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The TOGETHER Platform Trial

Revolutionizing Global Health Clinical Trials

McMaster University

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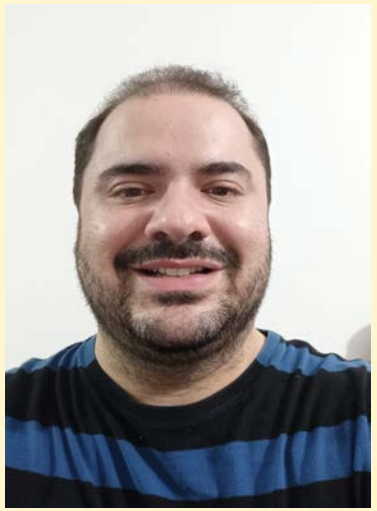
Pandemic Surge – March 2020



Dr. Eduardo Augusto
Associate Professor
Division of Medicine
Pontificia Universidade Católica
de Minas Gerais

Dr. Daniela Carla
Associate Professor
Division of Medicine
Pontificia Universidade Católica
de Minas Gerais

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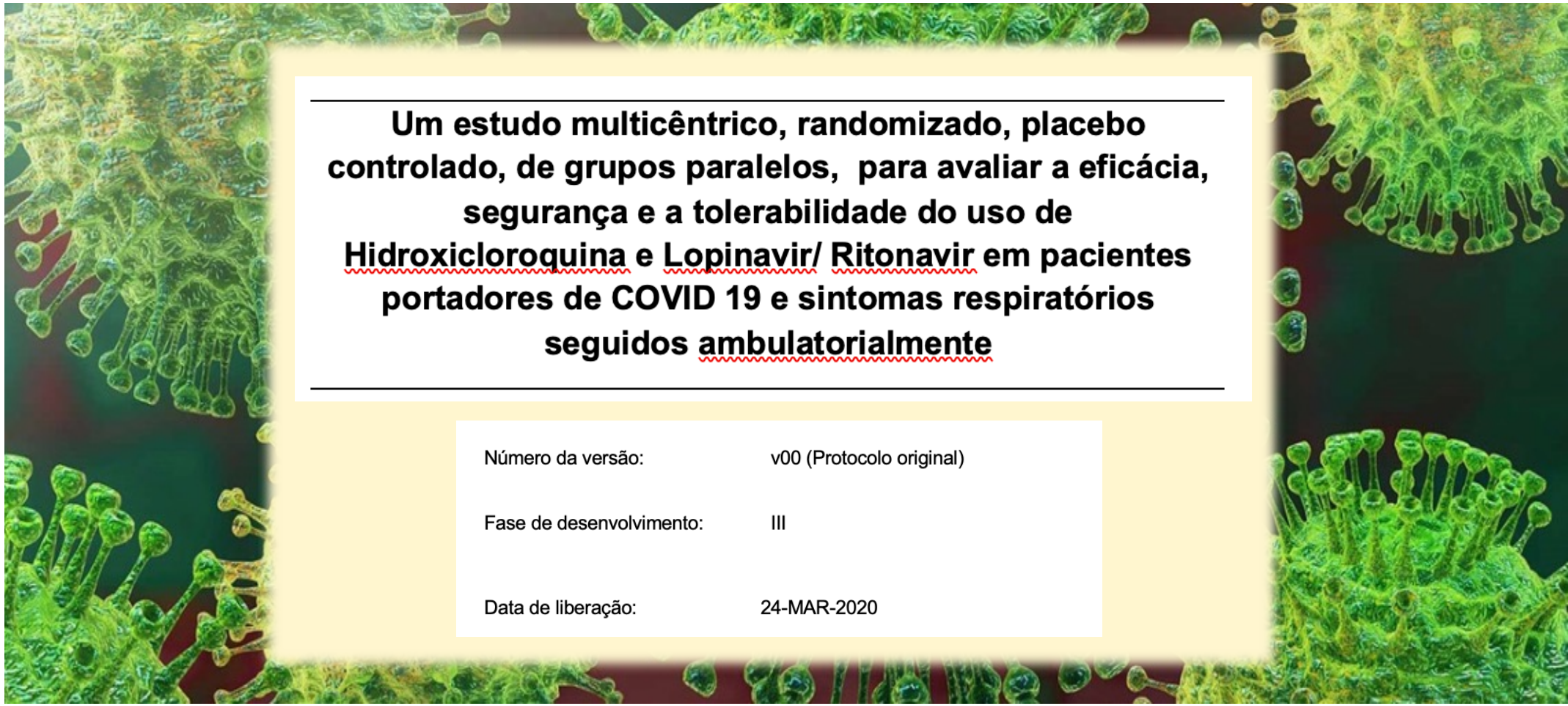

Um estudo multicêntrico, randomizado, placebo controlado, de grupos paralelos, para avaliar a eficácia, segurança e a tolerabilidade do uso de Hidroxicloroquina e Lopinavir/ Ritonavir em pacientes portadores de COVID 19 e sintomas respiratórios seguidos ambulatorialmente

Número da versão:	v00 (Protocolo original)
Fase de desenvolvimento:	III
Data de liberação:	24-MAR-2020

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 – driven by placebo-arm primary endpoints

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Patient Centered Research

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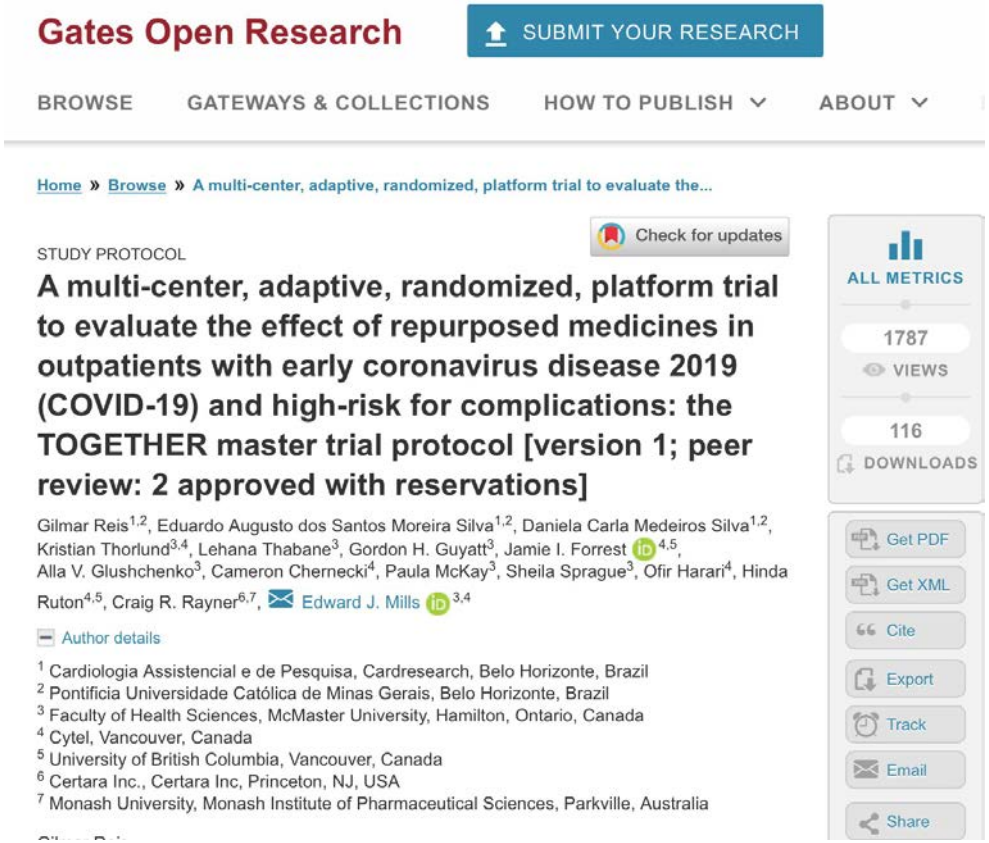
TOGETHER Trial Overview

- Randomized adaptive platform trial
- Received ethics board approval in Brazil (CEP/ CONEP#: 41174620.0.1001.5120), and Canada (HiREB#: 13390)
- Frist trial initiated on June 2, 2020
- Second trial started on January 20, 2021
- Planned interim analysis
- 13 arms completed



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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: 2 approved with reservations]

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

[1] Cardiologia Assistencial e de Pesquisa, Cardresearch, Belo Horizonte, Brazil
[2] Pontificia Universidade Católica de Minas Gerais, Belo Horizonte, Brazil
[3] Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[4] Cytel, Vancouver, Canada
[5] University of British Columbia, Vancouver, Canada
[6] Certara Inc., Certara Inc, Princeton, NJ, USA
[7] Monash University, Monash Institute of Pharmaceutical Sciences, Parkville, Australia

