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# Early Treatment of COVID-19 with Repurposed Therapies: The TOGETHER Adaptive Platform Trial

Building Platform Trial Infrastructure for Infectious Diseases

McMaster University

PUC Minas

www.togethertrial.com

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# Co-Principal Investigators

**Dr. Gilmar Reis**
Associate Professor
Division of Medicine
Pontificia Universidade Catòlica
de Minas Gerais

**Dr. Edward Mills**
Professor
Health Research Methods,
Evidence, and Impact
McMaster University

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# Senior Investigators

**Dr. Gordon Guyatt**

Distinguished Professor

Health Research Methods, Evidence and Impact, McMaster University

**Dr. Lehana Thabane**

Professor

Health Research Methods, Evidence and Impact, McMaster University

President-elect, Society for Clinical Trials (SCT)

**Dr. Eric Lenze**

Professor

Department of Psychiatry, Washington University in St. Louis

**Dr. Craig Rayner**

Associate Professor

Monash University

President, Integrated Drug Development

Certara Inc.

**Dr. Angela Reiersen**

Associate Professor

Department of Psychiatry, Washington University in St. Louis

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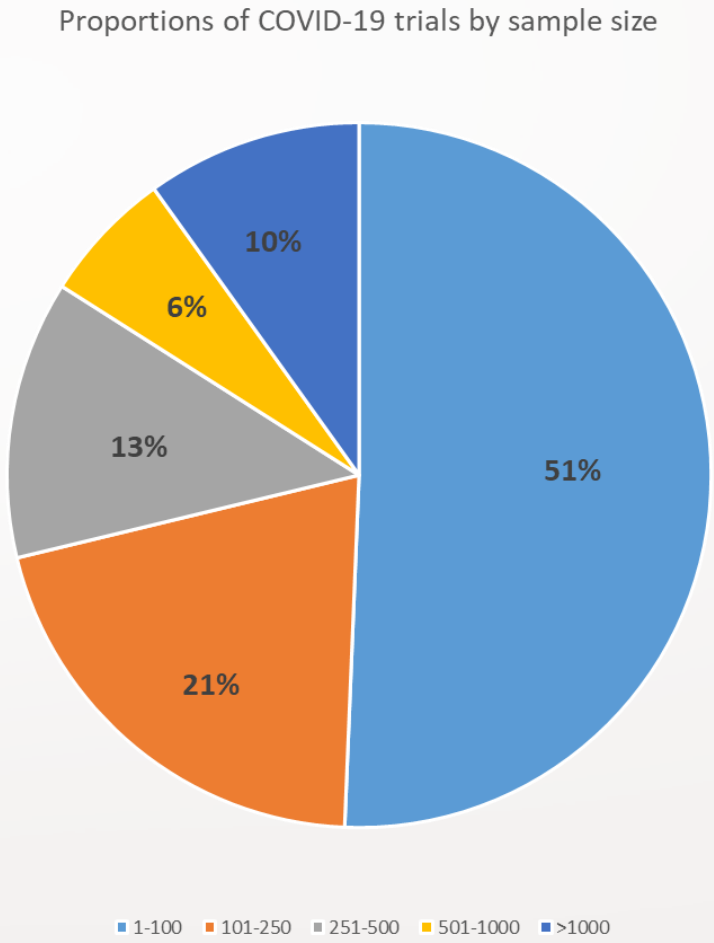
# Clinical trials in COVID-19 are small, and likely underpowered

- Of the 2,908 trials captured in our registry, over half (51%) intend to recruit **100 patients or less.**
  - **The median sample size across all trials is 100**
- Despite being small individually, these trials correspond to over **74,054** participants collectively.
- Looking at trials investigating HCQ alone (or vs. standard of care), in a **hospitalized setting only**, this corresponds to 4,893 patients – **over three times the total N of the HCQ arm of the RECOVERY trial.**
- Individually, these small trials are not meaningful, but collectively, they represent an extraordinary untapped source of data.



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# What makes useful trials different?

- Remap-Cap
- Solidarity
- Recovery
- Principle
- TOGETHER

REMAP-CAP

RECOVERY
Randomised Evaluation of COVID-19 Therapy

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older people

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# Master Protocols and Platform Trials

REVIEW ARTICLE THE CHANGING FACE OF CLINICAL TRIALS

## Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.



HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. THE standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

**Table 1. Types of Master Protocols.**

| Type of Trial | Objective |
|---|---|
| Umbrella | To study multiple targeted therapies in the context of a single disease |
| Basket | To study a single targeted therapy in the context of multiple diseases or disease subtypes |
| Platform | To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm |

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# Perpetual trials

**Builds trial infrastructure**

- Creation of trial centers and clinical recruitment sites
- Formation of committees and charters (e.g. DSMC, Steering, and Event adjudication)
- Trains and retains trial management staff

**Trial Design**

- Adaptive randomization and other adaptive design features
- Longitudinal modeling to determine probabilities of success or failure
- Shared control patients
- No specific sample sizes

