

## **Effect of Early Treatment with Metformin on Risk of Emergency Care and Hospitalization Among Patients with COVID-19: The TOGETHER Randomized Platform Clinical Trial**

TOGETHER COLLABORATIVE GROUP\*

\* Writing committee listed below on behalf of the TOGETHER Collaborative Group. TOGETHER trial collaborators are listed at the end of the manuscript

Gilmar Reis, MD\*

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[administrador@cardresearch.org](mailto:administrador@cardresearch.org)

Eduardo Augusto dos Santos Moreira Silva, MD

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[duduaugusto1@yahoo.com.br](mailto:duduaugusto1@yahoo.com.br)

Daniela Carla Medeiros Silva, MD

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[daninhamed@yahoo.com.br](mailto:daninhamed@yahoo.com.br)

Lehana Thabane, PhD

Department of Health Research Methods, Evidence, and Impact, McMaster University Hamilton, Ontario, Canada

[ThabanL@mcmaster.ca](mailto:ThabanL@mcmaster.ca)

Aline Cruz Milagres, RN

Department of Public Health, Montes Claros State University, Brazil

[aline.milagres2@gmail.com](mailto:aline.milagres2@gmail.com)

Thiago Santiago Ferreira, MD

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[thiagosantiagoferreira@gmail.com](mailto:thiagosantiagoferreira@gmail.com)

Castilho Vitor Quirino dos Santos

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[vitor-quirino@hotmail.com](mailto:vitor-quirino@hotmail.com)

Adhemar Dias de Figueiredo Neto, MD

Public Health Fellowship Program, Governador Valadares Public Health Authority, Brazil

[adhemarfigueiredo@hotmail.com](mailto:adhemarfigueiredo@hotmail.com)

Eduardo Diniz Callegari, MD

Public Health, Mental and Family Medicine Department, Ouro Preto Federal University, Brazil

[edudiniz\\_18@hotmail.com](mailto:edudiniz_18@hotmail.com)

Leonardo Cançado Monteiro Savassi, MD

Public Health Fellowship Program, Governador Valadares Public Health Authority, Brazil

[Savassi@ufop.edu.br](mailto:Savassi@ufop.edu.br)

Maria Izabel Campos Simplicio, BScPharm

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[izabelcampos05@gmail.com](mailto:izabelcampos05@gmail.com)

Luciene Barra Ribeiro, RN

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[lucienebarraribeiro@yahoo.com.br](mailto:lucienebarraribeiro@yahoo.com.br)

Rosemary Oliveira

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil

[roliveira@cardresearch.org](mailto:roliveira@cardresearch.org)

Ofir Harari, PhD

Cytel Inc, Vancouver, British Columbia, Canada

[Ofir.Harari@cytel.com](mailto:Ofir.Harari@cytel.com)

Holly Bailey, MSc

Cytel Inc, Vancouver, British Columbia, Canada

[Holly.Bailey@cytel.com](mailto:Holly.Bailey@cytel.com)

Alla V. Glushchenko, MD, PhD

Department of Health Research Methods, Evidence, and Impact, McMaster University Hamilton, Ontario, Canada

[aglushchenko@platformsciences.ca](mailto:aglushchenko@platformsciences.ca)

Sheila Sprague, PhD

Department of Health Research Methods, Evidence, and Impact, McMaster University Hamilton, Ontario, Canada

[sprags@mcmaster.ca](mailto:sprags@mcmaster.ca)

Paula McKay, MSc

Department of Health Research Methods, Evidence, and Impact, McMaster University Hamilton, Ontario, Canada

[mckayp@mcmaster.ca](mailto:mckayp@mcmaster.ca)

Craig R. Rayner, PharmD

Certara Inc. New Jersey, USA

[craig.rayner@certara.com](mailto:craig.rayner@certara.com)

Hinda Ruton, MSc

Cytel Inc, Vancouver, British Columbia, Canada

[Hinda.Ruton@cytel.com](mailto:Hinda.Ruton@cytel.com)