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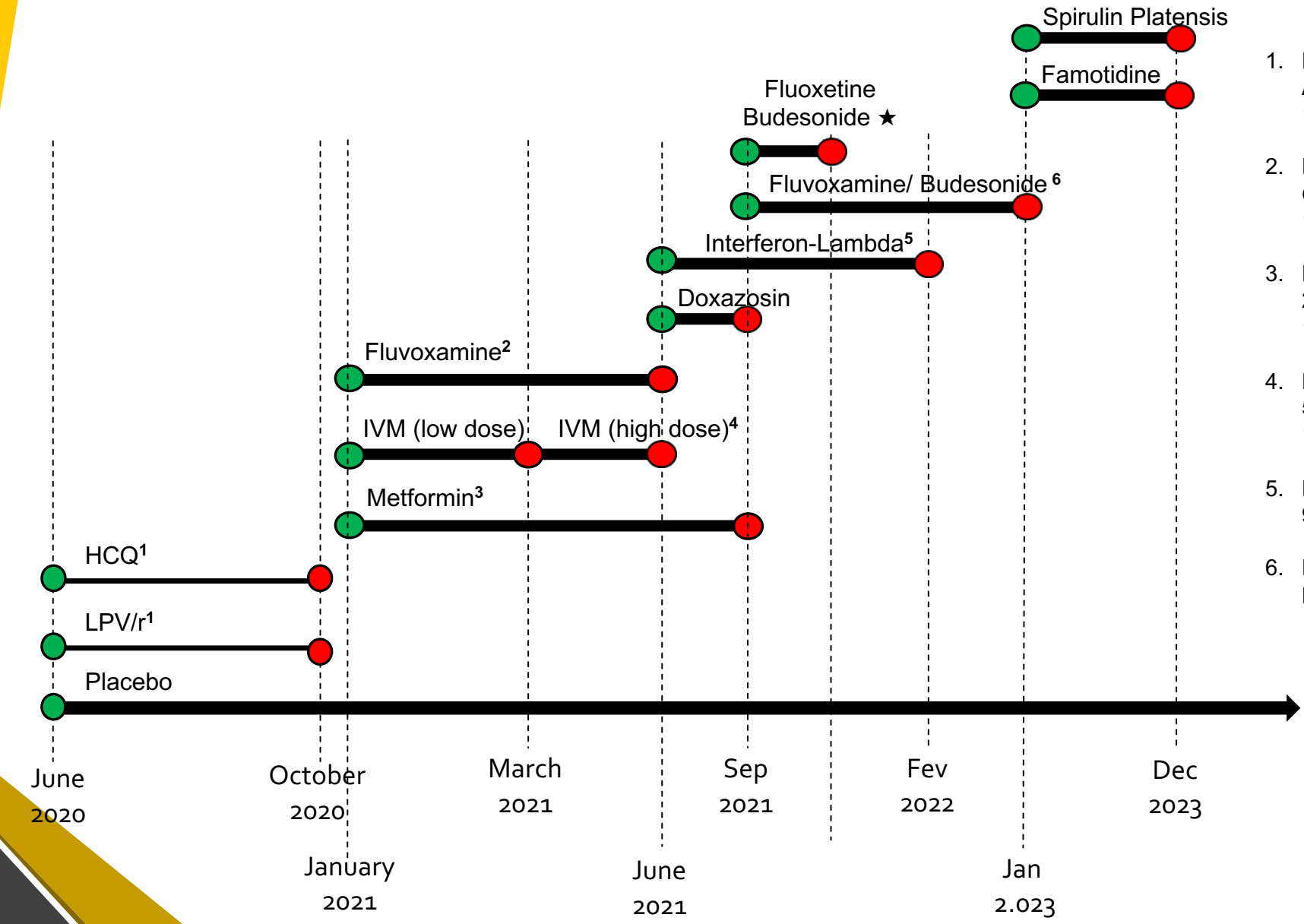
Trial Setting

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
11. Sabará (Santa Casa de Misericordia)
12. Contagem (Hosp. Santa Rita)
13. Itaúna
14. Igarapé

Intervention Timeline



1. Reis G et al. JAMA Netw Open. 2021 Apr 1;4(4):e216468. doi: 10.1001/jamanetworkopen.2021.6468
2. Reis G et al. Lancet Glob Health. 2021 Oct 27:S2214-109X(21)00448-4. doi: 10.1016/S2214-109X(21)00448-4
3. Reis G et al. Lancet Reg Health Am. 2022 Feb;6:100142. doi: 10.1016/j.lana.2021.100142.
4. Reis G, et al. N Engl J Med. 2022 May 5:NEJMoa2115869. doi: 10.1056/NEJMoa2115869.
5. Reis G et al. N Engl J Med. 2023 Feb 9. doi: 10.1056/NEJMoa2209760
6. Reis G et al. Ann Intern Med 2023 May. doi: 10.7326/M22-3305.

★ Anticov Consortia

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CARDO RESEARCH

Publications

JAMA Network | Open

Original Investigation | Infectious Diseases

Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19

The TOGETHER Randomized Clinical Trial

Gilmar Reis, MD; Eduardo Augusto dos Santos Moreira Silva, MD; Daniela Carla Medeiros Silva, MD; Lehana Thabane, PhD; Gurmit Singh, PhD; Jay J. H. Park, MSc; Jamie I. Forrest, MPH; Ofir Harari, PhD; Castilho Vitor Quirino dos Santos; Ana Paula Figueiredo Guimarães de Almeida, MD; Adhemar Dias de Figueiredo Neto, MD; Leonardo Cançado Monteiro Savassi, MD; Aline Cruz Milagres, RN; Mauro Martins Teixeira, MD; Maria Izabel Campos Simplicio, BScPharm; Luciene Barra Ribeiro, RN; Rosemary Oliveira; Edward J. Mills, PhD; for the TOGETHER Investigators

JAMA Network | Open

RCT: Effect of Early Treatment With Hydroxychloroquine vs Lopinavir Plus Ritonavir on Risk of Hospitalization Among Patients With COVID-19

POPULATION

308 Men, 377 Women

Patients with COVID-19

Median 53 y (18-94 y)

SETTINGS / LOCATIONS

7 Clinical sites, Minas Geraise, Brazil

INTERVENTION

685 Patients randomized, **606** patients analyzed

198 Hydroxychloroquine (HCQ) Oral
800 mg loading dose, then 400 mg daily for 9 d

200 Lopinavir and ritonavir (L+R)
Oral loading doses of 800 mg of lopinavir and 200 mg of ritonavir every 12 h, followed by 200 mg and 50 mg of each, respectively, every 12 h for 9 d

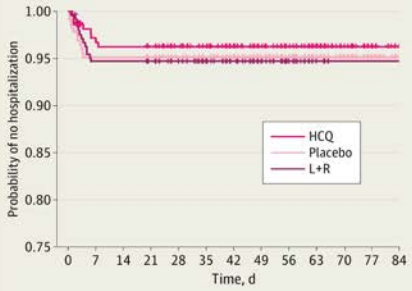
208 Placebo
Oral placebo talc tablet

PRIMARY OUTCOMES

The primary outcomes were COVID-associated hospitalization and death assessed at 90 d after randomization

FINDINGS

The proportion of COVID-associated hospitalization was 3.7% in the HCQ group, 5.7% in the L+R group, and 4.8% in the placebo group, with no significant differences. There were 3 deaths: 1 in the placebo group and 2 in the L+R intervention group.



No differences in hospitalization rate between interventions:
HCQ: HR, 0.76; 95% CI, 0.30-1.88
L+R: HR, 1.16; 95% CI, 0.53-2.59

Reis G, Moreira Silva EAS, Medeiros Silva DC, et al; TOGETHER Investigators. Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: the TOGETHER randomized clinical trial. *JAMA Netw Open*. 2021;4(4):e216468. doi:10.1001/jamanetworkopen.2021.6468

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Fluvoxamine

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**

Summary

Background Recent evidence indicates a potential therapeutic role of fluvoxamine for COVID-19. In the TOGETHER trial for acutely symptomatic patients with COVID-19, we aimed to assess the efficacy of fluvoxamine versus placebo in preventing hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19.

Methods This placebo-controlled, randomised, adaptive platform trial done among high-risk symptomatic Brazilian adults confirmed positive for SARS-CoV-2 included eligible patients from 11 clinical sites in Brazil with a known risk factor for progression to severe disease. Patients were randomly assigned (1:1) to either fluvoxamine (100 mg twice daily for 10 days) or placebo (or other treatment groups not reported here). The trial team, site staff, and patients were masked to treatment allocation. Our primary outcome was a composite endpoint of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 up to 28 days post-random assignment on the basis of intention to treat. Modified intention to treat explored patients receiving at least 24 h of treatment before a primary outcome event and per-protocol analysis explored patients with a high level adherence (>80%). We used a Bayesian analytic framework to establish the effects along with probability of success of intervention compared with placebo. The trial is registered at ClinicalTrials.gov (NCT04727424) and is ongoing.

