS) memory assessment scale on day 28 post randomization
- Time from treatment to death (randomization up to 28 days)
- Adverse events, adverse reactions to the study medications, and the proportion of participants who are adherent with the medications will also be assessed

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

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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 55 years or undergoing current cancer treatment

l) Patients with documented fever at screening (>38°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 / treatment.

Patients who meet any of the following criteria are excluded:

1. Diagnostic examination for SARS-CoV-2 negative associated with acute flu-like symptoms (patient with negative test taken early and becoming positive a few days later is eligible, if he/she is <7 days after the onset of flu-like symptoms);
18. Known hypersensitivity and/or intolerance to IPs, or taking medications contraindicated by IPs;

19. 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 kit. On the day of randomization, 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 be randomly assigned to different placebo durations or regimens.

Randomization and allocation
Participants are randomly assigned with equal allocation using a pre-generated randomized list based on block sizes of 8. The block sizes may be increased or decreased depending on the number of active treatment arms. Allocation of participants to treatment arms is uniform across all concurrent interventions as well as placebo. Treatment allocation occurs using a central WhatsApp number where study staff text blocking criteria (e.g. age and co-morbidities) and an unblinded pharmacist replies to the message within 5-10 minutes with the medication letter and randomization number.

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 be randomized to different placebo durations or regimens.

The randomization is stratified by clinical site and by age (<50 years vs. ≥50 years). The randomization sequence for each clinical site is prepared by the unblinded study pharmacist at each participating clinical site. Allocation of treatment assignment is concealed from all other study personnel.

Blinding
Randomization information is kept confidential by an unblinded statistician. 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 data 1.

Study outcomes
The primary outcome of the trial is a composite of 1) emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) and 2) hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications.

Secondary outcomes include: 1) viral clearance and viral load, 2) time to clinical improvement, defined as the first day on which the participant reports a score of 0 on the WHO Clinical Worsening Scale, 3) number of days with respiratory symptoms since randomization, 4) time to hospitalization for any cause, 5) time to hospitalization due to COVID-19 progression, 6) all-cause, cardiovascular, and respiratory death and time to death from any causes, 7) WHO clinical worsening scale scores over the follow-up period, 8) WHO clinical worsening scale scores during the treatment phase, 9) health-related quality of life (PROMIS global health scale (“Global-10”), and, 10) cognitive status (Telephone Interview for Cognitive Status [TICS]). Adverse events, adverse reactions to the study medications and the proportion of participants who are non-adherent with the study drugs will also be assessed. 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. Participants will self-collect nasal swab and saliva for RT-PCR on day 3 and day 7 after randomization. Participants are instructed on this...
Table 1. Interventional Products (IPs) of evaluation in the TOGETHER trial (previous and current).

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


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.

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. Auditing of the trial occurs at the central level with 50–60% Source Data Verification (SDV).

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 DSMC 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 DSMC are followed-up by study physicians.

Members of the Data Safety and Monitoring Committee include Dr William Cameron of University of Ottawa (Canada), Dr James Orbinski of York University (Canada), Dr Sonal Singh of University of Massachusetts (USA), Dr. Kristian Thorlund of McMaster University (Canada) and Dr. Jonas Haggstrom of Cytel Inc. (Sweden).

Sample size
Our trial applies sample size reassessment according to observed events. The trial is a platform adaptive trial design with three
### Table 2. Schedule of study activities.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Day 1</th>
<th>Day 2±1 day</th>
<th>Day 3±1 day</th>
<th>Day 4±1 day</th>
<th>Day 5±1 day</th>
<th>Day 7±1 day</th>
<th>Day 10±2 days</th>
<th>Day 14±2 days</th>
<th>Day 28±3 days</th>
<th>Day 60±5 days or Early Termination±5 days</th>
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</thead>
<tbody>
<tr>
<td>Informed Consent</td>
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<td>SARS-CoV-2 Rapid Test</td>
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<td>Eligibility Criteria Review</td>
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<td>Co-morbidities and Risk Factors</td>
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<td>Substance Abuse</td>
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<td>PROMIS Global Health Scale</td>
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<td>Nasopharyngeal Swab</td>
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<td>Hospitalization / Emergency Room Visits</td>
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<td>Respiratory Symptoms</td>
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<td>Adverse Drug Reactions</td>
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<td>Vaccination Status</td>
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<td>TICS scale - Memory Evaluation</td>
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**Legend**

1. **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.
2. 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.
3. 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.
4. Visits through telephone contact, video call, telemedicine are calculated from the randomization date.
5. After signing the Informed Consent Form.
6. 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.
7. Maintain the administration of the IP according to schedule. Discontinue it if adverse events prevent the IP from continuing.
9. 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.

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 the risk of hospitalization and emergency room care at least 6 hours in duration due to complications directly related to COVID-19. The sample size of 681 patients per arm was chosen for each experimental group to achieve 80% power with 0.05 two-sided Type I 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%. The sample size calculation will be revised based on the outcomes that occurred during the interim analyses. Blind analysis of outcomes with simulations will be conducted to limit type I errors within the 5% tolerance range (97.5% or greater probability of superiority over the control group). Individual treatment arms can be stopped if there are no acceptable projections of benefit at the expense of futility.

**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-analysis 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 shown that this approach is, in some ways, equivalent to the power prior approach of Chen and...
Ibrahim², 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 data¹.

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. Multiple imputation will be employed where statistical models require adjustment for baseline covariates with up to 20% missing values. No multiple imputation of outcomes will be performed.

We will use Bayesian inference for dichotomous outcomes, adjusting for covariates when necessary. Similarly, 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
  - Diabetes mellitus (yes or no);
  - Cardiovascular disease (yes or no);
  - Lung disease (yes or no);
  - Immunosuppressed patients / use of corticosteroid therapy (Yes or No);
  - 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 ICO DA Workbench will follow the standard operating procedures developed by the ICO DA 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 recruited more than 3000 patients to date. The trial has previously evaluated the effect of hydroxychloroquine or lopinavir/ritonavir on risk of hospitalization⁴. An arm evaluating metformin vs. placebo was stopped early by the DSMC for futility. Other arms evaluating ivermectin and fluvoxamine are continuing. Future planned evaluations will include 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 incorporate 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-2.⁵,⁶,⁷ Proposed therapies for SARS-CoV-2 are based on previous clinical experience directed against SARS-CoV-1 and Middle East respiratory syndrome (MERS).⁸ 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 MERS⁹. 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 adults, 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 trials. Furthermore, other new molecules such as remdesivir and monoclonal antibodies have had inconsistent findings. 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 patients. In a preliminary study of adult outpatients with early COVID-19, patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. In another recent trial of favipiravir, an RNA-dependent RNA polymerase inhibitor, also did not show any statistically significant benefit in terms of mortality in the general group of patients with mild to moderate COVID-19. 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. 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 disease. Thus, by blocking acute virus replication, early nMAb intervention would potentially induce a better clinical outcome against COVID-19.

Our study has several limitations. Perhaps 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 enrollment. 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. 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

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

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).
References


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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., 2021\(^1\), or Marshall et al., 2020\(^2\)). 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/ritonavir) 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, ritonavir/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, ritonavir/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?)

References

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.

Reviewer Report 06 September 2021
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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., 2021); 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., 2020). 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., 2005). 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., 2005) 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-variates 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, 2012)? 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, 2018) due to the relatively high risk of incorrect selections.

References
Abstract | Publisher Full Text

**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.