Lessons Learned from the Gates MRI Virtual COVID-19 Trial

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NIH Collaboratory Grand Rounds
March 12, 2021
• Gates MRI overview
• Gates MRI COVID-19 platform protocol
• Clinical operations of the 100% virtual trial model
• Lessons learned to inform future clinical trials
GATES MRI OVERVIEW
Technology gap between rich and poor countries has narrowed, but remains large.

Progress in LMIC reflects absorption of pre-existing technologies – not “at-the-frontier” inventions.

Cutting-edge technologies and approaches are needed to address immunologically and epidemiologically complex diseases – disproportionately affecting the poor.

HOW TO ADDRESS THIS?

• Support/Grants to Product Developers to allow LMIC focus

• Establish an Institute with a singular focus on bridging the divide
OUR MISSION

DEVELOP PRODUCTS TO ...

TUBERCULOSIS
Accelerate the end of the tuberculosis epidemic

MALARIA
Eradicate malaria

ENTERIC AND DIARRHEAL DISEASES
End diarrheal deaths in children

MATERNAL NEONATAL & CHILD HEALTH
Reduce adverse birth outcomes and mortality
GATES MRI AT A GLANCE

Location
Cambridge, MA (HQ), Seattle

Structure
Fully funded through a grant from the Gates Foundation

Portfolio
Initial focus on TB drugs, BCG booster/prevention vx, malaria vx with novel adjuvants, shigella vaccines, MNCH portfolio

Size
~100 as of March 2021

Quality Management System
Quality and compliance systems implemented
THE COVID-19 THERAPEUTICS ACCELERATOR

**Founding Donors**

- Bill & Melinda Gates Foundation
- Wellcome Trust
- Mastercard

**Contributing Donors**

- Avast Foundation
- Chan Zuckerberg Initiative
- UK Aid
- Michael & Susan Dell Foundation
- Madonna
- EOT
- Zhang Yiming

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1. Testing approved drugs for activity against COVID-19
2. Screening libraries of thousands of compounds with confirmed safety data
3. Considering new investigational compounds and monoclonal antibodies

$\rightarrow$ PrEP / PEP

$\rightarrow$ Mild

$\rightarrow$ Severe

Recommend for development with industry partners through grants...

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COVID-19 THERAPEUTICS ACCELERATOR

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GATES MRI COD-01-T01

A RANDOMIZED CONTROLLED, ADAPTIVE PLATFORM TRIAL TO EVALUATE SAFETY AND EFFICACY OF INTERVENTIONS FOR HIGH-RISK PEOPLE WITH MILD COVID-19 DISEASE
PLATFORM CORE PROTOCOL

• Primary goal of the program:
  / Assess safety and efficacy of interventions for **early mild COVID-19 disease** (per Gates MRI endpoint definition) and prioritize interventions for further development
  / Support evaluations of antiviral agents, host-directed therapies, monoclonal antibodies and hyperimmunoglobulin
  / Focus on **out-patients at high risk for progression based on age, comorbidity and BMI**

• **Intended to provide informative data to:**
  / Support decision and development plan for Phase 3 in consultation with key stakeholders
  / Support recommendations by regulators and policy makers for use in treating COVID-19 disease

- Inclusion of 4 to 8 interventions with sample size up to 4000
- Allow adding arms and sharing controls
- First intervention: Licensed oral anticoagulant, rivaroxaban (Xarelto)
  • All participants completed follow up on Mar 11

- Statistical Analysis Plan
- Intervention 01 Protocol
- Intervention 02 Protocol
- Intervention 03 Protocol
- Core Protocol
GATES MRI COVID-19 CLINICAL ENDPOINT DEFINITION