Findings The study team screened 9803 potential participants for this trial. The trial was initiated on June 2, 2020, with the current protocol reporting randomisation to fluvoxamine from Jan 20 to Aug 5, 2021, when the trial arms were stopped for superiority. 741 patients were allocated to fluvoxamine and 756 to placebo. The average age of participants was 50 years (range 18–102 years); 58% were female. The proportion of patients observed in a COVID-19 emergency setting for more than 6 h or transferred to a teritary hospital due to COVID-19 was lower for the fluvoxamine group compared with placebo (79 [11%] of 741 *vs* 119 [16%] of 756); relative risk [RR] 0·68; 95% Bayesian credible interval [95% BCI]: 0·52–0·88), with a probability of superiority of 99·8% surpassing the prespecified superiority threshold of 97·6% (risk difference 5·0%). Of the composite primary outcome events, 87% were

Lancet Glob Health 2021

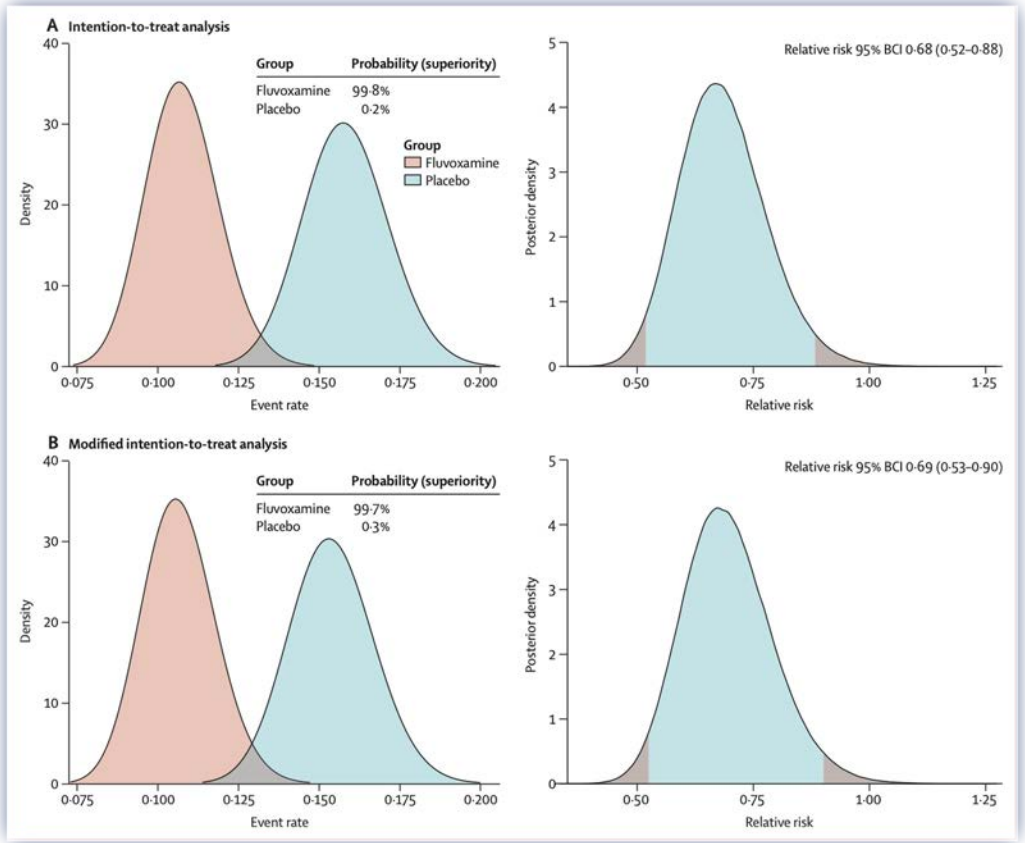
Published Online October 27, 2021 https://doi.org/10.1016/S2214-109X(21)00448-4

See Online/Comment https://doi.org/10.1016/S2214-109X(21)00501-5

For the Portuguese translation of the abstract see Online for appendix 1

*Investigators are listed in appendix 2

Research Division, Cardresearch - Cardiologia Assistencial e de Pesquisa, Belo Horizonte, Brazil (G Reis PhD, E A dos S Moreira-Silva PhD, D C Medeiros Silva PhD, T S Ferreira MD, C V Q dos Santos, V H de Souza Campos, L B Ribeiro RN, M I C Simplicio BScPharm, R Oliveira); Department of Medicine, Pontifícia Universidade Católica de Minas Gerais, Belo Horizonte, Brazil (G Reis, E A dos S Moreira Silva,



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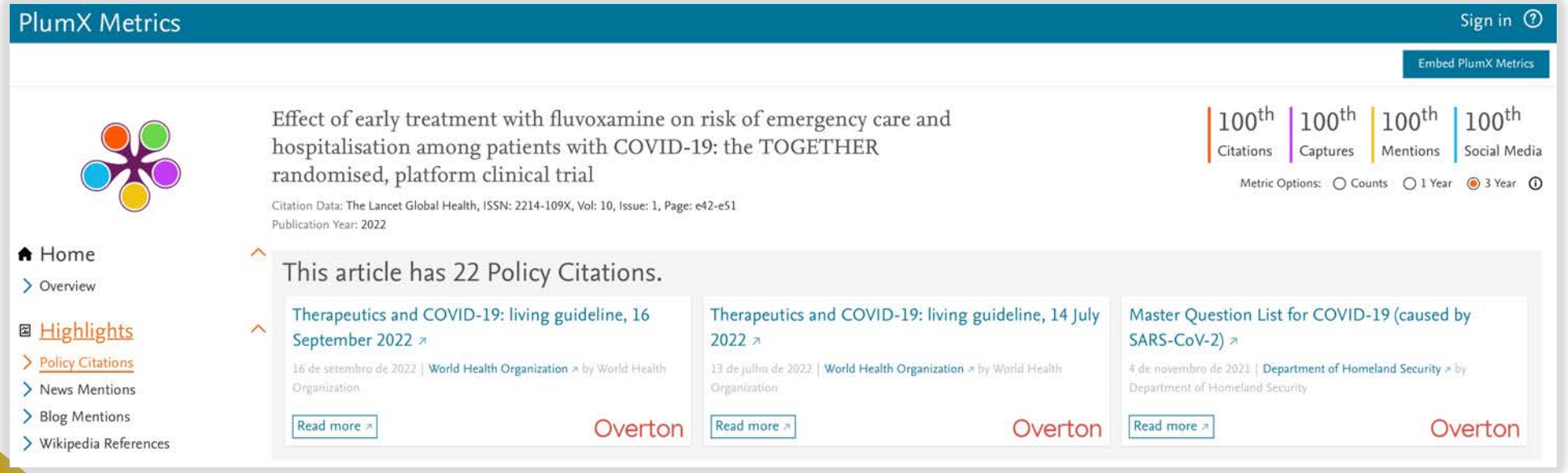
CARDO RESEARCH

Publications

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**



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August 6, 2021: Early Treatment of COVID-19 with Repurposed Therapies: The TOGETHER Adaptive Platform Trial (Edward Mills, PhD, FRCP)

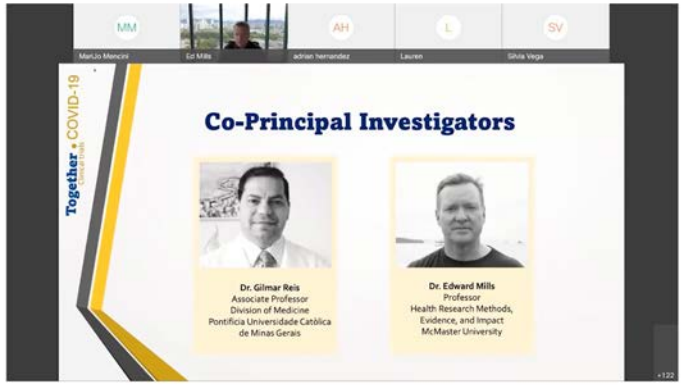
Speaker

Edward Mills, PhD, FRCP
Professor Department of Health Research Methods, Evidence & Impact McMaster University, Canada

Topic

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

Slides



Keywords

COVID-19 treatment; Adaptive Platform Trial; Fluvoxamine; Repurposed therapies, TOGETHER Trial

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Bill & Melinda Gates Foundation, 2022

23–26 October 2022
Brussels, Belgium & Virtual

GRAND CHALLENGES ANNUAL MEETING 2022

Dear Gilmar,

We look forward to seeing you in Brussels, Belgium for the upcoming Grand Challenges Annual Meeting 2022. We have reserved a room for you at the The Hotel Brussels.

Please review this email and ensure your hotel dates are accurate. ***If you need to modify your hotel dates, please reply to this email.*** Do not contact the hotel directly.

External speakers

Rapid Detection & Outbreak Response

- Frank Møller Aarestrup, Cand.med.vet., PhD, Dr. med – Professor, Head of Research Group for the National Food Institute at the Technical University of Denmark

  Frank Møller Aarestrup is leading the Research group for Genomic Epidemiology at the Danish Technical University Food, which performs research with the aim of reducing the global burden of infectious diseases with a special focus on antimicrobial resistance. The group established Global Surveillance, an umbrella of projects focused on detecting, analyzing, and distributing information on emerging infectious diseases, antimicrobial resistance, etc. to create an evidence-based early warning system. The group created the Center for Genomic Epidemiology to provide and facilitate access to bioinformatics resources and run free online services to allow all countries, institutions, and individuals to take advantage of novel sequencing data. He also leads a project funded by DANIDA developing technology for whole genome sequencing with basic IT tools under primitive conditions in the bush by examining microorganisms found in samples from waterholes[5].