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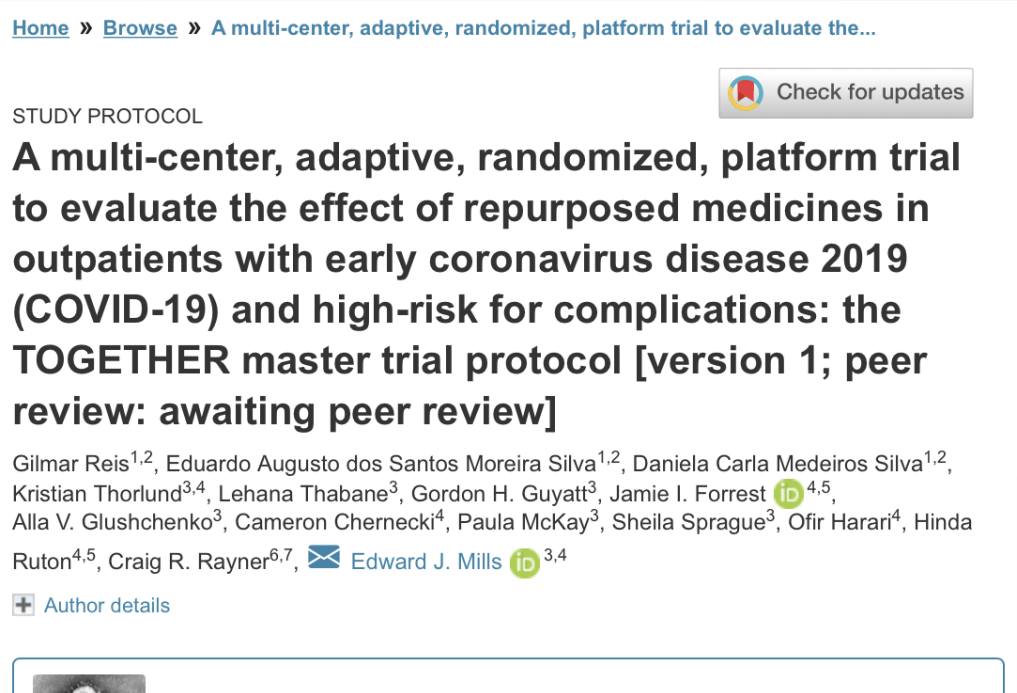
# TOGETHER Trial Overview

- Randomized adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients
- Received ethics board approval in Brazil (CEP/CONEP#: 41174620.0.1001.5120), and Canada (HiREB#: 13390)
- Data and Safety Monitoring Committee provides independent oversight
- The trial was initiated on June 2, 2020
- Enrollment into the fluvoxamine arm began on January 15, 2021
- Planned interim analysis of the fluvoxamine arm with the data cut from August 2nd, 2021



Home » Browse » A multi-center, adaptive, randomized, platform trial to evaluate the...

Check for updates

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: awaiting peer review]**

Gilmar Reis[1,2], Eduardo Augusto dos Santos Moreira Silva[1,2], Daniela Carla Medeiros Silva[1,2], Kristian Thorlund[3,4], Lehana Thabane[3], Gordon H. Guyatt[3], Jamie I. Forrest[4,5], Alla V. Glushchenko[3], Cameron Chernecki[4], Paula McKay[3], Sheila Sprague[3], Ofir Harari[4], Hinda Ruton[4,5], Craig R. Rayner[6,7], Edward J. Mills[3,4]

Author details

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# Trial Setting

**Clinical Sites In Minas Gerais:**

1. Sete Lagoas
2. Ibirité
3. Brumadinho
4. Governador Valadares
5. Montes Claros
6. Nova Lima
7. Santa Luzia
8. Ouro Preto
9. Belo Horizonte
10. Betim

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# Inclusion Criteria

1. Patients over the age of 18
2. Presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date
3. Positive rapid test for SARS-CoV-2 antigen
4. At least one additional criterion for high-risk:
    - Diabetes mellitus
    - Systemic arterial hypertension
    - Symptomatic lung disease
    - Symptomatic asthma patients
    - Smoking
    - Obesity
    - Transplant patients
    - Patient with stage IV chronic kidney disease or on dialysis
    - immunosuppressed
    - History of cancer in the last 0.5 years or undergoing current cancer treatment.
    - Age greater than 50 years

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# Exclusion Criteria

1. Diagnostic examination for SARS-CoV2 negative associated with acute flu-like symptoms
2. Acute respiratory condition compatible with COVID-19 treated in the primary care and requiring hospitalization
3. 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
6. Acute flu showing at least one of the criteria below:
   - Respiratory Rate > 28 / min;
   - $SaO_2$ < 90% or < 93% on nasal oxygen therapy at 10 L / min;
   - $PaO_2$ / $FIO_2$ < 300 mm Hg;
7. Use of serontonin receptor inhibitors
8. Use of the following medications in the last 14 days:
   - Monoamine Oxide Inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide);
   - Use of iodinated contrasts during treatment until 05 days after the end;
   - Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome - AIDS);
9. Severe psychiatric disorders or major depression
10. Pregnant or breastfeeding patients
11. History of severe ventricular cardiac arrhythmia
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. History of liver cirrhosis or Child-Pugh C classification
17. 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

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# Randomization

- Patients screened for eligibility
- Informed consent obtained
- Randomized to intervention or placebo
- Randomization stratified:
  - To account for other arms in the trial
  - Clinical site
  - Age (≥50 years *vs* <50 years)