Gordon H. Guyatt, MD

Department of Health Research Methods, Evidence, and Impact, McMaster University Hamilton, Ontario, Canada

[guyatt@mcmaster.ca](mailto:guyatt@mcmaster.ca)

†Corresponding Authors: **Gilmar Reis MD, PhD**

Address: Director - Research Division  
CARDRESEARCH – Cardiologia Assistencial e de Pesquisa  
Associate Professor of Medicine  
Pontificia Universidade Católica de Minas Gerais  
Rua Domingos Vieira 300, Sala 606 – Santa Efigenia  
Belo Horizonte – Minas Gerais  
Brazil – ZIP: 30.150-242  
Email: [administrador@cardresearch.org](mailto:administrador@cardresearch.org)  
[greis@pucminas.br](mailto:greis@pucminas.br)

**Edward Mills PhD, FRCP**  
Professor  
Health Research Methods, Evidence & Impact  
McMaster University  
Hamilton, Ontario, Canada  
Email: [millsej@mcmaster.ca](mailto:millsej@mcmaster.ca)  
Phone: 778 317 8530

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**ABSTRACT (365)**

**BACKGROUND** Observational studies have postulated a therapeutic role of metformin for COVID-19 disease. We aimed to determine whether metformin is an effective treatment for high-risk patients with early symptomatic COVID-19 in an outpatient setting using a prospective, randomized clinical trial.

**METHODS** We used a placebo-controlled, randomized, platform trial conducted in Brazil. Recently symptomatic adults positive for SARS-CoV-2 were enrolled. We enrolled eligible patients over the age

of 50 years or with a known risk factor for disease progression. Patients were randomly assigned to either a placebo or metformin arm (750 mg twice daily for 10 days or placebo, twice daily for 10 days). The primary outcome was a composite of emergency room visits due to clinical worsening of COVID-19 (requiring observation for > 6 hours) or hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) within 28 days of randomization. Secondary outcomes included death, viral clearance, adverse events, adverse drug reactions, and cause of mortality. We used a Bayesian framework to determine probability of success of the interventions.

**RESULTS** The trial was initiated June 2, 2020. We randomized patients to metformin starting January 15, 2021 to April 3, 2021, after which the independent Data and Safety Monitoring Committee recommended stopping enrollment of metformin arm due to futility. We recruited 423 participants, 217 were randomized to the metformin arm and 206 to the placebo arm. More than half of participants (55.6%) were over the age of 50 years and 57.0% were female. Median age was 52 (range 18-90), with IQR 17. The proportion of patients hospitalized or visited an emergency room for 6 hours was not different between the metformin and placebo group (relative risk [RR] 1.15 [95 % Credible Intervals 0.73; 1.83]), probability of superiority 0.27. We found no significant differences between the metformin and placebo group on viral clearance through day 7 (Odds ratio [OR], 1.04, 95% Confidence Intervals 0.91-1.18) or other secondary outcomes.

**CONCLUSIONS** In this randomized trial, metformin did not demonstrate any benefit on COVID-19 associated emergency room observations or hospitalization or other secondary clinical outcomes. This trial demonstrates that expedient clinical trials can be implemented in low-income settings even during periods of crisis.

Registration: ClinicalTrials.gov: NCT04727424.

## INTRODUCTION

The pathogenesis of SARS-CoV-2 is strongly associated with an over activation of the inflammatory response, a life-threatening condition known as a ‘cytokine storm’.<sup>1,2</sup> SARS-CoV-2 infection has led to more than 177 million confirmed cases globally and more than 3.8 million deaths as of June 18, 2021. Brazil has the highest national COVID death count, 500,800, since the start of pandemic.<sup>3</sup> Mortality is high in some patient groups. Those with chronic cardiovascular diseases such as clinically overt heart failure, coronary artery disease, dilated LV cardiomyopathy have higher mortality in the course of the disease. Likewise, patients with diabetes, chronic respiratory diseases and systemic arterial hypertension have high mortality, compared to individuals with COVID-19 without these comorbidities.<sup>4</sup>

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

Some repurposed drugs have demonstrated activity against coronaviruses in pre-clinical studies.