- Alfonso Valencia, PhD - Life Sciences Department Director at the Barcelona Supercomputing Center

  Alfonso Valencia is a Biologist by training with a Ph.D. in Biochemistry and Molecular Biology by the Universidad Autónoma de Madrid. He is ICREA Research Professor and Director of the Life Sciences Department at the Barcelona Supercomputing Centre (BSC), Director of the Spanish National Bioinformatics Institute (INB) and head of the Spanish Node of the European Bioinformatics Infrastructure ELIXIR. The main interest of his group is the study of the molecular bases of cancer and other diseases, by bringing an evolutionary perspective to the study of the interplay between genomics and epigenomics. His research is largely carried out in the context of large-scale genome projects, where they develop new computational methods for the study of genome/phenotype relationships from ML/AI to NLP/text mining.

Instant & Broad Immunity

- Anna Marie Pyle, PhD – Co-Founder and Scientific Advisor at RIGImmune, Yale Sterling Professor, and Howard Hughes Medical Institute Investigator

  Anna Marie Pyle co-discovered the RIG-I receptor family and she conducted many of the first structural and biochemical investigations on RIG-I. Dr. Pyle is also a specialist in RNA structure, synthesis, and design. She designed the SLRs for selective targeting of RIG-I, and she developed them as antitumor and anticancer compounds in collaboration with Dr. Iwasaki. Dr. Pyle has designed other types of bioactive RNA molecules for studies of RNA processing and protein recognition.

- Gilmar Reis, MD, PhD – Principal Investigator on lambda interferons work

  Gilmar Reis is now serving as an associate professor of medicine at the Department of Medicine, Pontifical Catholic University of Minas Gerais (PUC-Minas), since 2001. He also was a director of the PUC-Minas Medical School at Contagem, MG, Brazil (2015–2020). He built up a large cardiovascular research clinic (CARDRESEARCH) in Belo Horizonte, focusing on global health evaluation, epidemiological evaluation of cardiac risk factors, and patient-centered clinical research with emphasis on cardiovascular chronic conditions. During the COVID-19 pandemic, he proposed the TOGETHER Trial in partnership with scientists from McMaster University and built up a large primary care clinical research frame network focusing on COVID-19 early mild disease patients.

- Ryan Muldoon - CEO of PrEP Biopharm

  Ryan Muldoon co-founded PrEP Biopharm Ltd. as a spinout from Johnson & Johnson after spending 15 years as a commercial executive at Janssen, Forest Laboratories, and Bristol-Myers Squibb. Immediately prior to co-founding PrEP Biopharm, he was responsible for New Business Development within the Infectious Diseases & Vaccines group at Janssen, helping to secure several licenses and acquisitions for the group. While at Janssen, he also was the Global Commercial Leader for Viral Hepatitis. Prior to Janssen, Ryan spent time at Bristol-Myers Squibb as the global marketing

[5] Tanzania gains access to life-saving equipment - DTU Food

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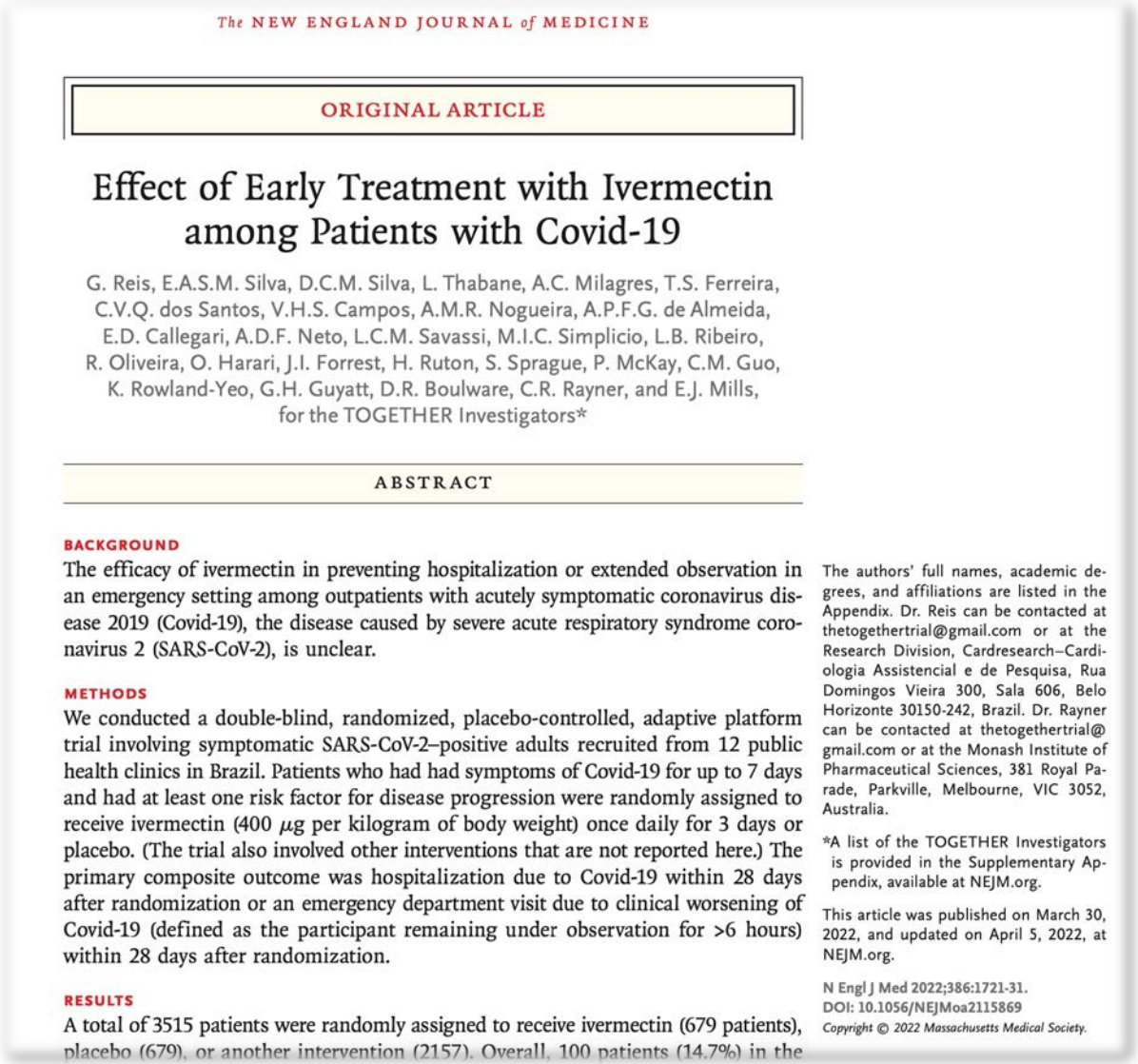
Ivermectin and COVID-19



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

BACKGROUND

The efficacy of ivermectin in preventing hospitalization or extended observation in an emergency setting among outpatients with acutely symptomatic coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is unclear.

METHODS

We conducted a double-blind, randomized, placebo-controlled, adaptive platform trial involving symptomatic SARS-CoV-2–positive adults recruited from 12 public health clinics in Brazil. Patients who had had symptoms of Covid-19 for up to 7 days and had at least one risk factor for disease progression were randomly assigned to receive ivermectin (400 μg per kilogram of body weight) once daily for 3 days or placebo. (The trial also involved other interventions that are not reported here.) The primary composite outcome was hospitalization due to Covid-19 within 28 days after randomization or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization.

RESULTS

A total of 3515 patients were randomly assigned to receive ivermectin (679 patients), placebo (679), or another intervention (2157). Overall, 100 patients (14.7%) in the

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Reis can be contacted at thetogethertrial@gmail.com or at the Research Division, Cardresearch–Cardiologia Assistencial e de Pesquisa, Rua Domingos Vieira 300, Sala 606, Belo Horizonte 30150-242, Brazil. Dr. Rayner can be contacted at thetogethertrial@gmail.com or at the Monash Institute of Pharmaceutical Sciences, 381 Royal Parade, Parkville, Melbourne, VIC 3052, Australia.

*A list of the TOGETHER Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 30, 2022, and updated on April 5, 2022, at NEJM.org.

N Engl J Med 2022;386:1721-31.
DOI: 10.1056/NEJMoa2115869

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ORIGINAL ARTICLE

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

Gilmar Reis, M.D., Ph.D., Eduardo A.S.M. Silva, M.D., Ph.D., Daniela C.M. Silva, M.D., Ph.D., Lehana Thabane, Ph.D., Aline C. Milagres, R.N., Thiago S. Ferreira, M.D., Castilho V.Q. dos Santos, Vitoria H.S. Campos, Ana M.R. Nogueira, M.D., Ana P.F.G. de Almeida, M.D., Eduardo D. Callegari, M.D., Adhemar D.F. Neto, M.D., Ph.D., et al., for the TOGETHER Investigators*

Metrics ⓘ

May 5, 2022
N Engl J Med 2022; 386:1721-1731
DOI: 10.1056/NEJMoa2115869

This research output has an **Altmetric Attention Score** of **17594**. This is our high-level measure of the quality and quantity of online attention that it has received. This Attention Score, as well as the ranking and number of research outputs shown below, was calculated when the research output was last mentioned on **04 June 2024**.