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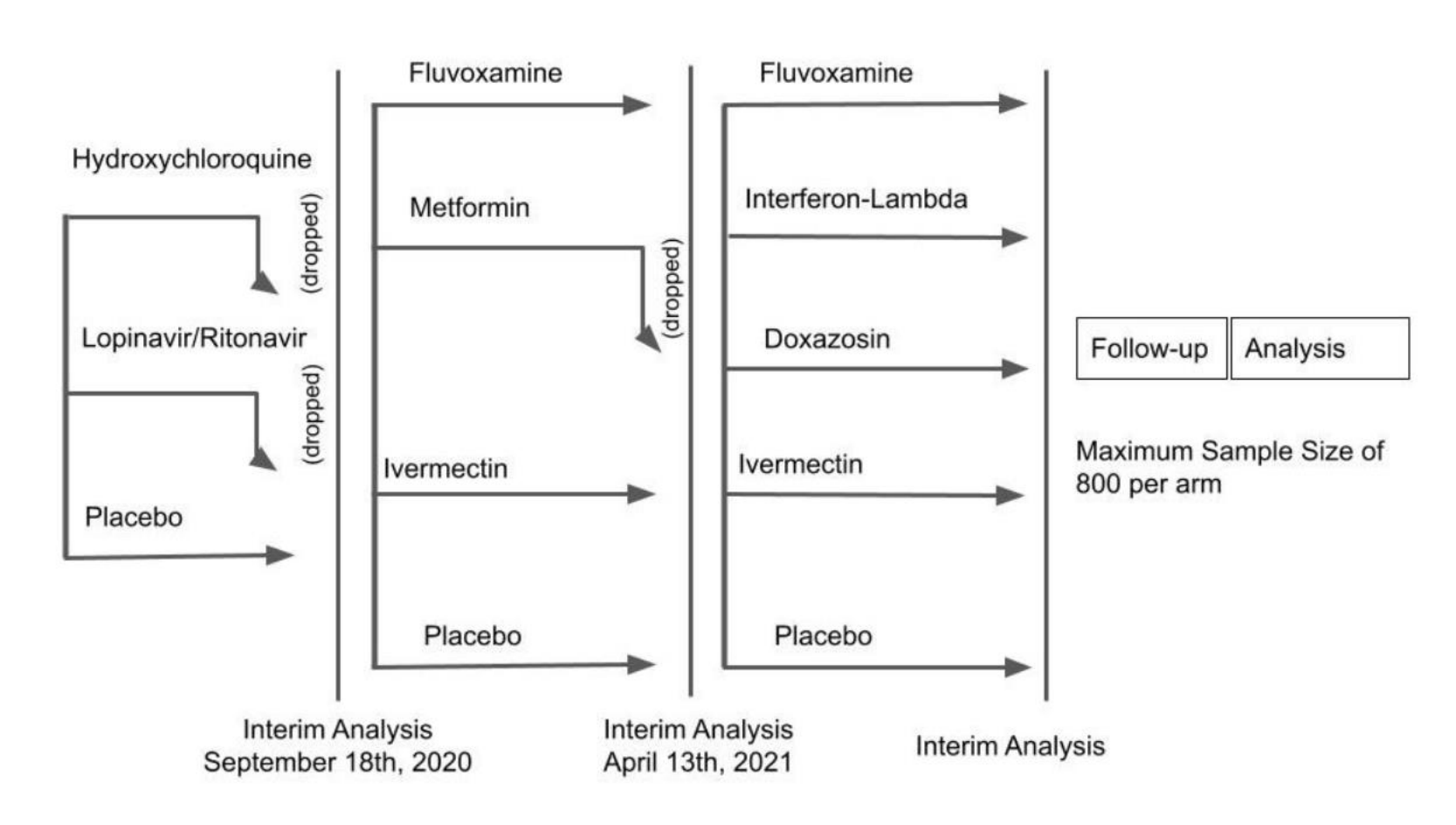
# Trial Schema



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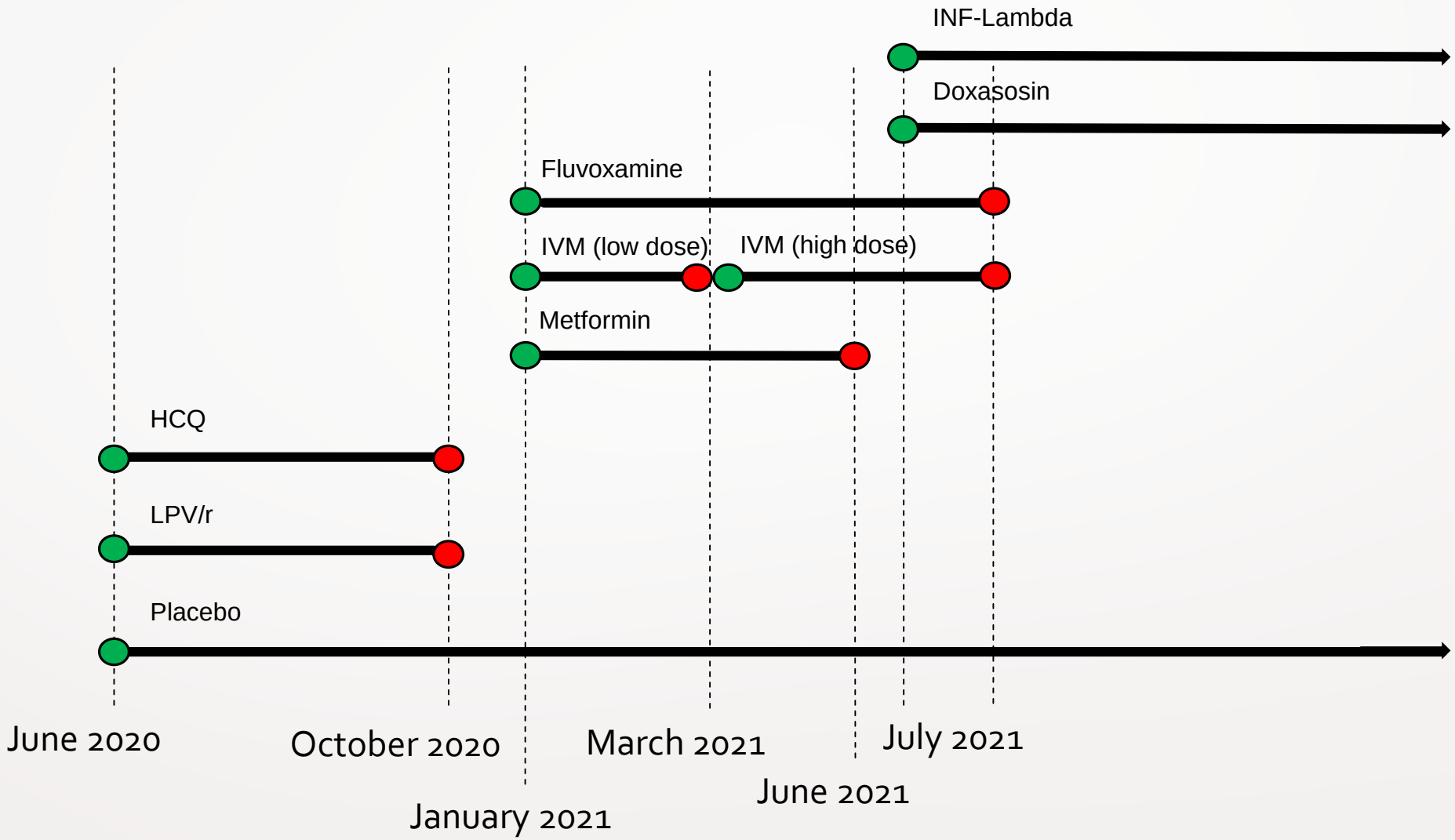
# Intervention Timeline