Metformin is the most commonly prescribed type 2 diabetes medication due to its ability to lower blood glucose by suppressing hepatic glucose production. In addition to its ability to lower blood glucose, metformin decreases levels of TNF $\alpha$ , adipokines and IL-6, and increases levels of IL-10, which have been observed both in experimental studies and in studies carried out in patients with type 2 diabetes mellitus and are more prevalent in women.<sup>5-7</sup> The effects associated with the reduction in circulating adipokines may minimize the degree of inflammatory response and thus reduce the severity of the disease.<sup>8</sup>

Retrospective observational studies and systematic reviews of observational studies have all suggested that the clinical complications and mortality in patients with COVID-19 may be lower in patients using metformin.<sup>9-11</sup>

Considering these potentially important findings and the safety profile of metformin, there is a need for randomized trials using this drug in patients with COVID-19. Treating COVID-19 early in outpatient settings may be key to preventing progression of the disease.<sup>12</sup> To evaluate the efficacy of metformin to prevent progression of COVID-19 and hospitalization among outpatients with laboratory-documented SARS-CoV-2, we conducted a randomized, placebo-controlled adaptive platform trial in Minas Gerais, Brazil. Among eight different interventions evaluated in this platform trial, we report here on the clinical evaluation of metformin using a common placebo control group. This flexible platform trial design allows for additional agents to be added and tested with standardized operating procedures outlined in a single overarching protocol called a master protocol.<sup>13-15</sup>

## **METHODS**

### **STUDY DESIGN AND OVERSIGHT**

The TOGETHER Trial is a randomized adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients. Platform trials can evaluate several intervention arms. The trial was designed and conducted in partnership with local public health authorities from ten participating cities in Brazil. The trial began on June 2, 2020 and began enrolling into the metformin arm on January 15th 2021. The protocol was approved in compliance with the International Conference of Harmonization – Good Clinical Practices, as well as local regulatory requirements. The trial was approved for research ethics by local ethics board in Brazil (CAAE: 41174620.0.1001.5120) as well as well as the Hamilton Integrated Research Ethics Board (HiREB) in Canada. The full protocol, statistical analysis plan, and additional details are appended in the web-appendix. We used the adaptive designs CONSORT extension (ACE) statement for reporting this trial.<sup>16,17</sup>

### **PARTICIPANTS**

We included participants if they were at least 18 years or older, presented to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date, had positive rapid test for SARS-CoV-2 antigen performed at the time of screening or patient with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset. Eligible participation also required at least one additional criterion for high-risk: diabetes mellitus; systemic arterial hypertension requiring at least one oral medication for treatment; known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion); symptomatic lung disease and / or being treated (emphysema, fibrosing diseases); symptomatic asthma patients requiring chronic use of agents to control symptoms; smoking; obesity, defined as BMI > 30 kg / m<sup>2</sup> (weight and height information provided by the patient); transplant patients; patient with stage IV chronic kidney disease or on dialysis; immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy; patients with a history of cancer in the last 05 years or undergoing current cancer treatment. Patients (age  $\geq$  50 years) did not need any other risk criteria.

Patients who meet any of the following criteria were excluded from the study:

1. Diagnostic examination for SARS-CoV2 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);
2. Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need;
3. Patients with acute respiratory condition due to other causes;
4. Patients who have received vaccination for SARS-CoV2;