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The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Reis G et al. DOI: 10.1056/NEJMoa2115869

CLINICAL PROBLEM

Inexpensive, widely available, effective treatments for coronavirus disease 2019 (Covid-19) are needed. Results from trials examining the efficacy of the antiparasitic drug ivermectin have been discordant.

CLINICAL TRIAL

Design: A large, double-blind, randomized, placebo-controlled, adaptive platform trial initiated in June 2020 to test potential treatments for Covid-19 in Brazil assessed the efficacy of ivermectin treatment among outpatients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who had had symptoms of Covid-19 for up to 7 days and had at least one risk factor for disease progression.

Intervention: 1358 adults were randomly assigned to receive either ivermectin (400 μg per kilogram of body weight per day) for 3 days or matching placebo between March and August 2021. The primary outcome was hospitalization due to Covid-19 or prolonged emergency department observation (>6 hours) due to clinical worsening of Covid-19 within 28 days after randomization.

RESULTS

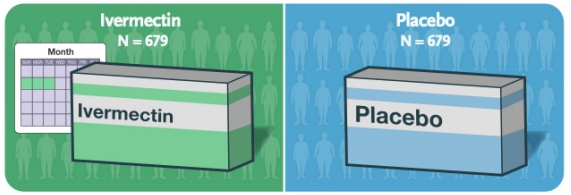
Efficacy: Within 28 days after randomization, the incidence of hospital admission for Covid-19 or prolonged emergency department observation due to clinical worsening of Covid-19 was similar in the two groups.

Safety: There were no important between-group differences in the incidence of adverse events during the treatment period.

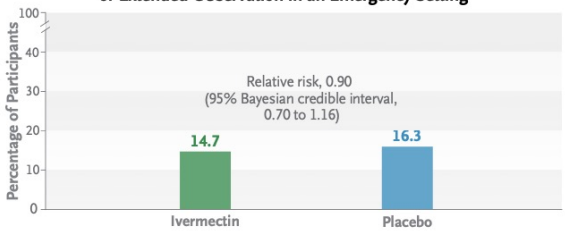
LIMITATIONS

- The trial was initially designed to test 1 day of ivermectin treatment, as is commonly used for parasitic diseases, but treatment was changed to 3 days after feedback from advocacy groups.
- Off-label use of ivermectin is promoted by paramedical groups and is widespread in Brazil. The authors attempted to screen potential participants for previous ivermectin use.

Links: Full Article | NEJM Quick Take



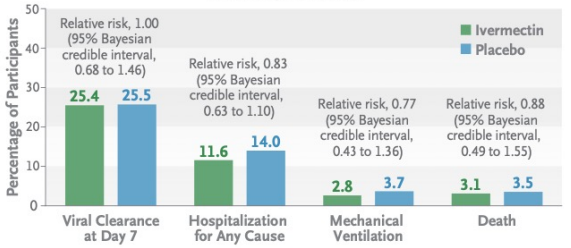
Covid-19–Related Hospitalization or Extended Observation in an Emergency Setting



Adverse Events during Treatment Period

	Ivermectin N = 679	Placebo N = 679	Estimated Treatment Effect (95% Bayesian credible interval)
Grade 3	6.0% (41)	7.4% (50)	0.82 (0.55 to 1.22)
Grade 4	2.5% (17)	2.7% (18)	0.95 (0.49 to 1.80)
Grade 5	3.1% (21)	3.5% (24)	0.81 (0.45 to 1.42)

Secondary Outcomes



CONCLUSIONS

Early use of ivermectin did not lead to a lower incidence of hospital admission for Covid-19 or prolonged emergency department observation due to clinical worsening among patients at risk for disease progression.

CARD RESEARCH

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Treatment with Pegylated Interferon Lambda for Covid-19

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The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Reis can be contacted at reisg1@mcmaster.ca or at the Department of Health Research Methods, Evidence, and Impact, McMaster University Medical Centre, 1280 Main St. West, 2C Area, Hamilton, ON L8S4K1, Canada. Dr. Glenn can be contacted at jeffrey.glenn@stanford.edu or at the Department of Medicine, 269 Campus Dr., Stanford, CA 94305-5171.

*The TOGETHER Investigators are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2023;388:518-28.
DOI: 10.1056/NEJMoa2209760

ABSTRACT

BACKGROUND

The efficacy of a single dose of pegylated interferon lambda in preventing clinical events among outpatients with acute symptomatic coronavirus disease 2019 (Covid-19) is unclear.

METHODS

We conducted a randomized, controlled, adaptive platform trial involving predominantly vaccinated adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brazil and Canada. Outpatients who presented with an acute clinical condition consistent with Covid-19 within 7 days after the onset of symptoms received either pegylated interferon lambda (single subcutaneous injection, 180 μg) or placebo (single injection or oral). The primary composite outcome was hospitalization (or transfer to a tertiary hospital) or an emergency department visit (observation for >6 hours) due to Covid-19 within 28 days after randomization.

RESULTS

A total of 933 patients were assigned to receive pegylated interferon lambda (2 were subsequently excluded owing to protocol deviations) and 1018 were assigned to receive placebo. Overall, 83% of the patients had been vaccinated, and during

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RESEARCH SUMMARY

Early Treatment with Pegylated Interferon Lambda for Covid-19

Reis G et al. DOI: 10.1056/NEJMoa2209760

CLINICAL PROBLEM

Convenient, widely available, and effective therapies to treat Covid-19 in outpatients are needed. SARS-CoV-2 infection induces weak expression of naturally produced type III interferons — an early line of defense against respiratory viruses — in infected cells. Whether an exogenous source of interferons, such as pegylated interferon lambda, can treat early SARS-CoV-2 infection is unknown.

CLINICAL TRIAL

Design: A phase 3, adaptive platform, randomized, placebo-controlled trial assessed the efficacy and safety of pegylated interferon lambda in adult outpatients in Brazil and Canada who were at high risk for severe illness soon after they received a diagnosis of Covid-19.

Intervention: 1949 adults presenting within 7 days after symptom onset with a positive rapid test for SARS-CoV-2 and with at least one high-risk criterion (e.g., age ≥50 years, diabetes mellitus, and hypertension leading to the use of medication) were assigned to receive a single subcutaneous injection of pegylated interferon lambda (180 μg) or placebo. Most patients had received at least one dose of Covid-19 vaccine. The primary outcome was a composite of Covid-19–related hospitalization (or referral to a tertiary hospital) or admission to an emergency department (ED) (observation for >6 hours) within 28 days after randomization.

RESULTS

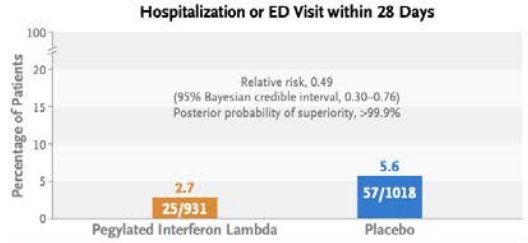
Efficacy: The risk of Covid-19–related hospitalization or an ED visit was approximately 50% lower in the interferon group than in the placebo group. Results were consistent regardless of vaccination status.

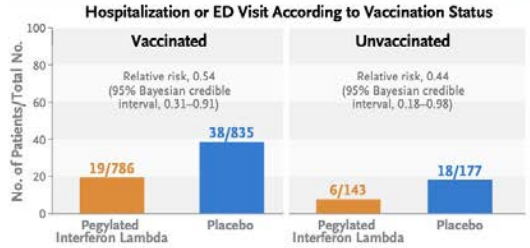
Safety: The incidence of adverse events was similar in the two groups.

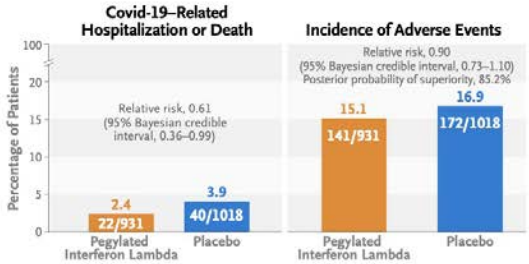
REMAINING QUESTIONS

- Since the completion of the trial, a polymorphism in the innate antiviral response gene *OAS1* has been linked to clearance of SARS-CoV-2, and a common haplotype could indicate a greater likelihood of response to pegylated interferon lambda and other interferons.

