Adaptive Platform Trial Scientific Meeting

September 28 – 29 • Toronto, Canada

CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

The TOGETHER Adaptive Platform Trial

Jamie Forrest, PhD

Executive Director, TOGETHER Trial

Founding Partner and Executive Advisor, Purpose Life Sciences

McMaster University

PUC Minas

Purpose Life Sciences

together • COVID-19 clinical trials

Co-Principal Investigators

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Professor
Health Research Methods, Evidence, and Impact
McMaster University

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Associate Professor
Division of Medicine
Pontificia Universidade Catòlica de Minas Gerais

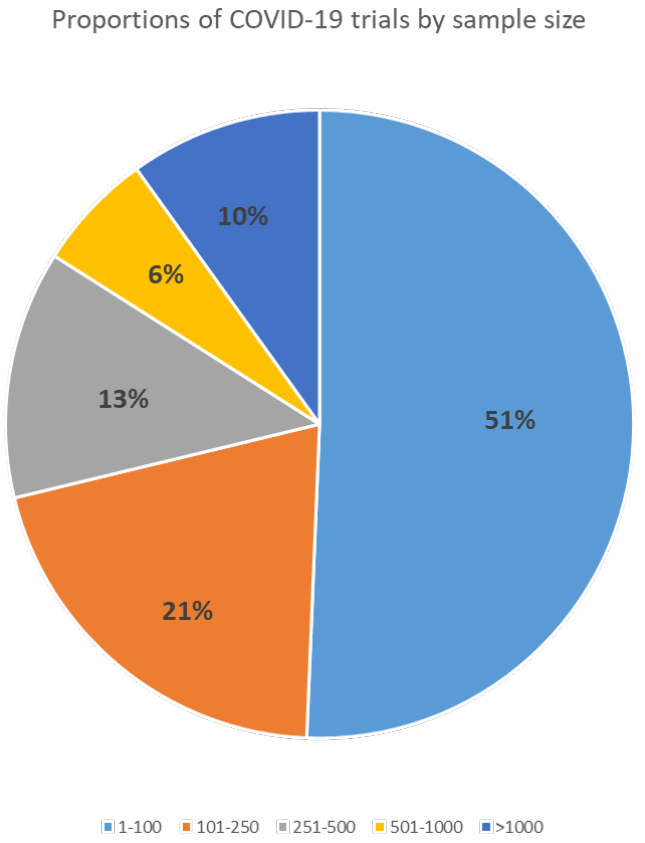
Topics

- Trial Overview and History
- Study Setting
- Trial Methods
- Study Findings
- Global Partnerships & Capacity Building
- What's Next?

In the beginning

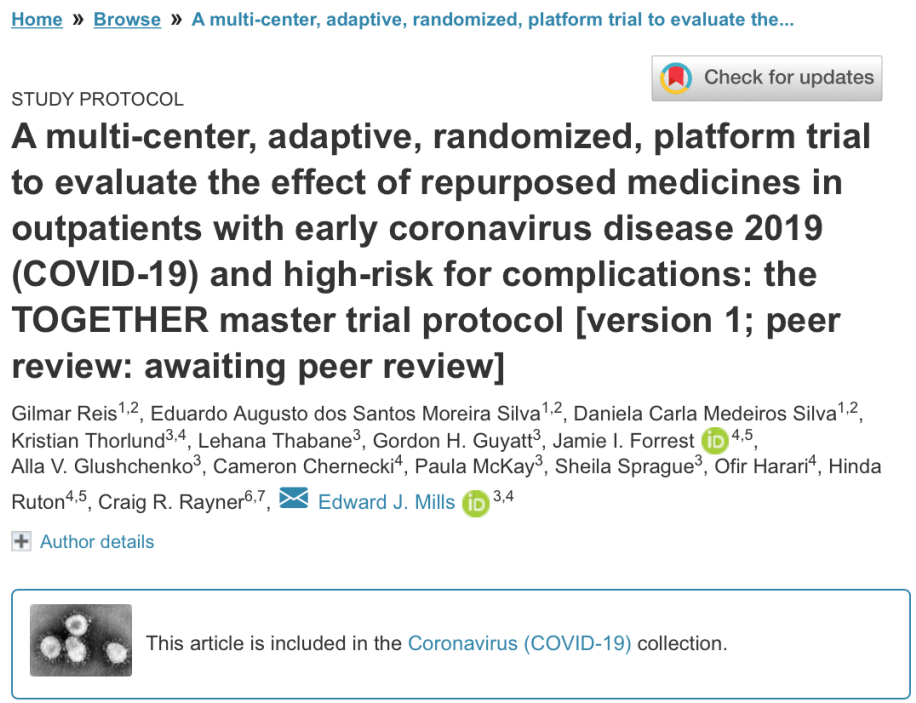
…Clinical trials in COVID-19 are small, and likely underpowered

- 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.



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



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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

This article is included in the Coronavirus (COVID-19) collection.

Outcomes

Primary Outcome:

- 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.