5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);
6. Acute flu showing at least ONE of the criteria below:
  - i. Respiratory Rate  $> 28$  / min;
  - ii. SaO<sub>2</sub>  $< 90\%$  or  $< 93\%$  on nasal oxygen therapy at 10 L / min;
  - iii. PaO<sub>2</sub> / FIO<sub>2</sub>  $< 300$  mm Hg;
7. Patients using serotonin receptor inhibitors: donepezil, sertraline;
8. Use of the following medications in the last 14 days:
  - i. Monoamine Oxide Inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide);
  - ii. Use of iodinated contrasts during treatment until 05 days after the end;
  - iii. Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome - AIDS);
9. Patients with severe psychiatric disorders or major depression not controlled or controlled with any of the prohibited drugs (item above);
10. Pregnant or breastfeeding patients;
11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with recovered ventricular fibrillation) or long QT syndrome;
12. History of diabetic ketoacidosis or clinical condition that maintains persistent metabolic acidosis;
13. Surgical procedure or use of contrast planned to occur during treatment or up to 5 days after the last dose of the study medication;
14. Current daily and / or uncontrolled alcoholism;

15. History of seizures in the last month or uncontrolled seizure;
16. Clinical history of liver cirrhosis or Child-Pugh C classification;
17. Patients with known severe degenerative neurological diseases and / or severe mental illness;
18. Inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol;
19. Known hypersensitivity and / or intolerance to fluvoxamine, ivermectin or metformin;
20. Inability to take oral medications;
21. Inability or unwillingness to follow research guidelines and procedures.

## **SETTING**

We involved the local public health authorities from participating cities, including facilitation of active partnerships with several levels of local public health structure in Brazil. The appended web-appendix lists the cities and investigators.

## **TRIAL PROCEDURES**

Upon presentation, if participants agreed, we obtained written informed consent and then the procedures for screening were performed. Each participant was initially screened to identify those who met the eligibility criteria. As soon as a participant met all the eligibility criteria, he/she began the baseline visit phase. The following activities were carried out during the screening/randomizing visit: performing the rapid antigen test for COVID-19 (Panbio, Abbott), obtaining demographics, medical history and concomitant medications information, performing pregnancy test for women of childbearing age,

assessing co-morbidities and risk factors, collecting exposure to Index Case Information, WHO clinical worsening scale, PROMIS Global Health Scale.

The trial consisted of face-to-face screening visits (day 0) and follow-up visits completed through telephone contact and social media applications using video-teleconferencing. Follow-up visits were performed on days 1, 2, 3, 4, 5, 7, 10, 14, and 28. Participants were also contacted at day 60, to assess long-term outcomes. Participants who prematurely discontinued the product under investigation remained in the study, according to intention to treat. Unscheduled visits (during the treatment period) could occur at any time in case of adverse events.

Considering the extremely transmissible characteristic of SARS-CoV-2 and the isolation recommendations of positive individuals, limited vital sign data were collected. Cardiac safety was assessed using a 6-lead ECG (Kardiamobile, Mountain View, CA). The digital recordings were de-identified and transferred to a central facility (Cardresearch, Belo Horizonte, Brazil) for reading. Oxygen status was assessed using a pulse oximeter for non-invasive arterial oxygen saturation (SpO<sub>2</sub>) and pulse (Jumper Medical Equipment, Shenzhen, China), and temperature using a standard digital oral thermometer. Mid-turbinate nasal swab kits and sterile recipient storage were provided for collection of nasopharyngeal swab or sputum/saliva. They were performed by the first quarter of participants enrolled in the trial at days 3 and 7.

Patients were contacted on a daily basis during the study drug period for medical adherence, adverse drug reactions, adverse events, WHO clinical worsening scale, respiratory symptoms, any hospitalization/emergency room visits, concomitant medications information, and PROMIS Global Health Scale (day 14, 28 and 60).

## **TRIAL INTERVENTIONS**

We randomized patients to the metformin and placebo arms stratified to account for other arms in the trial. Randomization was stratified by clinical site and age ( $\geq 50$  years vs  $< 50$  years). Patients,

investigators, health-care providers and sponsors were masked to the study drug assignment. The randomization schedule was prepared by the study pharmacist and provided to blinded site staff.

Patients assigned to the metformin arm received 750 mg dose twice daily for a period of 10 days. Patients assigned to the placebo arm received corresponding tablets of inert material (talc). Placebo tablets were matched for the same number of tablets as active metformin (placebo of metformin).