Links: Full Article | NEJM Quick Take

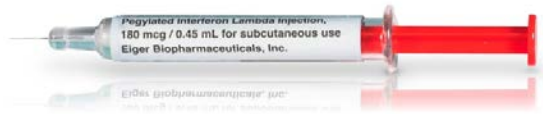






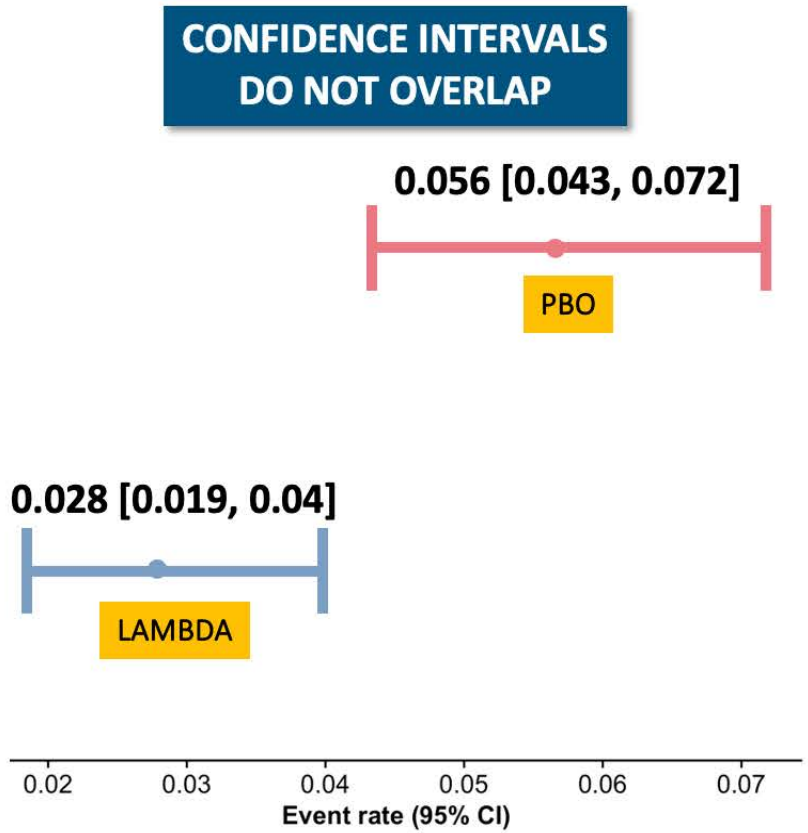
CONCLUSIONS

Among high-risk, symptomatic, largely vaccinated outpatients with a recent diagnosis of Covid-19, those who received a single subcutaneous injection of pegylated interferon lambda had a lower risk of Covid-19–related hospitalization or an ED visit within 28 days than those who received placebo.



Lambda Highly Superior Compared to Placebo

NON-OVERLAPPING CONFIDENCE INTERVALS



Statistical analysis conducted in a Bayesian framework
Prespecified Threshold of Superiority = 97.6%

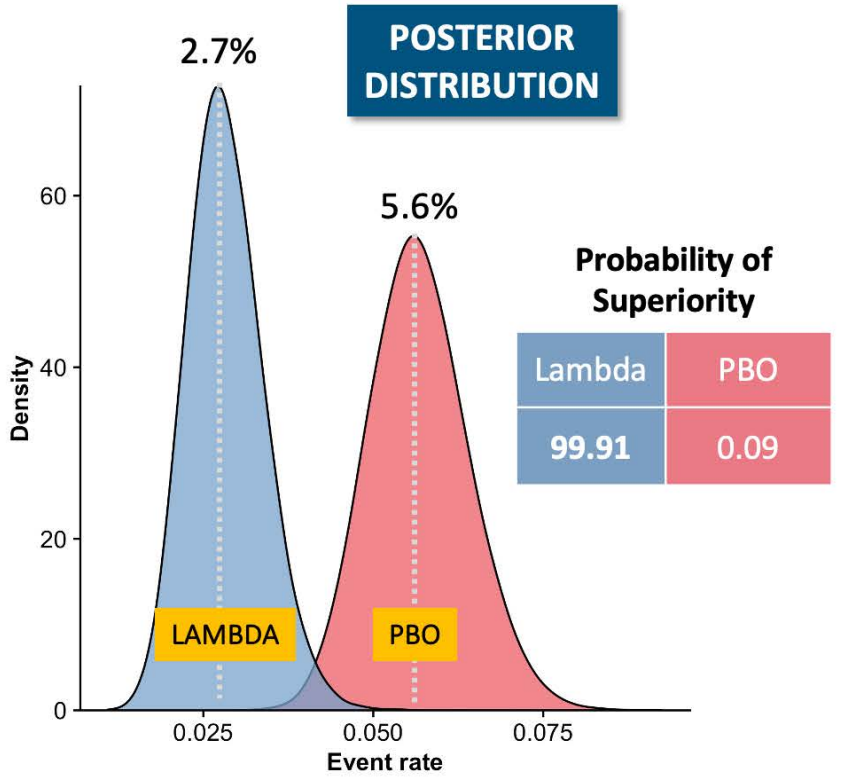
Lambda Final Results

Lambda Highly Superior Compared to Placebo

***99.91% PROBABILITY OF SUPERIORITY*, SURPASSING PRESPECIFIED SUPERIORITY THRESHOLD OF 97.6%**

Risk	Lambda n=916	Placebo n=1020	Risk Reduction (95% BCI)	Probability of Superiority*
Hospitalizations or ER visits	25 (2.7%)	57 (5.6%)	**50%** (23 - 69%)	99.9%
Hospitalizations	21 (2.3%)	41 (4%)	**42%** (5 - 66%)	98.4%

- 1 death in Lambda group; 4 deaths in Placebo group
- 84% patients were vaccinated
- Incidence of any adverse event was indistinguishable between Lambda and Placebo group



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Statistical analysis conducted in a Bayesian framework
Prespecified Threshold of Superiority = 97.6%

Fluvoxamine - Budesonide

- ~ 1.400 participants
- DSMB (02 Aug 2022): Met primary endpoint for efficacy

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CARDO RESEARCH

Fluvoxamine - Budesonide

Annals of Internal Medicine

ORIGINAL RESEARCH

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

A Randomized Platform Trial

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Background: Previous trials have demonstrated the effects of fluvoxamine alone and inhaled budesonide alone for prevention of disease progression among outpatients with COVID-19.

Objective: To determine whether the combination of fluvoxamine and inhaled budesonide would increase treatment effects in a highly vaccinated population.

Design: Randomized, placebo-controlled, adaptive platform trial. (ClinicalTrials.gov: NCT04727424)

Setting: 12 clinical sites in Brazil.

Participants: Symptomatic adults with confirmed SARS-CoV-2 infection and a known risk factor for progression to severe disease.

Intervention: Patients were randomly assigned to either fluvoxamine (100 mg twice daily for 10 days) plus inhaled budesonide (800 mcg twice daily for 10 days) or matching placebos.

Measurements: The primary outcome was a composite of emergency setting retention for COVID-19 for more than 6 hours, hospitalization, and/or suspected complications due to clinical progression of COVID-19 within 28 days of randomization. Secondary outcomes included health care attendance (defined as hospitalization for any cause or emergency department visit lasting >6 hours), time to hospitalization, mortality, patient-reported outcomes, and adverse drug reactions.

Results: Randomization occurred from 15 January to 6 July 2022. A total of 738 participants were allocated to oral fluvoxamine plus inhaled budesonide, and 738 received placebo. The proportion of patients observed in an emergency setting for COVID-19 for more than 6 hours or hospitalized due to COVID-19 was lower in the treatment group than the placebo group (1.8% [95% credible interval {CrI}, 1.1% to 3.0%] vs. 3.7% [95% CrI, 2.5% to 5.3%]; relative risk, 0.50 [95% CrI, 0.25 to 0.92]), with a probability of superiority of 98.7%. No relative effects were found between groups for any of the secondary outcomes. More adverse events occurred in the intervention group than the placebo group, but no important differences between the groups were detected.

Limitation: Low event rate overall, consistent with contemporary trials in vaccinated populations.

Conclusion: Treatment with oral fluvoxamine plus inhaled budesonide among high-risk outpatients with early COVID-19 reduced the incidence of severe disease requiring advanced care.

Primary Funding Source: Latona Foundation, FastGrants, and Rainwater Charitable Foundation.

Ann Intern Med. doi:10.7326/M22-3305 **Annals.org**

For author, article, and disclosure information, see end of text.

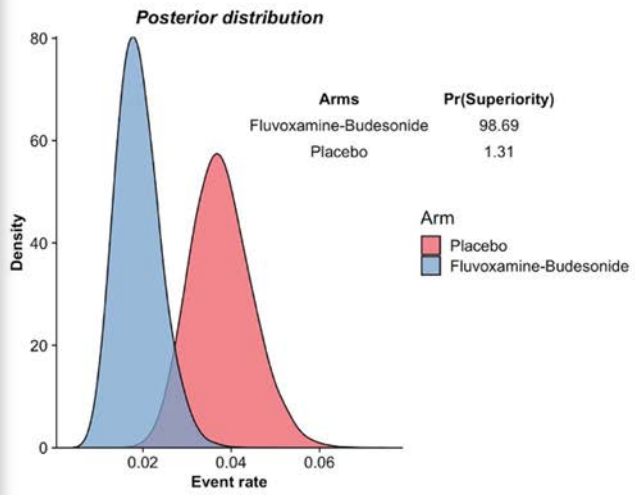
This article was published at Annals.org on 18 April 2023.

A list of the TOGETHER Investigators is provided in the Supplement (available at Annals.org).