Outcomes

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

Key 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

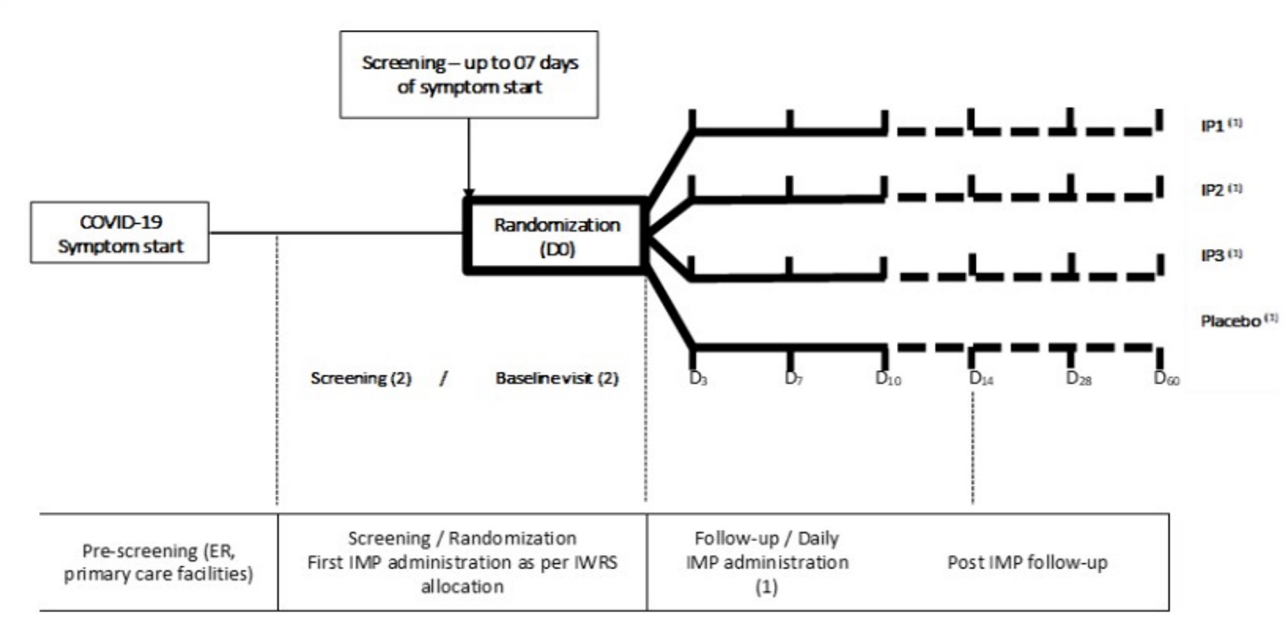
Exclusion Criteria

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;
   - SaO2 < 90% or < 93% on nasal oxygen therapy at 10 L / min;
   - PaO2 / FIO2 < 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);

Exclusion Criteria Continued

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

Data Collection



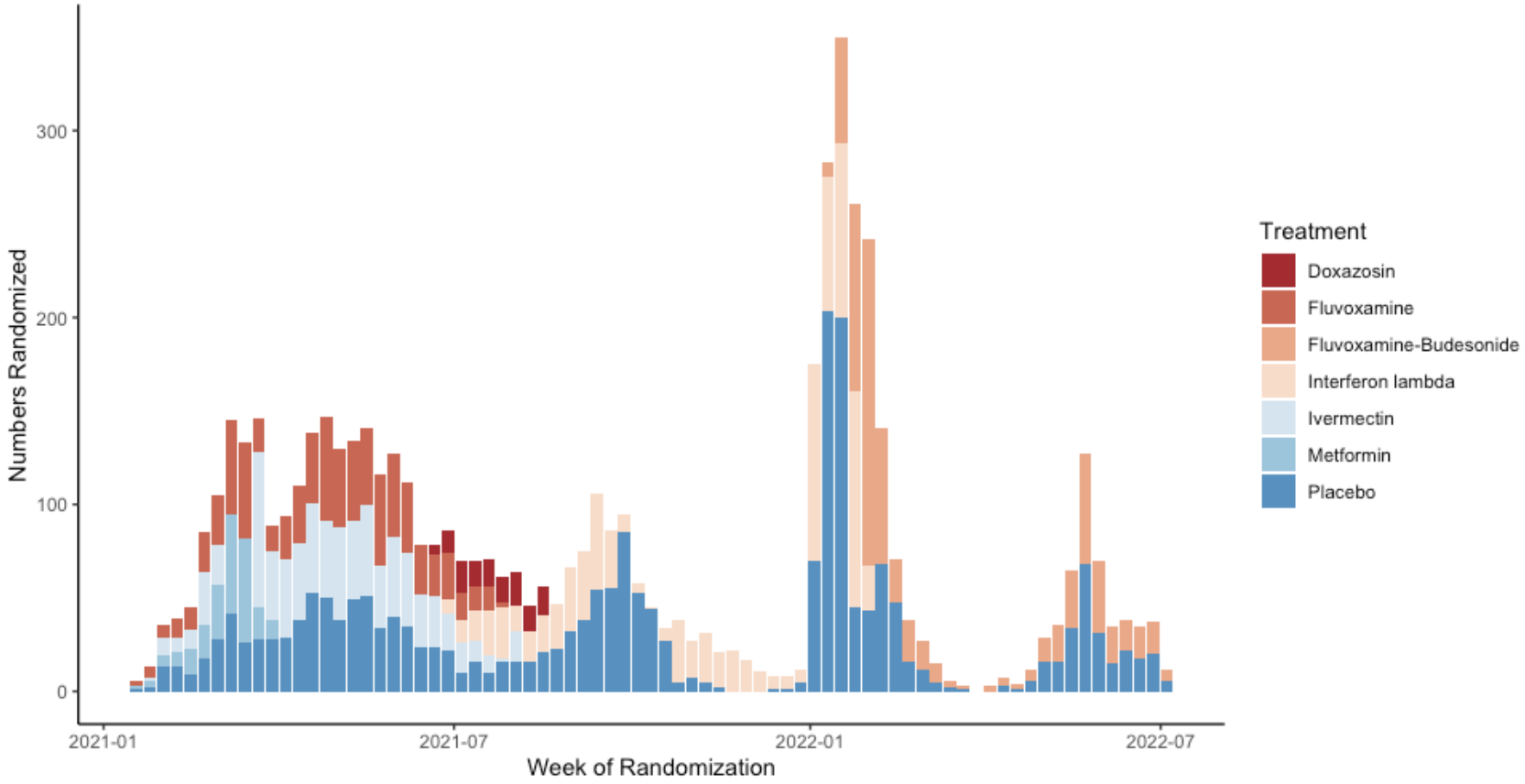
- Participants were contacted on Days 1, 2, 3, 4, 5, 7, 10, 14, and 28 via telephone and social media applications
- Participants were contacted at day 60 to assess long-term outcomes
- All SAEs were documented and reported as per local regulatory requirements
- Data were entered into the trial's EDC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