- Participants are enrolled in scale 2 (mild)
- Endpoint of progression of disease is scale 3 and up (moderate or severe disease category and higher)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Category</th>
<th>Endpoint definition</th>
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</table>
| 1     | Asymptomatic/symptoms similar to pre-COVID status | • No symptoms and signs AND  
• No limitation of daily activities |
| 2     | Mild     | • Symptomatic AND  
• No shortness of breath AND  
• No hypoxemia (O2 saturation ≥94% in ambient air) |
| 3     | Moderate or severe | • Symptomatic AND  
• Shortness of breath OR tachypnea (respiratory rate ≥ 20 min)* OR hypoxemia (<94% in ambient air)* |
| 4     | Critically ill | • Symptomatic AND  
• Receiving high flow oxygen OR non-invasive mechanical ventilation |
| 5     | Critically ill with invasive mechanical ventilation or extrapulmonary complication | • Symptomatic AND  
• Receiving invasive mechanical ventilation OR Life threatening or debilitating extrapulmonary complications |
| 6     | Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO) | • Symptomatic AND  
• Receiving ECMO |
| 7     | Death    | • Death |
## PRIMARY OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
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<tr>
<td><strong>To characterize safety of study intervention</strong></td>
<td><strong>Primary</strong></td>
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<td>Through end of study</td>
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<td>• Frequencies of grade 3 AEs and grade 4 AEs</td>
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<td>• AEs resulting in treatment discontinuation</td>
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<td>• All SAEs</td>
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<td><strong>To assess efficacy of study intervention</strong></td>
<td>Through Day 28</td>
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<td>• <strong>Options for primary efficacy endpoint (selection is based on the intervention)</strong></td>
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<td>• Time to disease resolution defined by viral clearance AND symptoms resolution</td>
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<td>• Time to disease resolution, defined as symptoms resolution</td>
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<td>• Progression to moderate disease or severe category or greater (Gates MRI ordinal scale $\geq 3$)</td>
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KEY INCLUSION CRITERIA

- **Age and sex**
  - Male and female ≥18 years of age at the time of informed consent

- **Type of participant**
  - Participants must be at high-risk for COVID-19 disease progression by fulfill at least one of the following criteria at screening
    - Age ≥ 65 years
    - Presence of pulmonary disease, specifically chronic obstructive pulmonary disease, pulmonary hypertension
    - Diabetes mellitus (type 1 or type 2), requiring oral medication or insulin for treatment
    - Hypertension, requiring at least 1 oral medication for treatment
    - Immunocompromised status due to disease (e.g., those living with human immunodeficiency virus with a CD4 T-cell count of <200/mm3)
    - Immunocompromised status due to medication (e.g., persons taking 20 mg or more of prednisone equivalents a day, anti-inflammatory monoclonal antibody therapies, or cancer therapies)
    - Body mass index ≥35 kg/m2 (based on self-reported weight and height)
    - Any chronic disease that is associated with high risk for severe COVID disease in the opinion of the investigator

- **COVID-19 characteristics**
  - Confirmed SARS-CoV-2 positive diagnostic test of ≤10 days at screening
  - Symptomatic for COVID-19 for ≤7 days at the time of randomization
    - Defined as having at least one of the following symptoms of COVID-19 that is of new onset or has worsened from baseline, and include
      - Fever, chills, myalgia, arthralgia, headache, fatigue, cough, sore throat, nasal congestion, nausea, vomiting, or diarrhea

- **Informed consent**
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<th>Visits</th>
<th>Screening (≤ 5 days of Day 1)</th>
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<th>Day 8</th>
<th>Day 10</th>
<th>Day 12</th>
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<td>Clinical status assessment using ordinal scales for Gates MRI and WHO</td>
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<td>AEs assessment (including bleeding events)</td>
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<td>Self-collection of nasal SARS-CoV-2 diagnostic test</td>
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**SCHEDULE OF PROCEDURES**

(USED IN FIRST INTERVENTION TRIAL OF RIVAROXABAN)
CLINICAL OPERATIONS
OF THE 100% VIRTUAL TRIAL MODEL
COVID-19 THERAPEUTICS ACCELERATOR (CTA) FOCUS: PROPHYLAXIS AND MILD/EARLY DISEASE

A NEW CLINICAL TRIAL PARADIGM IS REQUIRED TO MATCH...

“\(\text{I skate to where the puck will be, not where it has been}\)” - Wayne Gretzky
PROACTIVE STRATEGY TO NEW PRODUCTS

Product Risk Assessment

Site + Operational Strategy

Fully Decentralized Metasite Model
- Remove all geographical barriers as the pandemic moves
- Allow for patient recruitment regardless of prescribing physician and physical location
- Limit SARS-CoV-2 transmission
- Single site covering all states

Why

Bricks & Mortar + (Metasite) Model
- Maintain brick and mortar sites for in clinic requirements
- Maintain KOL engagement
- Allow for patient recruitment at point of care

Why

Deliverables
Consistent pull through of data and aggregation in a central location
PARTICIPANT IDENTIFICATION & OUTREACH

- Community Testing & Lab Referral
  Enables patients to receive study materials at point of diagnosis