Fluvoxamine - Budesonide

Figure 2: Probability of efficacy and Bayesian relative risk of retention in a COVID-19 emergency setting or hospitalization for fluvoxamine vs. placebo (Panel A: Event rate; Panel B: Treatment policy relative risk

Panel A



Panel B

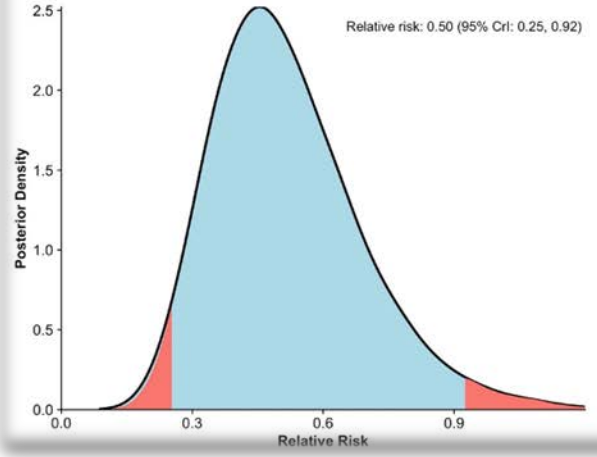
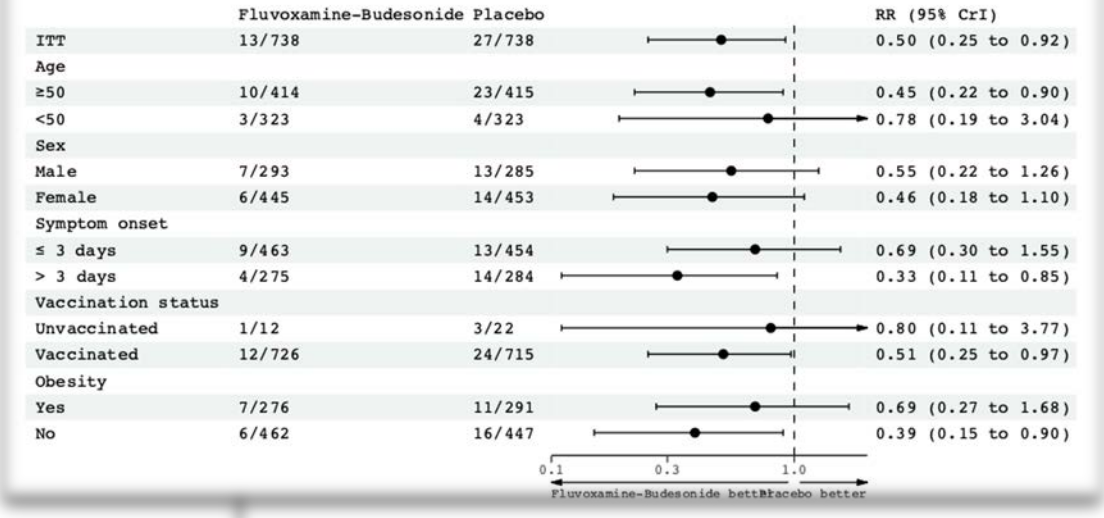


Figure 3: Sub-group analyses comparing fluvoxamine/budesonide vs matched placebo



	Fluvoxamine-Budesonide	Placebo	RR (95% CrI)
ITT	13/738	27/738	0.50 (0.25 to 0.92)
Age			
≥50	10/414	23/415	0.45 (0.22 to 0.90)
<50	3/323	4/323	0.78 (0.19 to 3.04)
Sex			
Male	7/293	13/285	0.55 (0.22 to 1.26)
Female	6/445	14/453	0.46 (0.18 to 1.10)
Symptom onset			
≤ 3 days	9/463	13/454	0.69 (0.30 to 1.55)
> 3 days	4/275	14/284	0.33 (0.11 to 0.85)
Vaccination status			
Unvaccinated	1/12	3/22	0.80 (0.11 to 3.77)
Vaccinated	12/726	24/715	0.51 (0.25 to 0.97)
Obesity			
Yes	7/276	11/291	0.69 (0.27 to 1.68)
No	6/462	16/447	0.39 (0.15 to 0.90)

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COVID-19 Burden

Event	None	Fluvoxamine[3]	Lambda Interferon[4]	Fluvoxamine/ Budesonide[5]
SIVEP/ Gripe[1]				
Hospitalizations	**1.615.428**			
Death	**518.180**			
Minas Gerais Data[2]				
SRAG	**216.990**			
Death	**65.881**			

1. Int J Equity Health. 2023 Nov 17;22(1):238. doi: 10.1186/s12939-023-02037-8
2. https://coronavirus.saude.mg.gov.br/images/2023/10/31-10-COVID-19_-_BOLETIM20231031.pdf
3. Lancet Glob Health. 2022 Jan;10(1):e42-e51.doi: 10.1016/S2214-109X(21)00448-4
4. Engl J Med. 2023 Feb 9;388(6):518-528.doi: 10.1056/NEJMoa2209760
5. Ann Intern Med. 2023 May;176(5):667-675. doi: 10.7326/M22-3305

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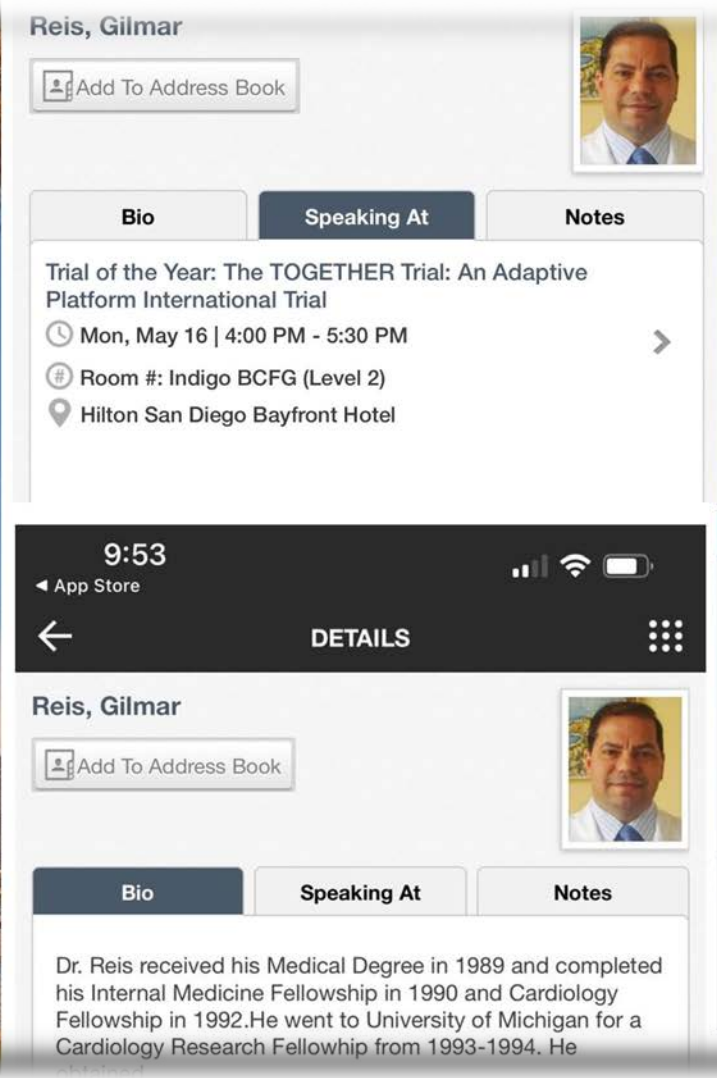
CARDO RESEARCH

COVID-19 Burden

Event	None	Fluvoxamine[3]	Lambda Interferon[4]	Fluvoxamine/ Budesonide[5]
		2021	2021/ 2022	2022/ 2023
SIVEP/ Gripe[1]				
Hospitalizations	1.615.428	- 48.463 (-3.0%)	- 1.050.028 (-65%)	- 177.697 (-11%)
Death	518.180	- 7.772 (-1.3%)	- 419.725 (-81%)	N/A
Minas Gerais Data[2]				
SRAG	216.990	- 6.510 (-3.0%)	- 141.043 (-65%)	- 23.868 (-11%)
Death	65.881	- 988 (-1.3%)	- 53.363 (-81%)	N/A

1. Int J Equity Health. 2023 Nov 17;22(1):238. doi: 10.1186/s12939-023-02037-8
2. https://coronavirus.saude.mg.gov.br/images/2023/10/31-10-COVID-19_-_BOLETIM20231031.pdf
3. Lancet Glob Health. 2022 Jan;10(1):e42-e51.doi: 10.1016/S2214-109X(21)00448-4
4. Engl J Med. 2023 Feb 9;388(6):518-528.doi: 10.1056/NEJMoa2209760
5. Ann Intern Med. 2023 May;176(5):667-675. doi: 10.7326/M22-3305

David Sackett Award



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CARD RESEARCH

The Together Trial

- 1ST Brazilian Adaptive Trial
- 41 publications in major medical journals.
- Best trial of the year 2021
- Well respected worldwide

Together • COVID-19 Clinical trials

CARDIO RESEARCH

The Together Trial

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Por que um projeto de combate a fome?