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# Outcomes

**Primary Outcomes:**

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

**Secondary Outcomes:**

- 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
- Adherence with medication

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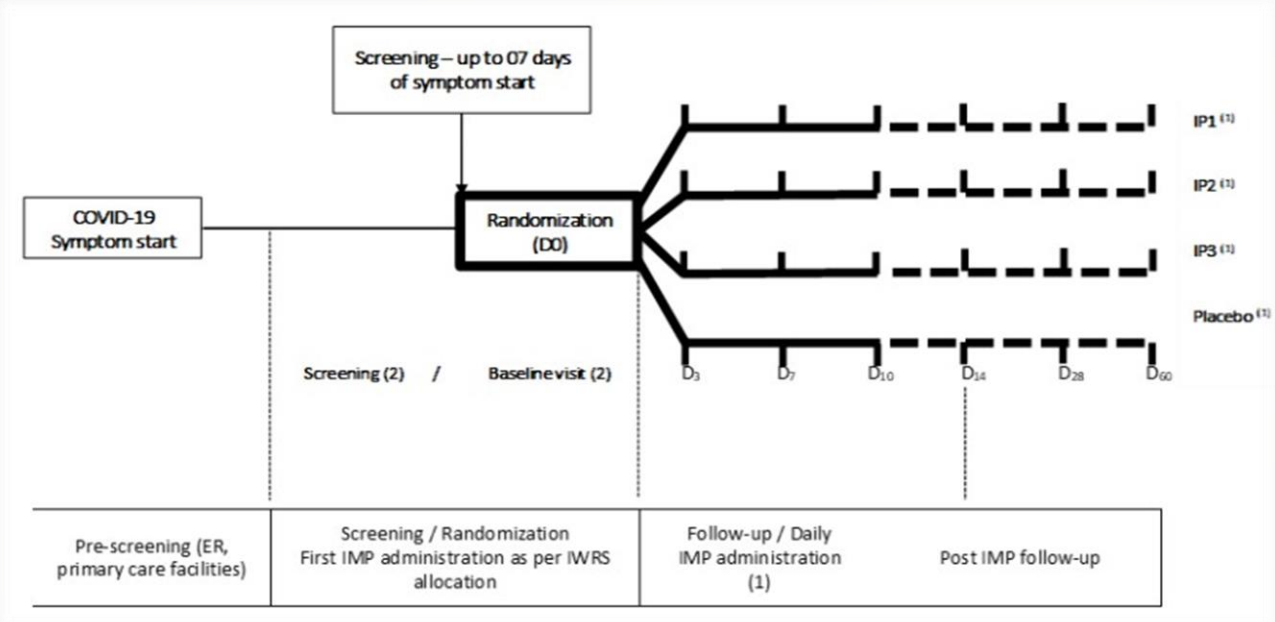
# Data Collection




- Participants were contacted on Days 1, 2, 3, 4, 5, 7, 10, 14, and 28 via telephone and social media applications
- Participants were contacted at day 60 to assess long-term outcomes
- All SAEs were documented and reported as per local regulatory requirements
- Data were entered into the trial's EDC system (IBM Clinical Development)

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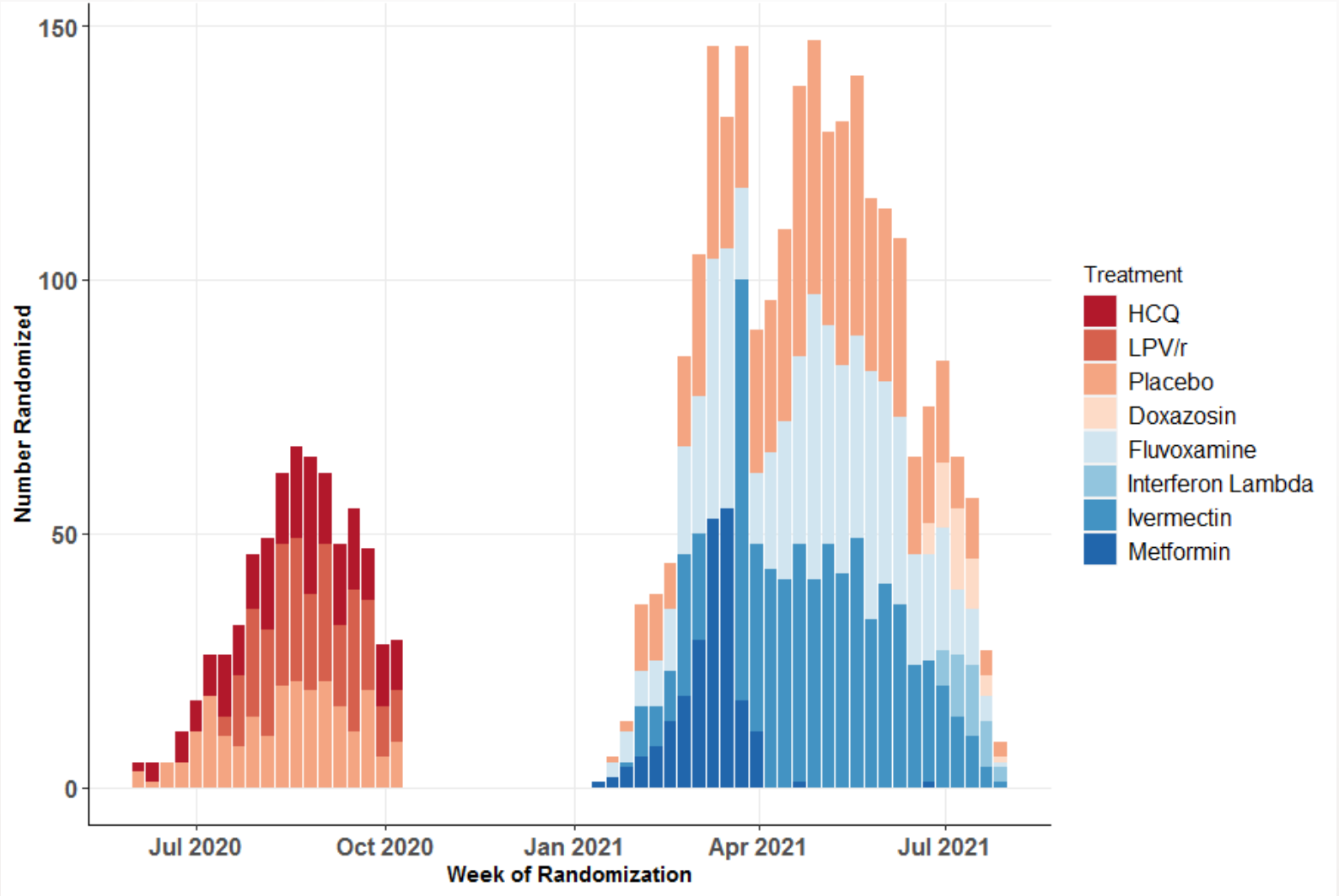
# Recruitment Over Time