Study monitoring

Study Setting

Community-based Approach

Recruitment Over time by Treatment



Study Findings

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Early Treatment with Ivermectin among Patients with Covid-19

G. Reis, E.A.S.M. Silva, D.C.M. Silva, L. Thabane, A.C. Milagres, T.S. Ferreira, C.V.Q. dos Santos, V.H.S. Campos, A.M.R. Nogueira, A.P.F.G. de Almeida, E.D. Callegari, A.D.F. Neto, L.C.M. Savassi, M.I.C. Simplicio, L.B. Ribeiro, R. Oliveira, O. Harari, J.I. Forrest, H. Ruton, S. Sprague, P. McKay, C.M. Guo, K. Rowland-Yeo, G.H. Guyatt, D.R. Boulware, C.R. Rayner, and E.J. Mills, for the TOGETHER Investigators*

ABSTRACT

Ivermectin Does Not Reduce Risk Of Covid Hospitalization, Large Study Finds

At some point it will become a waste of resources to continue studying an unpromising approach," one expert...

MARCH 30, 2022 | NYTIMES

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Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial

The Washington Post
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HEALTH

What is fluvoxamine, the antidepressant drug that shows promise in treating covid-19?

By Marisa Iati and Adela Suliman
October 28, 2021 at 7:11 a.m. EDT

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Randomized Controlled Trial > JAMA Netw Open. 2021 Apr 1;4(4):e216468.
doi: 10.1001/jamanetworkopen.2021.6468.

Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial

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VACCINES

Common Antidepressant Slashes Risk of COVID Death

Fluvoxamine is both inexpensive and highly effective at preventing mild COVID-19 from turning severe

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MATT'S TAKE

New Covid trial results may point toward better ways to study medicines

By Matthew Herper March 23, 2022

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Interferon therapy shows striking results against COVID-19

Given early, one shot sliced hospitalization risk by half in large trial

5 MAY 2022 · 4:00 PM · BY MEREDITH WADMAN

Articles

Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

*Gilmar Reis, Eduardo Augusto dos Santos Moreira-Silva, Daniela Carla Medeiros Silva, Lehana Thabane, Aline Cruz Milagres, Thiago Santiago Ferreira, Castilho Vitor Quirino dos Santos, Vitoria Helena de Souza Campos, Ana Maria Ribeiro Nogueira, Ana Paula Figueiredo Guimaraes de Almeida, Eduardo Diniz Callegari, Adhemar Dias de Figueiredo Neto, Leonardo Cançado Monteiro Savassi, Maria Izabel Campos Simplicio, Luciene Barra Ribeiro, Rosemary Oliveira, Ofir Harari, Jamie I Forrest, Hinda Ruton, Sheila Sprague, Paula McKay, Alla V Glushchenko, Craig R Rayner, Eric J Lenze, Angela M Reiersen, Gordon H Guyatt, Edward J Mills, for the TOGETHER investigators**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Early Treatment with Ivermectin among Patients with Covid-19

G. Reis, E.A.S.M. Silva, D.C.M. Silva, L. Thabane, A.C. Milagres, T.S. Ferreira, C.V.Q. dos Santos, V.H.S. Campos, A.M.R. Nogueira, A.P.F.G. de Almeida, E.D. Callegari, A.D.F. Neto, L.C.M. Savassi, M.I.C. Simplicio, L.B. Ribeiro, R. Oliveira, O. Harari, J.I. Forrest, H. Ruton, S. Sprague, P. McKay, C.M. Guo, K. Rowland-Yeo, G.H. Guyatt, D.R. Boulware, C.R. Rayner, and E.J. Mills, for the TOGETHER Investigators*

ABSTRACT

BBC NEWS

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Health | Coronavirus

Ivermectin: How false science created a Covid 'miracle' drug

6 October 2021

Reality Check

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Randomized Controlled Trial > JAMA Netw Open. 2021 Apr 1;4(4):e216468.
doi: 10.1001/jamanetworkopen.2021.6468.

Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial

nature

NEWS | 29 October 2021

Common antidepressant slashes risk of COVID death, study says

Fluvoxamine is both inexpensive and highly effective at preventing mild COVID-19 from turning severe.

Antidepressant Fluvoxamine Significantly Reduces Covid-19 Hospitalization

Patients who received the low-cost and widely available drug were far less likely to be hospitalized in a clinica...

OCTOBER 28, 2021 | WALL STREET JOURNAL

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

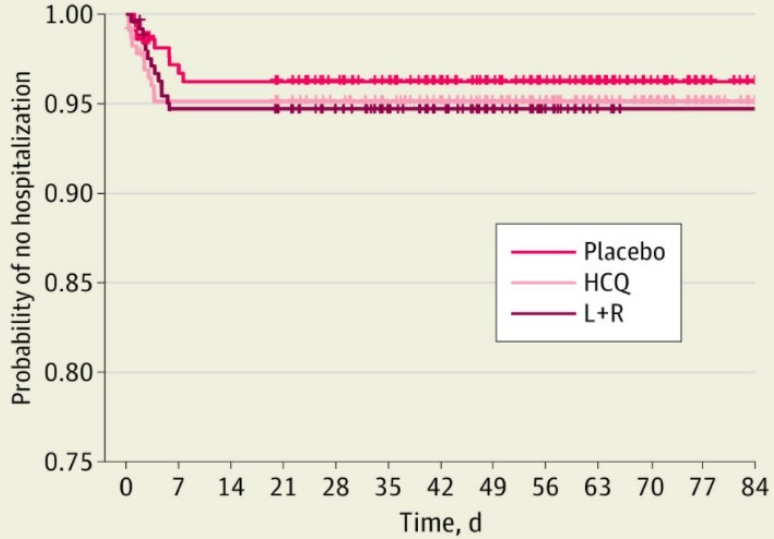
244 LPV/r: loading dose of 800 mg of lopinavir and 200 mg of ritonavir at the first 2 intakes, followed by 400 mg of lopinavir and 100 mg of ritonavir every 12 hours for the next 9 days.

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%);
11/227 participants from the control group (4.8%);



SETTINGS/LOCATIONS

7 Clinical sites, Minas Gerais, Brazil

PRIMARY OUTCOMES

COVID-associated hospitalization and death measured at day 90

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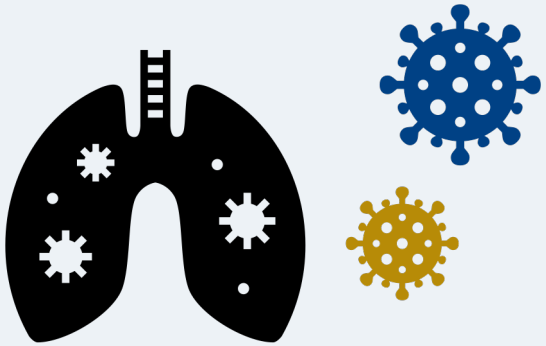
RCT: Effect of Early Treatment with Metformin on Risk of Emergency Care and Hospitalization Among Patients with COVID-19

POPULATION

182 Men, 241 Women



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

INTERVENTION

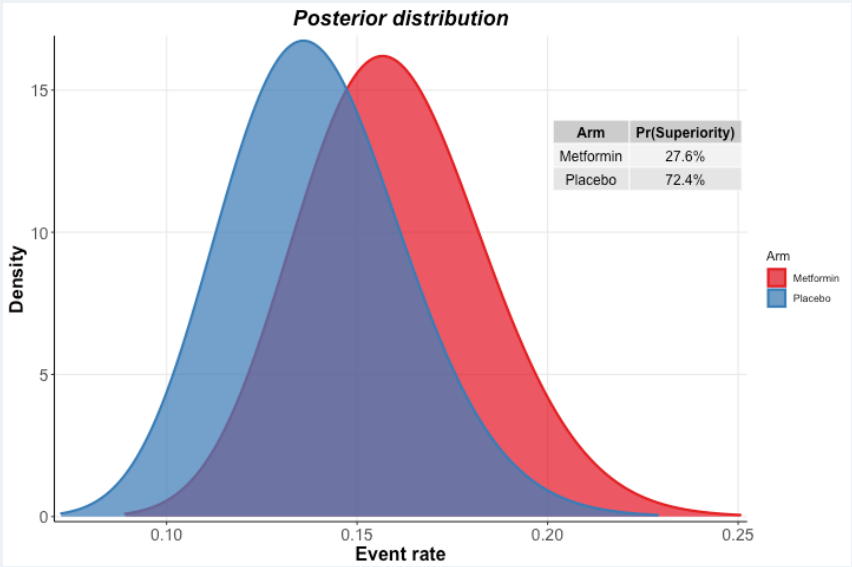
423 Patients Randomized, **372** patients analyzed

217 Metformin
750mg dose twice daily for 10 days

206 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 on Risk of Extended Emergency Care or Hospitalization Among Patients