### **PRIMARY OUTCOMES**

Our primary outcomes were to determine if the repurposed drug, metformin, reduces emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) or hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.

### **SECONDARY OUTCOMES**

Secondary outcomes were WHO clinical worsening scale, PROMIS global health scale, mortality defined and all-cause, cause-specific hospitalization, viral clearance and viral load, respiratory symptoms, adverse events, adverse drug reactions, and adherence. All serious and non-serious adverse events were reported as per local regulatory requirements. Reportable adverse events included serious AEs (SAE), AEs resulting in study medication discontinuation, and AEs assessed related to study medication.

### **STATISTICAL ANALYSIS**

Our study is adaptive and applies sample size re-estimation approaches. To plan for each arm, we assume minimum clinical utility of 37.5% (relative risk reduction) to achieve 80% power with 0.05 two-sided Type 1 error for a pairwise comparison against the placebo (talc) assuming a control event rate (CER) of 15%. This results in an initial plan to recruit 681 participants per arm. Planned interim analyses are conducted. Stopping thresholds for futility were established if the posterior probability of superiority was

less than 40% for this interim analyses. An arm can be stopped for superiority if the posterior probability of superiority meets the threshold of 97.6%

Baseline characteristics are reported as proportions or median and IQR for continuous variables. We applied a Bayesian framework for our primary analysis. Posterior efficacy of metformin for the primary outcome is calculated using the beta-binomial model for event rates, assuming informed priors based on the observational data for both placebo and metformin, for both Intention-to-Treat (ITT) and Per-Protocol (PP) analyses.

For viral clearance we fitted a longitudinal, mixed-effect logistic regression model with a treatment and time interaction term for binary patient outcomes (Covid-19 positive/negative) reported on day 3 and 7 from randomization, with subject random effect. PP analyses were considered sensitivity analyses to assess the robustness of the results. All analyses were performed using R version 4.0.3. Full details of the Statistical Analysis Plan (SAP) are appended.

## **DATA AND SAFETY MONITORING COMMITTEE**

We have a data safety monitoring board (DSMC) to provide an independent oversight for this trial. We planned an interim analysis of the metformin arm with the data cut from April 03, 2020.

## **RESULTS**

### **Population**

We enrolled our first patient in the metformin on January 15, 2021. The Data Monitoring and Safety Committee advised to stop enrolling patients to metformin because the posterior probability of efficacy was below the 40% futility threshold determined based on 200,000 simulation runs for three different relative risk reduction: 0%, 20%, and 37.5%.

By April 03, 2021, 423 participants were recruited and randomized to the metformin or the placebo group since January 15, 2021. The median age was 52 years (range 18-90); there were 241 participants (57.0%) were women (table 1). Most participants self-identified as mixed-race 387 (91.5%), 7 (1.7%) as white, 6 (1.4%) as black or African American, the rest self-identified as other or unknown 23 (5.4%). In total, 217 participants were allocated to the metformin arm, and 206 to the placebo arm (figure 1). With respect to covariates of age, BMI, and co-morbidities, the groups were generally well balanced (

Table 1).

### **Primary Outcomes**

Based on the Bayesian beta-binomial model, there was no evidence of a benefit in hospitalization or a six hour visit to an emergency room due to COVID-19 in the metformin arm versus placebo (relative risk [RR] 1.15, 95% credible interval (CrI) 0.73;1.83) for the ITT population and (RR 1.18, 95%CrI, 0.74;1.89) for the PP population. The probability that the event rates was lower in the metformin group compared to placebo was 27.4% for the ITT population and 23.9% for the PP population (figure 2). These posterior efficacy numbers were lower than the pre-specified 40% threshold set for the second interim analysis. In the metformin group 32 (17.2%) participants were hospitalized or spent six hours or more in an emergency room due to COVID-19 compared to 27 (14.5%) in the placebo group (Error! Reference source not found.2).

### **Secondary Outcomes**

#### **Virological clearance**

In our mixed-effect logistic regression model, the clearance for the metformin (odds ratio [OR], 1.04; 95% Confidence Interval [CI], 0.91-1.18) group did not differ in comparison with the control group (supplementary table 1) for the ITT population.