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# Previous Findings

- Hydroxychloroquine or lopinavir/ritonavir vs. placebo
  - Metformin vs. placebo
  - Ivermectin vs. placebo

# RCT: Effect of Early Treatment with Hydroxychloroquine (HCQ) or Lopinavir/ritonavir (LPV/r) on Risk of Extended Emergency Care or Hospitalization Among Patients with COVID-19

## POPULATION

**308 Men, 377 Women**

Patients with COVID-19 and expected hospital stays of ≤ 5 days

**Median 53 y (18-94 y)**

## INTERVENTION

**685** Patients Randomized

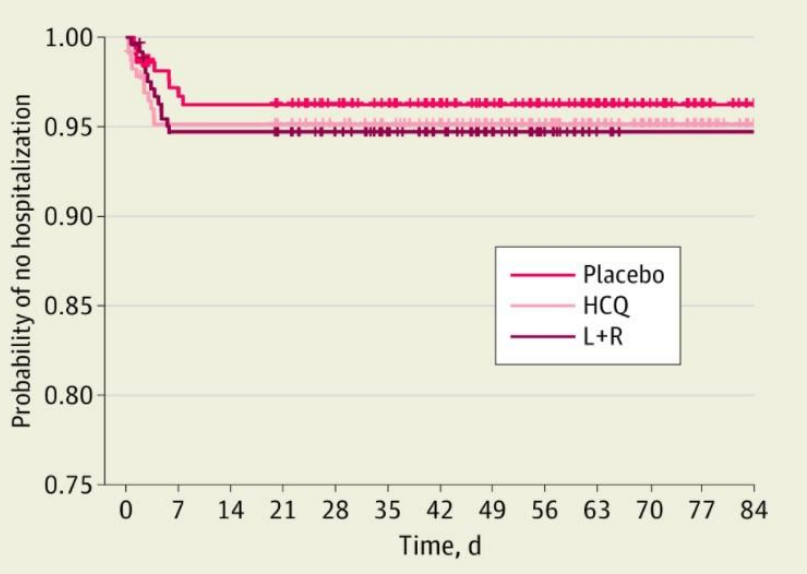
**214 HCQ:** loading dose of 800 mg at the time of randomization and then 400 mg in daily doses at 8:00 AM for 9 days

**244 LPV/r:** loading dose of 800 mg of lopinavir and 200 mg of ritonavir at the first 2 intakes, followed by 400 mg of lopinavir and 100 mg of ritonavir every 12 hours for the next 9 days.

**227 Placebo** Oral placebo talc tablet

## FINDINGS

**The following had a COVID-19–associated hospitalization:**
8/214 participants from the HCQ group (3.7%);
14/244 participants from the LPV/r group (5.7%);




## SETTINGS/LOCATIONS

**7 Clinical sites, Minas Gerais, Brazil**

## PRIMARY OUTCOMES

COVID-associated hospitalization and death measured at day 90

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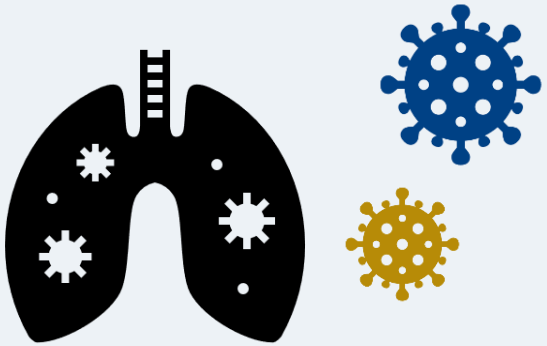
# RCT: Effect of Early Treatment with Metformin on Risk of Emergency Care and Hospitalization Among Patients with COVID-19

## POPULATION

**43% Men, 57% Women**



Patients with COVID-19 and expected hospital stays of ≤ 5 days
**Median 52 y (18-90 y)**