POPULATION

565 Men, 791 Women

Patients with COVID-19
Median 49 y (18-102 y)
Mean days of symptoms before randomization 3.8 days

INTERVENTION

1,356 Patients Randomized

679 Ivermectin
400mg for 3 days

679 Placebo
Oral placebo talc tablet

SETTINGS/LOCATIONS

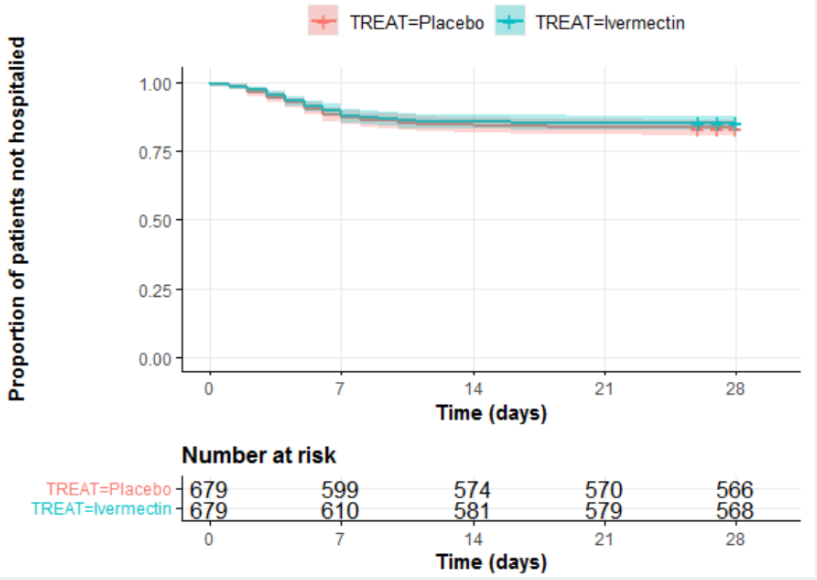
12 Clinical sites, Minas Gerais, Brazil

PRIMARY OUTCOMES

Hospitalization defined as admission to a COVID-19 emergency setting for >6 hours or referral to a tertiary hospital setting due to the progression of COVID-19 within 28 days of randomization

FINDINGS

The following had a COVID-19–associated hospitalization:
100/679 participants from the ivermectin group (14.7%)
111/679 participants from the placebo group (16.3%)



together • COVID-19 clinical trials

Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

*Gilmar Reis, Eduardo Augusto dos Santos Moreira-Silva, Daniela Carla Medeiros Silva, Lehana Thabane, Aline Cruz Milagres, Thiago Santiago Ferreira, Castilho Vitor Quirino dos Santos, Vitoria Helena de Souza Campos, Ana Maria Ribeiro Nogueira, Ana Paula Figueiredo Guimaraes de Almeida, Eduardo Diniz Callegari, Adhemar Dias de Figueiredo Neto, Leonardo Cançado Monteiro Savassi, Maria Izabel Campos Simplicio, Luciene Barra Ribeiro, Rosemary Oliveira, Ofir Harari, Jamie I Forrest, Hinda Ruton, Sheila Sprague, Paula McKay, Alla V Glushchenko, Craig R Rayner, Eric J Lenze, Angela M Reiersen, Gordon H Guyatt, Edward J Mills, for the TOGETHER investigators**

	Intention-to-treat analysis			Modified intention-to-treat analysis		
	N	n (%)	Relative risk (95% BCI)	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)	740	78 (11%)	0·69 (0·53–0·90)
Placebo	756	119 (16%)	1 (ref)	752	115 (15%)	1 (ref)

BCI=Bayesian credible interval.

Table 2: **Proportion of primary outcome events and relative risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for patients allocated fluvoxamine versus placebo**