## **Clinical Improvement**

In the mixed-effect logistic model, the clinical improvement, defined as the time participants reported a score of 0 on the World Health Organization clinical worsening scale for the metformin (OR 0.99; 95% CI, 0.97-1.01) group did not differ in comparison with the control group for the ITT population.

## **Adverse events**

The treatment-emergent adverse events were described in grades 1-5 based on the severity of the adverse event. There were 47 (21.7%) treatment-emergent adverse events in the metformin, of which 33 (15.2%) were serious and 1 (100%) leading to discontinuation. In the placebo arm, we recorded 42 treatment-emergent adverse events, of which 28 were serious (13.6%) with none leading to discontinuation. No significant differences were observed in grades, except there were less adverse events in the placebo arm at grade 3. Grade 3 indicates severe, or medically significant but not immediately life-threatening condition, hospitalization or prolongation of hospitalization is indicated. At the end of the trial, we recorded 16 (3.0%) fatalities, 9 (3.5%) in the placebo group and 7 (2.6%) in the metformin intervention group (grade 5) (Figure 3).

## **Adherence**

At the time, the recruitment of the metformin arm was stopped, 31 (14.0%) participants in the metformin group did not complete all phases of the study. Twenty (9.7%) participants did not complete the study in the placebo group (figure 1).

## **DISCUSSION**

We found no important effect of metformin over placebo for the early treatment of COVID-19 on the primary outcome of retention in emergency care or hospitalization. We similarly observed no benefit of metformin on any secondary outcome for any subgroup in our trial. Our independent DSMC, based on an

interim evaluation, made the decision to stop the metformin arm as no signal of treatment effect was detected according to pre-specified criteria as well as external evidence. Our study continues evaluating other interventions that exhibited more compelling signals of treatment effect as well as new interventions.

Our study is a platform adaptive design with multiple arms and the potential to add or drop arms for the purpose of efficiency.<sup>18</sup> Our DSMC has previously recommended stopping treatment arms for lack of benefit with hydroxychloroquine and also lopinavir/ritonavir.<sup>19</sup> Stopping treatment arms early for lack of treatment effect is an accepted strategy for reducing waste and, in the context of platform trials, allowing the trial to replace the treatment arms with next available interventions while maintaining the infrastructure of patient recruitment and staffing. Much has been reported about both the merits of interim evaluations and the potential for type 1 and type 2 error; in particular for stopping trials early for superiority.<sup>20,21</sup> In this case, our intervention arm was stopped early due to undetectable differences against placebo, and we have used this trial efficiency to replace the treatment arm with a new drug. The trial currently evaluates ivermectin, fluvoxamine, doxazosin, peginterferon lambda, and placebo.

Since the pandemic first began, there have been more than 2800 RCTs registered on [clinicaltrials.gov](https://clinicaltrials.gov), yet less than 300 have been reported and the vast majority of clinical trials have been small, with sample sizes less than 100. In many cases, the trials have been unsuccessful at recruiting as the local epidemics have occurred in waves and most trials did not have sustainable infrastructure to maintain staff or local interest for recruitment. The trials that have had the greatest contributions to our medical understanding tend to be the larger platform trials, such as SOLIDARITY, RECOVERY, PRINCIPLE, and REMAP-CAP. We actively collaborate with other investigators running trials with overlapping interventions so that they can be aware of our study decisions and determine whether they should influence their respective trials. The University of Minnesota study evaluating metformin among a matched population to ours has decided to continue randomizing to metformin (NCT04510194).