## INTERVENTION

**217** Patients

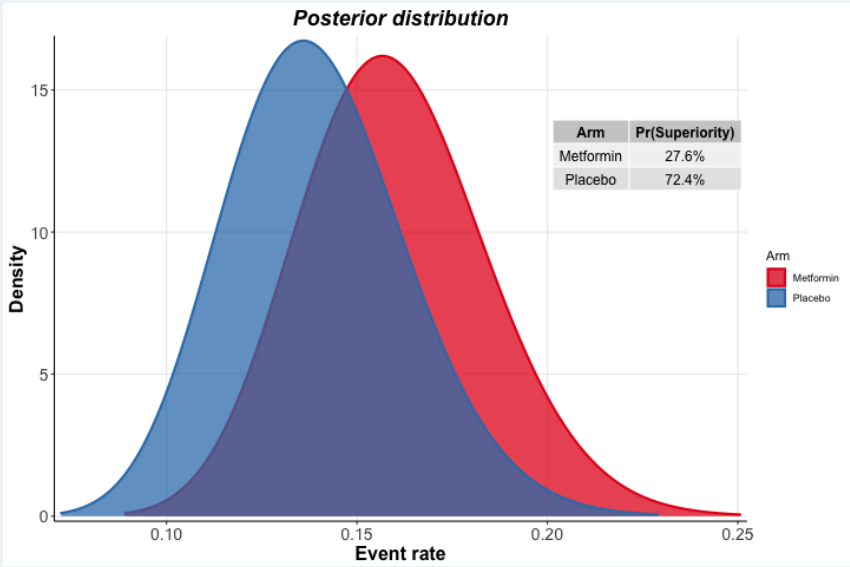
**Metformin** 750mg dose twice daily for 10 days

**206** patients

**Placebo** Oral placebo talc tablet

## FINDINGS

The proportion of patients with extended ER observation or hospitalization was the 32/217 (17.2%) for the metformin group and 27/206 (14.5%) in the placebo group




## SETTINGS/LOCATIONS

**10 Clinical sites, Minas Gerais, Brazil**

## PRIMARY OUTCOMES

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 within 28 days of randomization.

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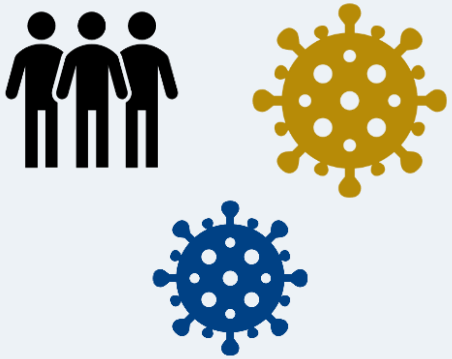
# RCT: Effect of Early Treatment with Ivermectin 3-day on Risk of Emergency Care and Hospitalization Among Patients with COVID-19

## POPULATION

**43% Men, 56% Women**



Patients with COVID-19 and expected hospital stays of ≤ 5 days
**Median 52 y (18-91 y)**

## INTERVENTION

**677** Patients,

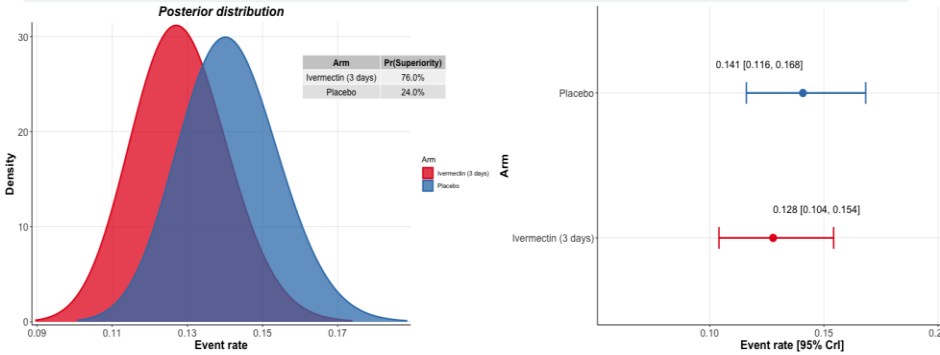
**Ivermectin** 400 mcg/kg up to 90kg weight every 24 hours for 3 days

**678** patients

**Placebo** Oral placebo talc tablet

## FINDINGS

The proportion of patients with extended ER observation or hospitalization was the 86/677 for the IVM group and 95/678 in the placebo group. Relative risk: 0.91 (0.69-1.19). Mortality relative risk: 0.82 (0.44-1.52)




## SETTINGS/LOCATIONS

**10 Clinical sites, Minas Gerais, Brazil**

## PRIMARY OUTCOMES

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 within 28 days of randomization.

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# Fluvoxamine

| | Fluvoxamine (742) | Placebo (738) |
|---|---|---|
| Female | 407 | 438 |
| Male | 335 | 300 |
| Age (SD) | 47.9 (13.2) | 47.8 (13.9) |
| Multiple co-morbidities | 135 | 123 |