Ensaio clínico TOGETHER: Uma das 03 mais importantes pesquisas em COVID-19 realizadas, Reconhecimento internacional - > 7.000 famílias atendidas domiciliarmente

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Projeto Alimentando Sonhos

Together • COVID-19 Clinical trials

A Fome: Flagelo mundial

- ✓ 61% da população brasileira convive com a insegurança alimentar

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A Fome no Brasil...

1 em cada 4 crianças estão em situação de fome crônica

50% das crianças no Brasil não recebem os nutrientes adequados nos primeiros 06 anos de vida

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A Fome no Brasil...

2 em cada 4 Idosos recebem menos de 1.5 salário mínimo mensalmente

1 em cada 3 idosos estão em situação de fome crônica

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Alimentando Sonhos

Um Projeto de Inclusão Social e Cidadania Através da Alimentação de Alto Valor Nutricional para Crianças em Situação de Vulnerabilidade Social

Acrônimo:	AlimentaSonho
Patrocinador:	David Sackett Research Institute
	Rua dos Otoni 735, Sala 1109, Santa Efigênia
	Belo Horizonte – MG- Brasil – 30.150-270

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Saúde e integração ampliada para a terceira idade através da complementação alimentar de alto valor nutricional: Projeto Viver+

Acrônimo: VIVER+

Patrocinador: David Sackett Research Institute

Rua dos Otoni 735, Sala 1109, Santa Efigênia

Belo Horizonte – MG- Brasil – 30.150-274

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Projeto Alimentando Sonhos/ Viver +

Alimentos de alto valor nutricional - complementação dietética

- Beneficiamento de soja
- Biomassa de banana

- Oferta diária
- Criança e familiares
- Período - 05 anos
- Acompanhamento semestral

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Projeto Alimentando Sonhos/ Viver +

Beneficiamento de soja

- 01 kg de soja = 10 litros de "leite de soja"
- Produtos panificados de soja
- Toda a unidade familiar contemplada

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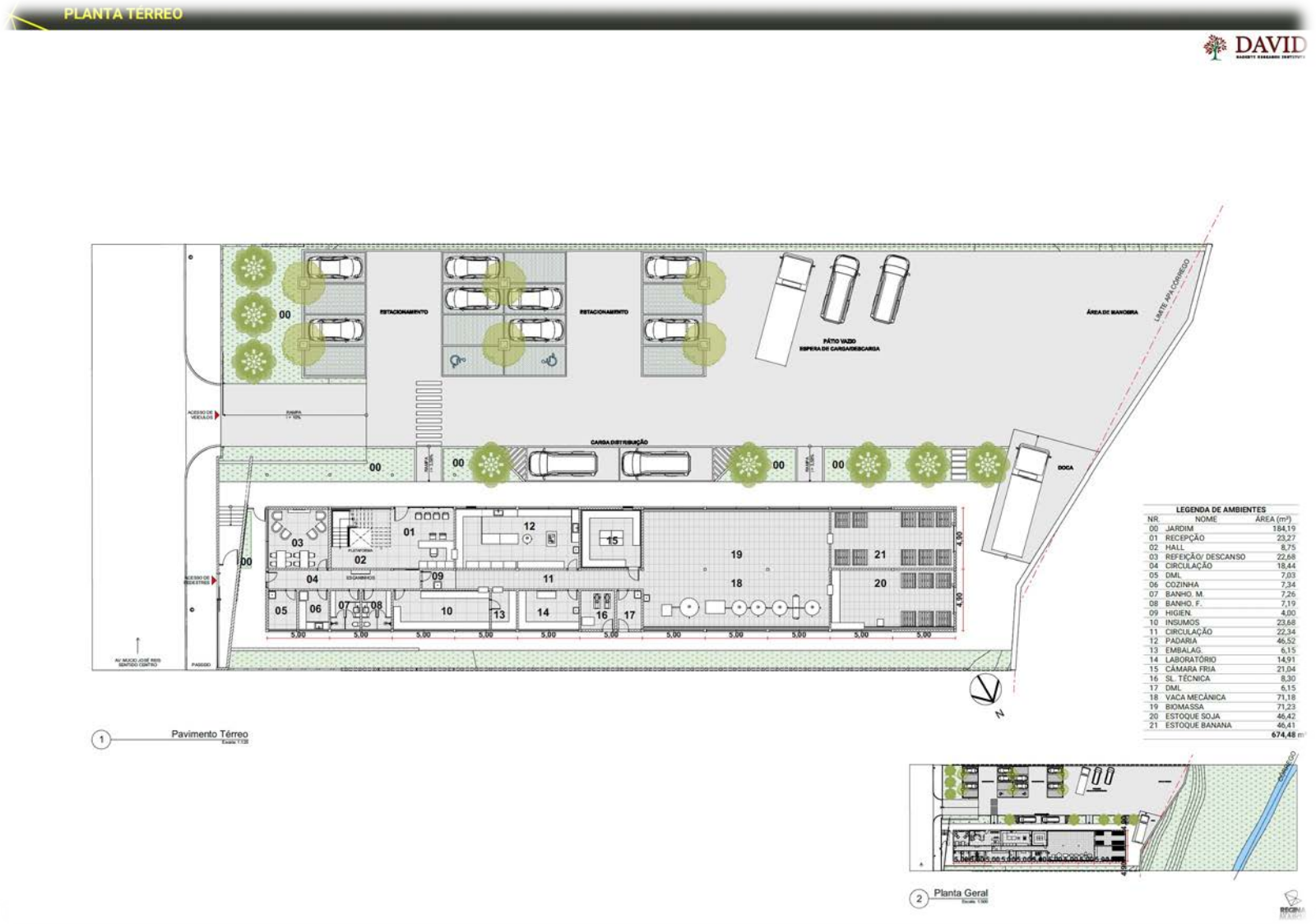
Projeto Alimentando Sonhos/ Viver +

Alcance do projeto

- **2.000 crianças** selecionadas pelo CAD ÚNICO
- **10.000 pessoas beneficiadas**
- Para cada 1 real investido **são gerados 5 reais**

Detalhes do projeto 1



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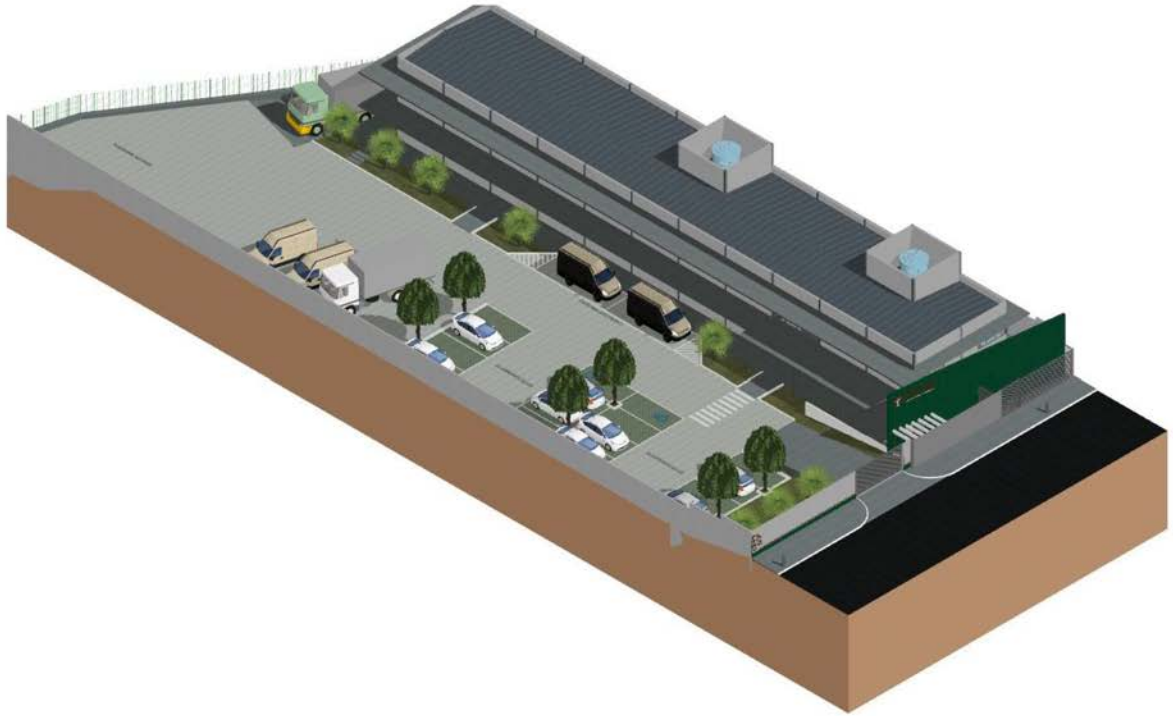
Detalhes do projeto 2

PERSPECTIVA FRONTAL



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Detalhes do projeto 3

FACHADA

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Nosso Futuro

- ✓ Estudar os problemas de saúde da população Mineira
- ✓ Dedicar a melhoria do cuidado cardiovascular na APS – SUS
- ✓ Projetos sociais & acadêmicos
- ✓ Expandir a rede de pesquisa

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OBRIGADO!

Thank You!

Merci!