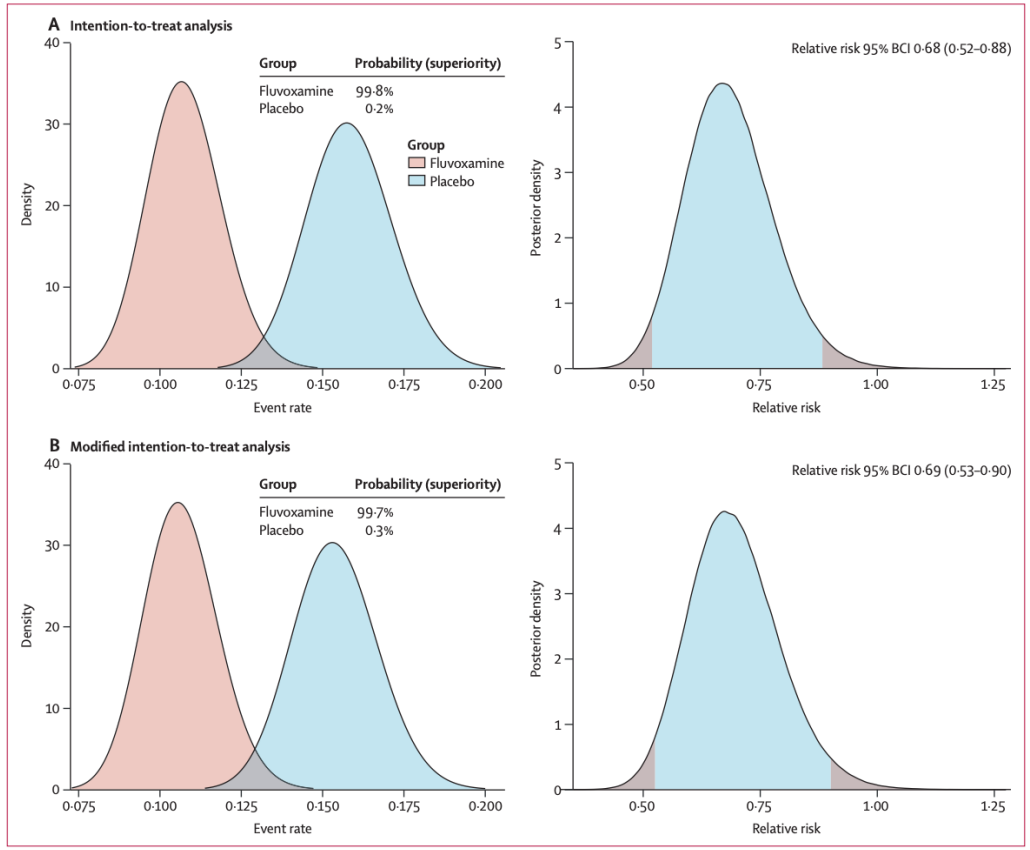


Figure 2: **Probability of efficacy and Bayesian relative risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for fluvoxamine versus placebo**
BCI=Bayesian credible interval.

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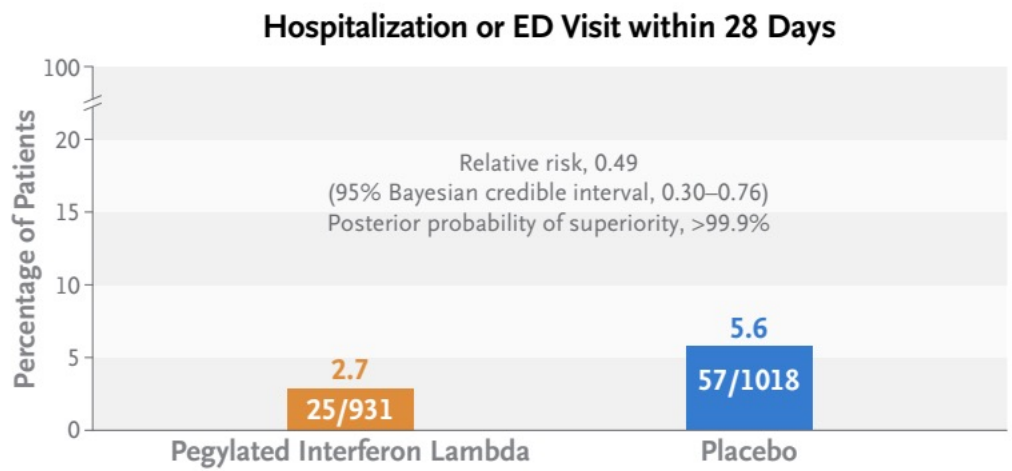
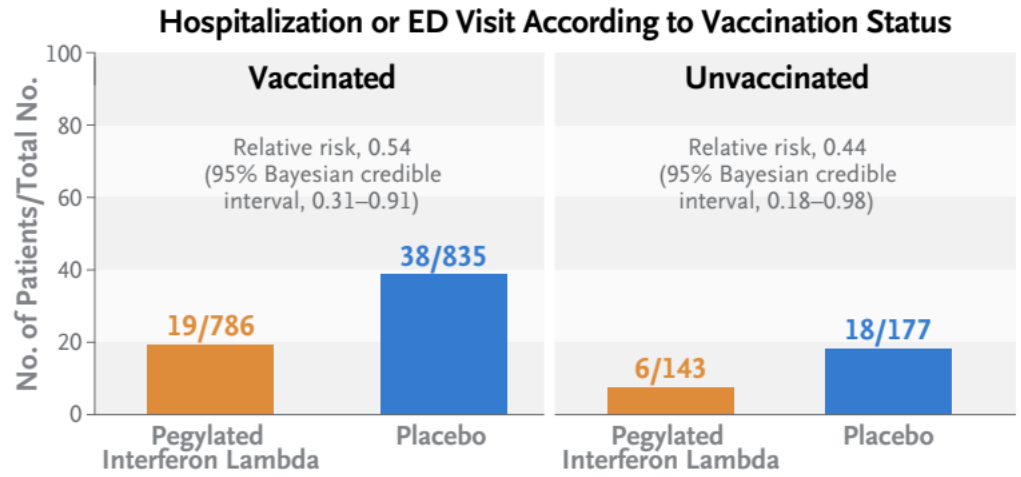
RESEARCH SUMMARY

Early Treatment with Pegylated Interferon Lambda for Covid-19

Reis G et al. DOI: 10.1056/NEJMoa2209760





Original Research | May 2023

Oral Fluvoxamine With Inhaled Budesonide for Treatment of Early-Onset COVID-19

A Randomized Platform Trial

Gilmar Reis, MD, PhD, Eduardo Augusto dos Santos Moreira Silva, MD, PhD, ... See More

Author, Article, and Disclosure Information

https://doi.org/10.7326/M22-3305

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Extensive research program

Early Treatment with Fluvoxamine among Patients with COVID-19: A Cost-Consequence Model