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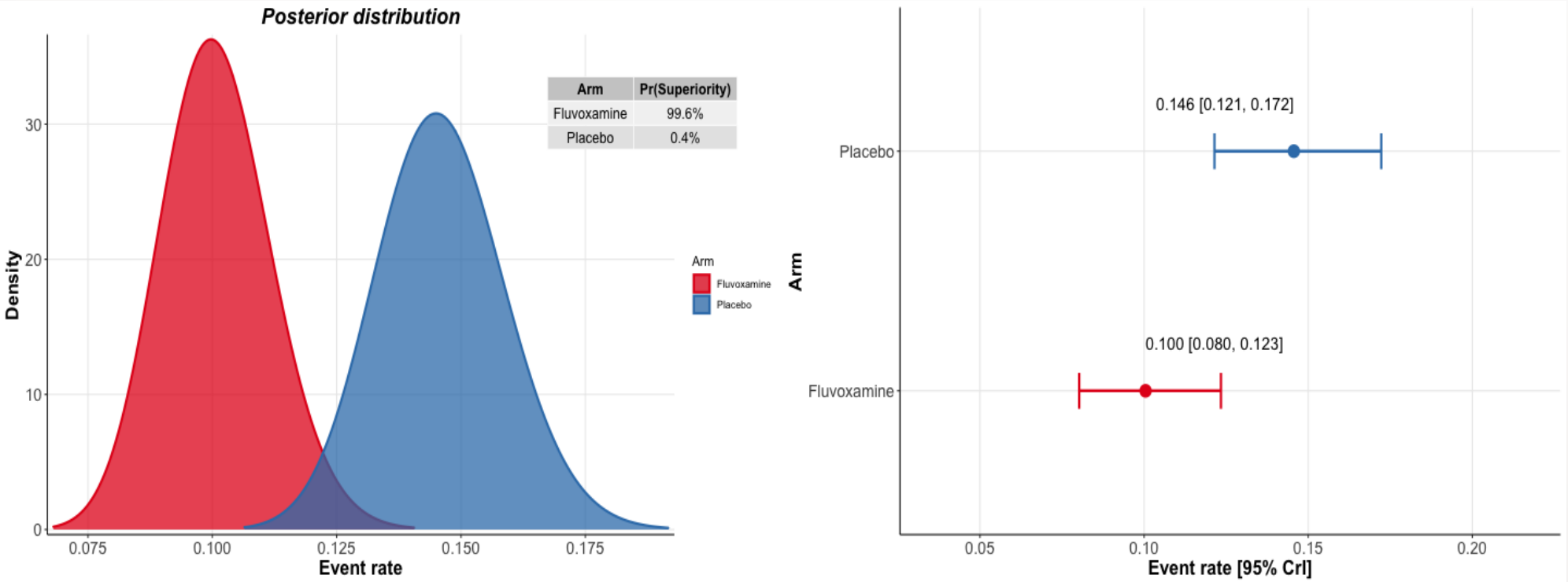
# Posterior Probability of Superiority of Fluvoxamine vs. Placebo on Emergency Room Observation for > 6 Hours or Hospitalization



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# Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

| Arm | Number of patients | Number of events | Relative risk+ [95% CrI] |
|---|---|---|---|
| **Fluvoxamine** | 742 | 74 | 0.69[0.52;0.91] |
| **Placebo** | 738 | 107 | **Reference** |

+ Calculated in a Bayesian framework

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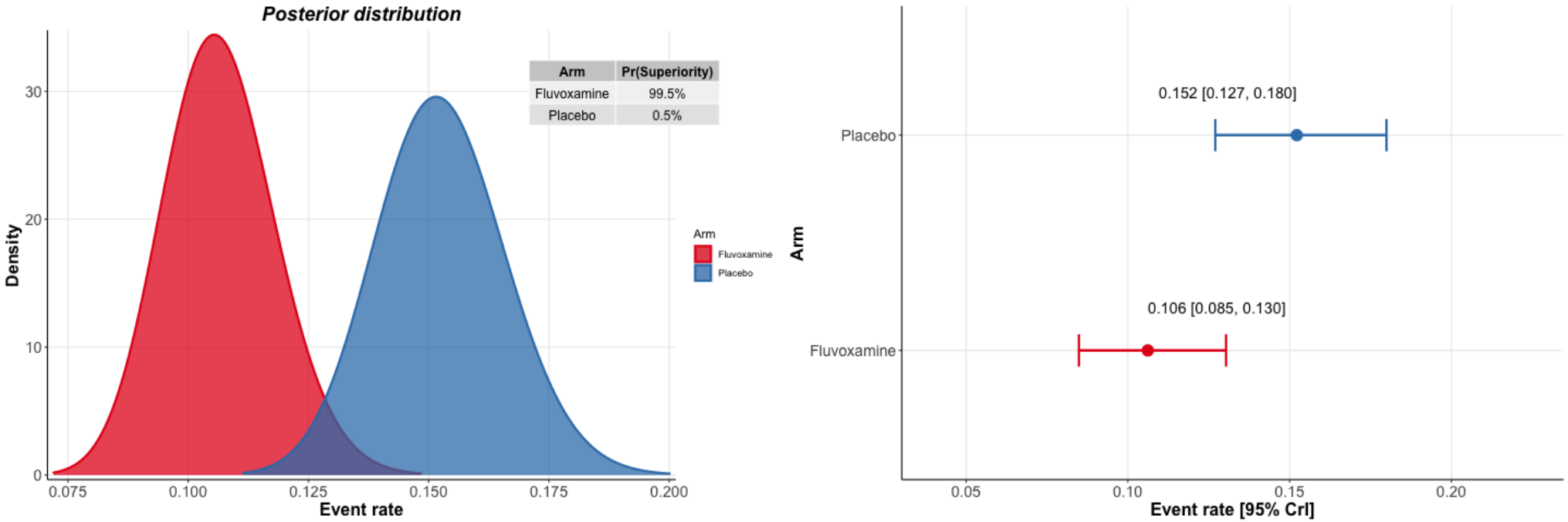
# Posterior Probability of Superiority of Fluvoxamine vs. Placebo on Emergency Room Observation for > 6 Hours or Hospitalization

**Patients with at least 28 days of Follow-up**



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# Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

**Patients with at least 28 days of Follow-up**

| Arm | Number of patients | Number of events | Relative risk⁺ [95% CrI] |
|---|---|---|---|
| **Fluvoxamine** | 702 | 74 | 0.70 [0.53;0.92] |
| **Placebo** | 706 | 107 | **Reference** |

