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

Building Platform Trial Infrastructure for Infectious Diseases
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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.
What makes useful trials different?

- Remap-Cap
- Solidarity
- Recovery
- Principle
- TOGETHER
Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

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

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

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>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</td>
</tr>
</tbody>
</table>

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.
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
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
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
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 serotonin 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
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)
Trial Schema
Intervention Timeline

- Placebo: June 2020
- LPV/r: October 2020
- HCQ: January 2021
- Fluvoxamine: March 2021
- Metformin: June 2021
- IVM (low dose): June 2021
- IVM (high dose): July 2021
- INF-Lambda: Doxasosin
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
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).
Recruitment Over Time
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)

**SETTINGS/LOCATIONS**

7 Clinical sites, Minas Gerais, Brazil

**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%);

**PRIMARY OUTCOMES**

COVID-associated hospitalization and death measured at day 90
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)

**SETTINGS/LOCATIONS**
10 Clinical sites, Minas Gerais, Brazil

**INTERVENTION**

**217 Patients**

- **Metformin** 750mg dose twice daily for 10 days
- **Placebo** Oral placebo talc tablet

**206 patients**

**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.

**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.
**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)

**SETTINGS/LOCATIONS**
10 Clinical sites, Minas Gerais, Brazil

**INTERVENTION**

677 Patients,

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

678 patients

Placebo Oral placebo talc tablet

**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.

**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)
# Fluvoxamine

<table>
<thead>
<tr>
<th></th>
<th>Fluvoxamine (742)</th>
<th>Placebo (738)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>407</td>
<td>438</td>
</tr>
<tr>
<td>Male</td>
<td>335</td>
<td>300</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>47.9 (13.2)</td>
<td>47.8 (13.9)</td>
</tr>
<tr>
<td>Multiple co-morbidities</td>
<td>135</td>
<td>123</td>
</tr>
</tbody>
</table>
Posterior Probability of Superiority of Fluvoxamine vs. Placebo on Emergency Room Observation for > 6 Hours or Hospitalization
Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Relative risk* [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>742</td>
<td>74</td>
<td>0.69[0.52;0.91]</td>
</tr>
<tr>
<td>Placebo</td>
<td>738</td>
<td>107</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Calculated in a Bayesian framework
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

Posterior distribution

<table>
<thead>
<tr>
<th>Arm</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>99.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Event rate [95% CRI]

- Fluvoxamine: 0.106 [0.085, 0.130]
- Placebo: 0.152 [0.127, 0.180]
Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Relative risk* [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>702</td>
<td>74</td>
<td>0.70 [0.53;0.92]</td>
</tr>
<tr>
<td>Placebo</td>
<td>706</td>
<td>107</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Calculated in a Bayesian framework
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
Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

Patients with at least 1 day of treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of patients</th>
<th>Number of event</th>
<th>Relative risk* [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>691</td>
<td>63</td>
<td>0.65[0.48;0.87]</td>
</tr>
<tr>
<td>Placebo</td>
<td>695</td>
<td>97</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Calculated in a Bayesian framework
Secondary Outcome: 
Relative Risk of Mortality for 
Fluvoxamine vs. Placebo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Relative risk* [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>742</td>
<td>17</td>
<td>0.71 [0.39;1.29]</td>
</tr>
<tr>
<td>Placebo</td>
<td>738</td>
<td>24</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Calculated in a Bayesian framework
Secondary Outcome: Viral Suppression at 7 Days
Fluvoxamine vs. Placebo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>0.75 (0.52 – 1.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>
## Treatment Assignment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall, $N = 165^1$</th>
<th>Placebo, $N = 92^1$</th>
<th>Fluvoxamine, $N = 73^1$</th>
<th>OR$^2$</th>
<th>95% CI$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days in Hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>123</td>
<td>60</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>7.0</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>4.5, 12.5</td>
<td>3.0, 12.2</td>
<td>5.5, 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Missing)</td>
<td>42</td>
<td>32</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (63%)</td>
<td>53 (62%)</td>
<td>46 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (37%)</td>
<td>32 (38%)</td>
<td>26 (36%)</td>
<td>0.80</td>
<td>0.39, 1.67</td>
</tr>
<tr>
<td>(Missing)</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Median (IQR)

$^2$ OR = Odds Ratio, CI = Confidence Interval
Readiness for Dissemination

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

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Platform Life Sciences
MMS Holdings
Cytel Inc
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Support

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