Our current study has both strengths and limitations. Strengths include the rapid recruitment and enrolment of patients at high-risk of developing severe COVID-19. Our recruitment strategy engaged with the local public health system, thus allowing recruitment that frequently exceeds twenty patients per day. Our understanding of the epidemiology of COVID-19 as well the disease progression and outcomes of patient importance have evolved since beginning this trial in June 2020. We made adaptations to the trial according to prespecified rules and in communication with the appropriate ethics review committees that allowed us to respond to the epidemic waves while maintaining high rates of recruitment. Unlike many outpatient clinical trials, our study involves direct patient contact through the use of medical students, nurses and physicians who do at-home visits as well as follow-up via telecommunications. Given the rapid recruitment of patients as well as the high event rate of emergency room visits and hospitalizations, we were able to evaluate the effects of interventions when portions of the planned population had been recruited. The period of time between first recruitment of a patient on metformin and discontinuing the treatment arm for our trial was 78 days. The rapid discontinuation of this treatment arm increased allocation to other treatment arms as well as allowed us to enter a new intervention into the trial for evaluation.

Limitations of our trial primarily relate to the challenges of conducting a trial in a disease that is not well characterized. No standard of care exists for early treatment of COVID-19 and various advocacy groups promote different interventions, including some of those evaluated in our trial. We mitigated this by inquiring of any treatments a patient may have tried as per their own decision-making or that of a prescribing clinician. The medical/scientific community still does not understand who is at greatest risk of disease progression from this disease as some patients with numerous risk factors do recover quickly while some others with less established risk factors may not. The rate of our primary endpoint occurring appears to have increased importantly from the beginning of the trial to the end of the trial. This is likely explained by the emergence of the predominant Gamma (P.1) variant during the conduct of this trial that

may exhibit greater transmission and worse clinical outcomes than earlier variants. This is, as yet, still poorly understood.

In conclusion, several retrospective observational studies<sup>9-11,22-25</sup> have suggested that metformin treatment may have potential benefit in patients with COVID-19. Repurposing existing drugs is an appealing strategy to respond to the pandemic. Our findings found no clinical benefit to support the use of metformin in an outpatient population. This adds to the evidence that metformin should not be specifically repurposed for the treatment of early COVID-19.

## **ACKNOWLEDGEMENTS**

The trial was supported by FastGrants and the Rainwater Foundation. GR and EJM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## **DATA SHARING**

Data can be shared with qualifying researchers who submit a proposal with a valuable research question to be assessed by the Together Trial Investigators. This Trial is registered at ClinicalTrials.gov: NCT04727424.

## **FUNDING**

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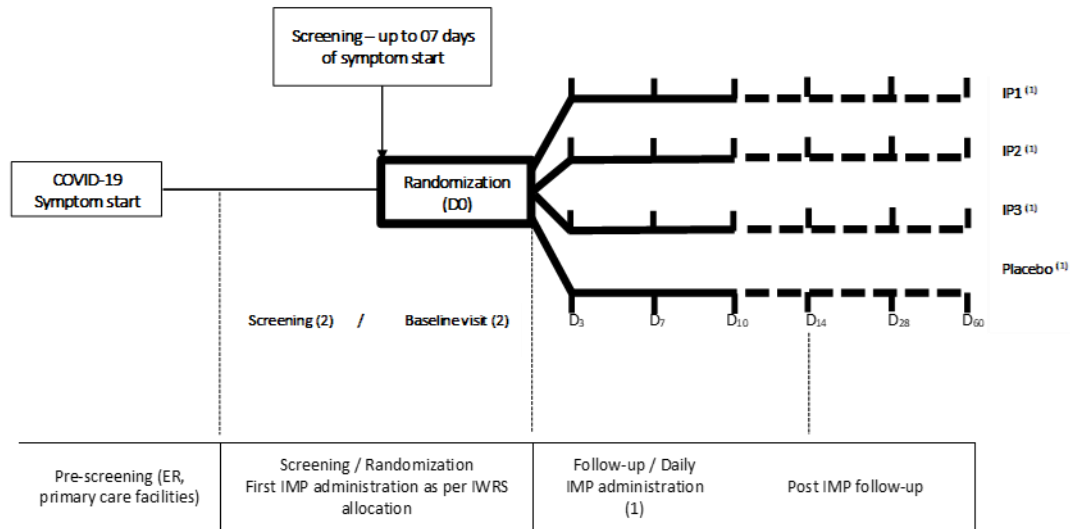
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Figure 1 Research flow diagram



Legend

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 07 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 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.