- Digital Media Campaign
  Positive Testing Referrals

- Direct-to-Patient Outreach by B&M Sites databases

- Community Outreach/Advertising

Participant Identification & Screening
High-risk population:

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ENROLL THROUGH A VIRTUAL SITE

Pre-screening

Pre-screening questionnaire

Pre-screening e-Consent & eligibility

Daily check for symptoms

Screening

• Clinical Coordinator collects participant information
• Investigator reviews all eligibility information
• Triggers COVID trial in a box shipment
• Clinical Coordinator confirms receipt

Study Visits

VIRTUAL SITE

Enables us to reach any participant, anywhere, from the comfort of their own home

High touch, concierge level experience

Confirmed test result

Multi-channel, data driven approach

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COVID TRIAL IN A BOX

3 key supply vendors provide different supplies to each participant that will be included in ONE BOX:

/ Fisher provide the study drug (Xarelto or PLB)
/ CERBA provide Pulse Oximeter, Digital Thermometer, Lab samples kits, PPE.
/ PPD provide TempTale4 and study information materials.

Science 37 Clinical Supply Group to have COVID Trial in a BOX

Fisher  CERBA  PPD

After randomization <72hrs before D1 Enrollment visit

Participant
PARTICIPANT JOURNEY

COVID-19 Symptoms start
- Participant interested in clinical trial
- Social Media
  - Participant sees the study Ads and signs up

Participant seeks testing to confirm Diagnosis
- Prior to screening within ≤ 7 days to Randomization
  - SARS COV-2 Test ≤ 10 days

Participant screened for Eligibility
- High Risk group

Site investigator schedule
- Day 1 visit
  - Re-confirm Eligibility

COVID Trial in A box is shipped DTP
- HOME
  - First Dose of Study IP

Participant randomized to either Xarelto or Placebo

Day 1
- COVID Trial in a Box is ready

Day 4 – Day 35
- HOME
  - Nasal Swabs self collected and shipped to Lab

Call center
- Participant contacted for Pre-screening

IRT System
- Participant randomized to either Xarelto or Placebo

Nasal Swabs self collected and shipped to Lab
Participant Demographics

States

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<tr>
<th>States</th>
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<td>WA</td>
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Ethnicity

- Not Hispanic or Latino: 89.7%
- Hispanic or Latino: 9.9%
- Other: 0.7%

Age

- 18-29: 17.1%
- 30-39: 27.9%
- 40-49: 35.4%
- 50-64: 14.8%
- 65+: 4.5%

Race

- White: 88.3%
- Black or African American: 7.5%
- Latino: 2.6%
- American Indian or Alaska Native: 0.9%
- Asian: 0.7%
- Other: 0.2%
ENGAGEMENT OF MINORITIES

• Lack of success in enrolling representative minorities directed to a change in the recruitment outreach strategy.

• Partnering with PROVOC as a specialized organization in engaging minorities.

• Developing new outreach campaign with new messaging and creative materials focusing on historically underserved and therefore harder-to-reach populations of Black and Latinx people.

• Establishing relationship with communities-based organizations CBO (i.e. NUL "National Urban League")

• Toward the end of the campaign, Black and Latinx sign ups audiences increased significantly.
WHERE ARE THE B&M SITES?

Third Wave of Feasibility

- Site profiles that are suitable for outpatient studies
- Epidemiology for each site reviewed and provided
- Projections, and a link to the JHU infographic for the site county
- PPD confirmed that all of these sites have COVID-19 testing facilities
- PPD gave priority to hospital sites over smaller outpatient clinics and dedicated research sites
LESSONS LEARNED
TO INFORM FUTURE CLINICAL TRIALS
LESSONS LEARNED SO FAR

Clinical trial design

- Offer SARS CoV-2 screening as part of the protocol
- Inclusion criteria:
  - Shorten the symptoms duration
  - Specify types of comorbidities
- Exclude shortness of breath with exertion as an endpoint
- Consider PRO instead of investigator assessment of symptoms resolution
- Statistical considerations to account for participants with negative SARS CoV-2 PCR at Day 1

Clinical trial operations

- Social media content appropriate for engaging minority communities
- Select B&M sites with strong ties to minority communities
- Ensure recruitment channels for participant identification through national testing network
- Warm transfers is the most successful method to engage and enroll eligible participants
- Site engagement is key for remote trial success
- 100% Remote trial is possible and no longer a huge challenge