Fergal P. Mills, Gilmar Reis, Lindsay A. Wilson, Kristian Thorlund, Jamie I. Forrest, Christina M. Guo, David R. Boulware, Edward J. Mills, and for the TOGETHER Investigators

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Article Category: Perspective

Resilient Clinical Trial Infrastructure in Response to the COVID-19 Pandemic: Lessons Learned from the TOGETHER Randomized

SERIES | CLINICAL TRIALS IN GLOBAL HEALTH | VOLUME 9, ISSUE 5, E711-E720, MAY 2021

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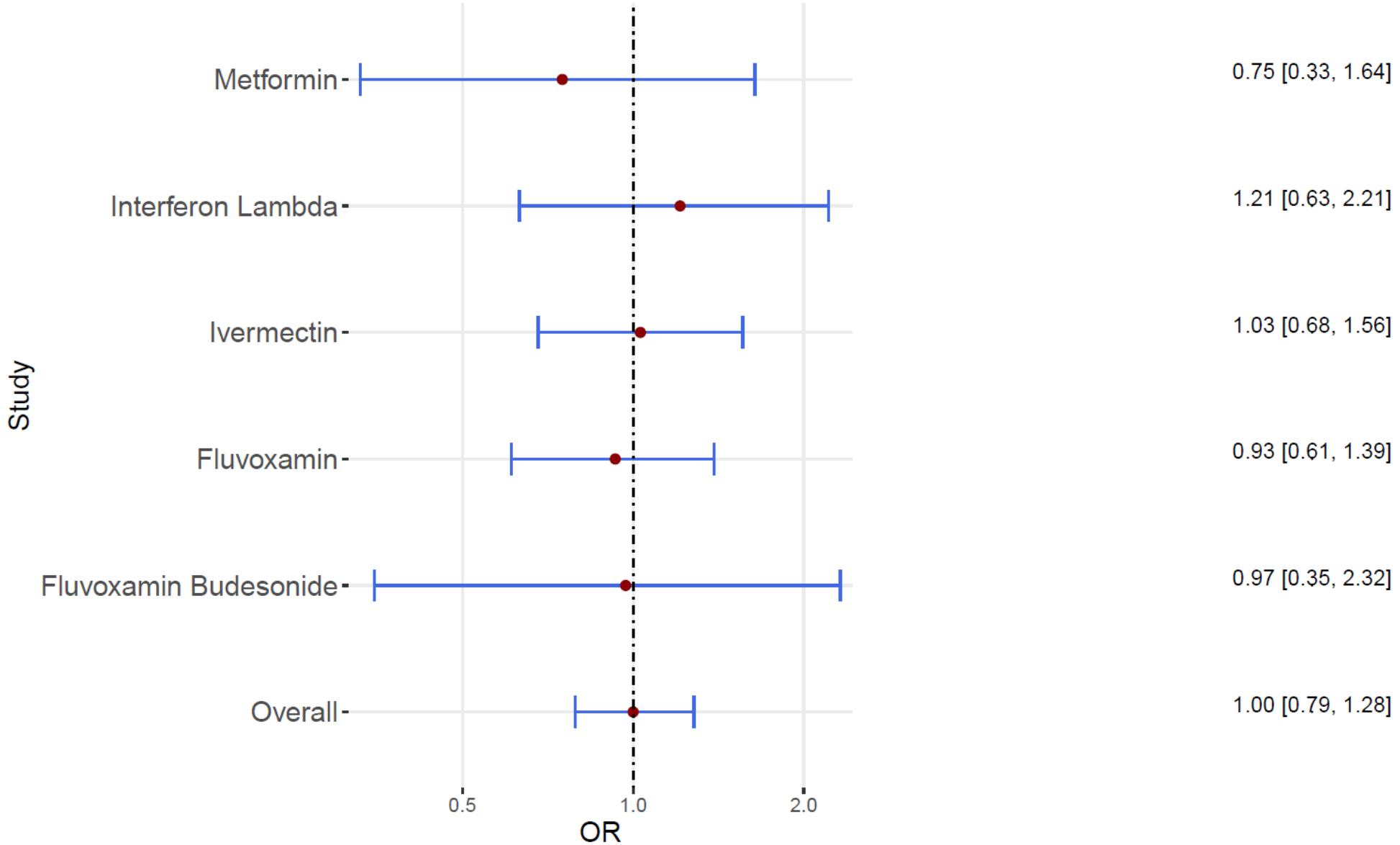
How COVID-19 has fundamentally changed clinical research in global health

Jay J H Park, MSc • Robin Mogg, PhD • Gerald E Smith, MSc • Etheldreda Nakimuli-Mpungu, PhD • Fyezah Jehan, MBBS • Craig R Rayner, PharmD • et al. Show all authors

Open Access • Published: May, 2021 • DOI: https://doi.org/10.1016/S2214-109X(20)30542-8 • Check for updates

How Relevant are matched placebos?