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**

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.
8. Assessment of late complications associated with COVID-19.
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.



Table 2. Interventional Products (IPs) of evaluation in the TOGETHER Trial (previous, current, and forthcoming)

<b>Investigational Product (IP)</b>	<b>Dose</b>	<b>Dosing schedule</b>	<b>Route of administration</b>	<b>Study status</b>
Hydroxychloroquine	400mg	Two tablets on Day 1, then 1 tablet for 9 days	Oral	Stopped early for futility, findings published[7]
Lopinavir/ritonavir	200/50mg	Four tablets twice a day on Day 1, then two tablets twice a day for 9 days	Oral	Stopped early for futility, findings published[7]
Fluvoxamine Maleate	100mg	One tablet every 12 hours for 10 days	Oral	Actively recruiting
Ivermectin	400 mcg/kg up to 90kg weight	3-6, 6mg tablets (weight dependent) every 24 hours for 3 days	Oral	Actively recruiting
Metformin Extended Release	750mg	One tablet every 12 hours for 10 days	Oral	Stopped early for futility, manuscript in development
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	Protocol amendment approved, randomization shortly forthcoming
Pegylated Interferon Lambda	180 mcg in 0.45 mL	One injection at randomization	Sub-cutaneous injection in lower abdomen	Protocol amendment approved, randomization forthcoming

## **TOGETHER COLLABERATIVE GROUP**

Gilmar Reis, MD1,2; Eduardo Augusto dos Santos Moreira Silva, MD1,2; Daniela Carla Medeiros Silva, MD1,2; Lehana Thabane, PhD3; Aline Cruz Milagres, RN5,6; Thiago Santiago Ferreira, MD1; Castilho Vitor Quirino dos Santos1,2; Adhemar Dias de Figueiredo Neto, MD6; Eduardo Diniz Callegari, MD7; Leonardo Cançado Monteiro Savassi, MD6; Maria Izabel Campos Simplicio, BScPharm1; Luciene Barra Ribeiro, RN1; Rosemary Oliveira1; Ofir Harfari, PhD4; Holly Bailey, MSc4; Alla V. Glushchenko, MD, PhD3; Sheila Sprague, PhD3; Paula McKay, MSc3; Craig R. Rayner, PharmD10; Hinda Ruton, MSc4; Gordon H. Guyatt, MD3; Edward J. Mills, PhD, FRCP3;

### Affiliations:

1. Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Brazil
2. Department of Medicine, Pontificia Universidade Católica de Minas Gerais, Brazil
3. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
4. Cytel Inc, Vancouver, British Columbia, Canada
5. Department of Public Health, Montes Claros State University, Brazil
6. Public Health Fellowship Program, Governador Valadares Public Health Authority, Brazil
7. Public Health, Mental and Family Medicine Department, Ouro Preto Federal University, Brazil
8. Public Health Care Division, City of Ibirité, Brazil
9. Drug Research and Development Center, Federal University of Minas Gerais, Belo Horizonte, Brazil
10. Certara Inc. New Jersey, USA

**Statistical Analysis Committee**

Ofir Harari, Hinda Ruton, Holly Bailey, Kristian Thorlund.

**Trial Steering Committee**

Edward J Mills, Gilmar Reis, Lehana Thabane, Gordon Guyatt

**Data Monitoring and Safety Committee**

Jonas Haggstrom, William Cameron, Sinal Singh

**Together Trial Coordinating Office**

Trial Management: Edward J Mills, Jamie I Forest, Gilmar Reis,

Clinical Team: Gilmar Reis, Eduardo Augusto dos Santos Moreira Silva, Daniela Carla Medeiros Silva

Data and Programming Team: Sheila Sprague, Paula McKay, Katheryne Scholtz

Statistics Team: Ofir Harari, Hinda Ruton, Holly Bailey,