⁺ Calculated in a Bayesian framework

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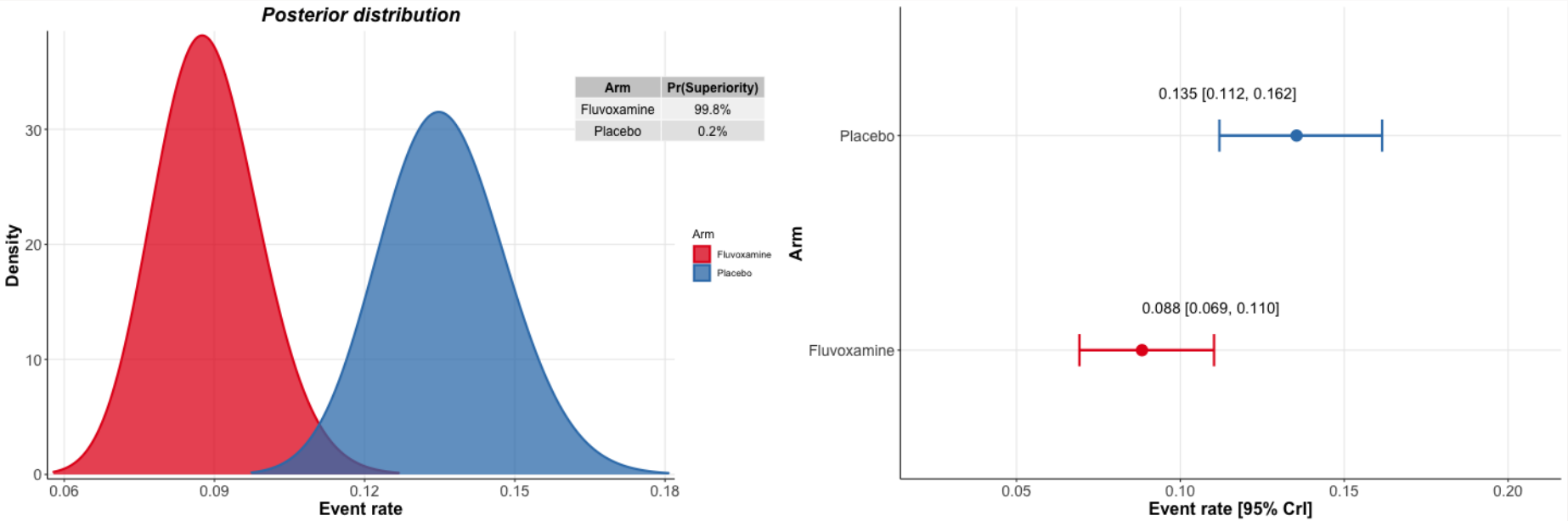
# Posterior Probability of Superiority of Fluvoxamine vs. Placebo on Emergency Room Observation for > 6 Hours or Hospitalization

**Patients with at least 1 day of treatment**



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# Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

**Patients with at least 1 day of treatment**

| Arm | Number of patients | Number of event | Relative risk+ [95% CrI] |
|---|---|---|---|
| **Fluvoxamine** | 691 | 63 | 0.65[0.48;0.87] |
| **Placebo** | 695 | 97 | **Reference** |

+ Calculated in a Bayesian framework

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# Secondary Outcome: Relative Risk of Mortality for Fluvoxamine vs. Placebo

| Arm | Number of patients | Number of events | Relative risk⁺ [95% CrI] |
|---|---|---|---|
| **Fluvoxamine** | 742 | 17 | 0.71 [0.39;1.29] |
| **Placebo** | 738 | 24 | **Reference** |

⁺ Calculated in a Bayesian framework

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# Secondary Outcome: Viral Suppression at 7 Days Fluvoxamine vs. Placebo

| Arm | Odds Ratio (95% CI) | P-value |
|---|---|---|
| **Fluvoxamine** | 0.75 (0.52 – 1.07) | 0.12 |
| **Placebo** | **Reference** | |

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| Variable | Treatment Assignment | | | | |
|---|---|---|---|---|---|
| | **Overall**, N = 165[1] | **Placebo**, N = 92[1] | **Fluvoxamine**, N = 73[1] | **OR**[2] | **95% CI**[2] |
| **Days in Hospital** | | | | 1.00 | 0.96, 1.04 |
| N | 123 | 60 | 63 | | |
| Median | 7.0 | 7.0 | 8.0 | | |
| IQR | 4.5, 12.5 | 3.0, 12.2 | 5.5, 12.5 | | |
| (Missing) | 42 | 32 | 10 | | |
| **Ventilator** | | | | | |
| No | 99 (63%) | 53 (62%) | 46 (64%) | — | — |
| Yes | 58 (37%) | 32 (38%) | 26 (36%) | 0.80 | 0.39, 1.67 |
| (Missing) | 8 | 7 | 1 | | |

[1] Median (IQR)

[2] OR = Odds Ratio, CI = Confidence Interval

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# Readiness for Dissemination

- International COVID-19 Data Alliance (ICODA)
- WHO Guidelines Synthesis Group (GRADE)
- UK NICE
- NIH

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# The TOGETHER Team

**Co-Principal Investigators:**
Edward Mills
Gilmar Reis

**Senior Investigators**:
Craig Rayner
Eric Lenze
Gordon Guyatt
Lehana Thabane
Angela Reiersen

**Data Management:**
James Bademian
Kathryne Scholtz
Mindy Wolf
Gerald Smith

**Statistics:**
Ofir Harari
Hinda Ruton
Holly Bailey

**Data and Safety Monitoring Committee:**
Kristian Thorlund (Chair)
Sonal Singh
William Cameron
James Orbinski
Jonas Haggstrom

**Trial Management Group:**
Eduardo Silva
Daniela Silva
Jamie Forrest
Cameron Chernecki
Sheila Sprague
Paula McKay
Aline Cruz Milagres
Thiago Santiago Ferraria
Castilho Vitor Quirino dos Santos
Adhemar Dias de Figueirdo Neto
Leonardo Cançado Monteiro Savassi
Maria Izabel Campos Simplicio
Luciene Barra Ribeiro
Rosemary Oliveira

**Pharmacist:**
Linèria Morais

**Communications:**
Greg Thomas-Reilly
Veronica McGuire

**Partner Institutions:**
McMaster University
PUC Minas Gerais
University of Ottawa
Platform Life Sciences
MMS Holdings
Cytel Inc
University de Ouro Preto

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# Support


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# Research Network

World Health Organization

McMaster University

ICODA International COVID-19 Data Alliance

Cytel

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PUC Minas

MONASH University

uOttawa

UFOP Universidade Federal de Ouro Preto

SCT Society for Clinical Trials

Washington University in St.Louis