- Placebos in TOGETHER were matched by days and route of administration
- Participants randomized to placebo group were given matched placebo proportional to the investigational study arms at that time in the platform
- No differences observed


Metformin
Interferon Lambda
Ivermectin
Fluvoxamin
Fluvoxamin Budesonide
Overall
Study
0.5
1.0
2.0
OR
0.75 [0.33, 1.64]
1.21 [0.63, 2.21]
1.03 [0.68, 1.56]
0.93 [0.61, 1.39]
0.97 [0.35, 2.32]
1.00 [0.79, 1.28]

Global Partnerships & Capacity Building

The Together Trial: Global Investigator Network

Rwanda: Scientific Research & Innovation
Prof Leon Mutesa

South Africa
Ezintsha
Dr Francois Venter

DRC
Prof J.J.Muyembe Tamfum

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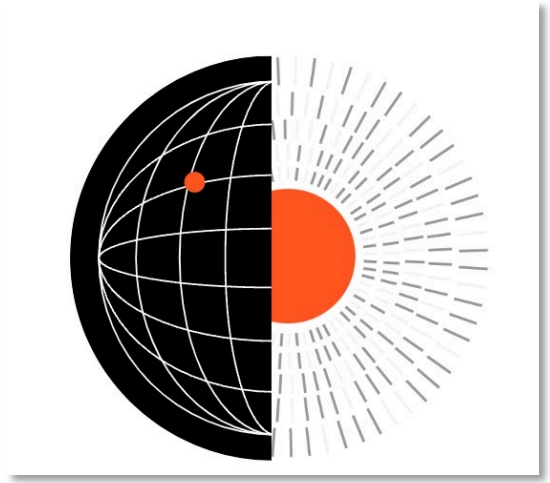
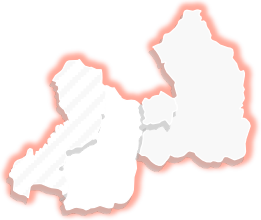
Pakistan
Prof Zulfiqar Bhutta

Brazil
CardResearch
Dr Gilmar Reis

Rwanda: Center for Family Health Research
Prof Etienne Karita

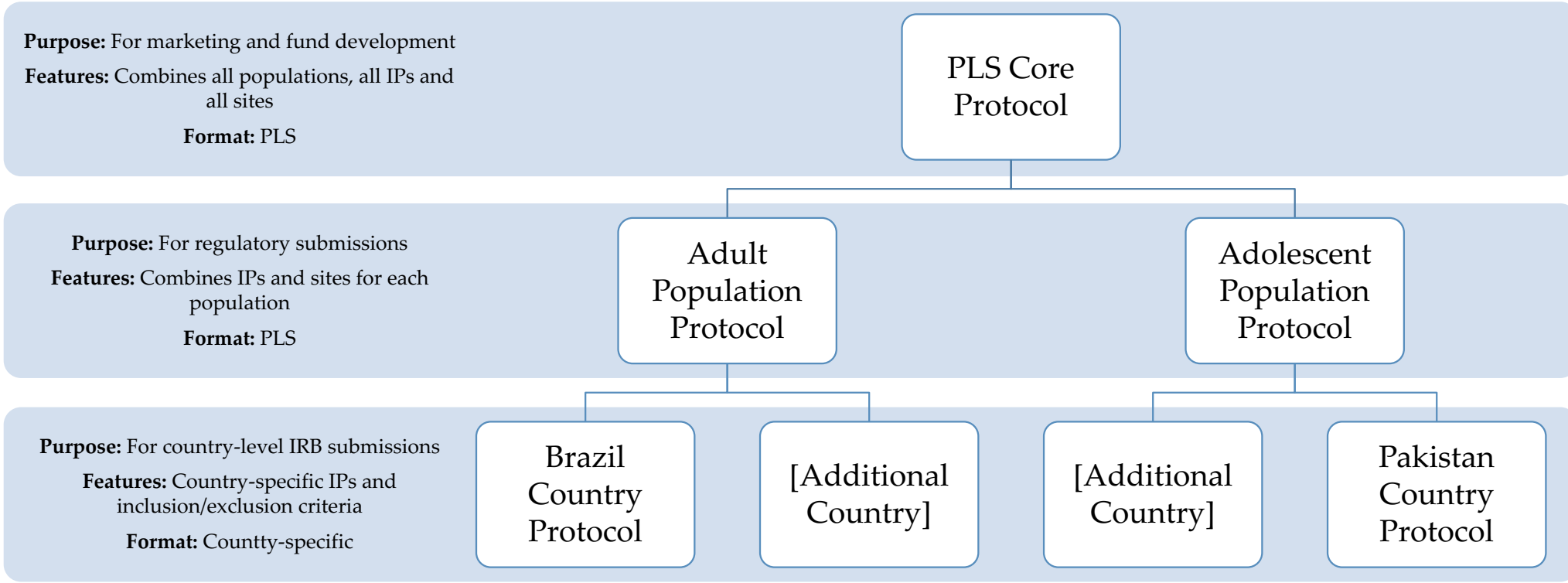
The Together Trial: LMIC Capacity Building





REVIVE: Long COVID

REVIVE Protocol Structure



Institutional Partners

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McMaster University

World Health Organization

ICODA
International COVID-19 Data Alliance

PUC Minas

MONASH University

UFOP
Universidade Federal de Ouro Preto

SCT
SOCIETY FOR CLINICAL TRIALS

Washington University in St. Louis

Thank you! Merci! Obrigado!

Jforrest@purposerlifesciences.com