

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Lessons Learned from the Gates MRI Virtual COVID-19 Trial

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NIH Collaboratory Grand Rounds

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OUTLINE

- Gates MRI overview
- Gates MRI COVID-19 platform protocol
- Clinical operations of the 100% virtual trial model
- Lessons learned to inform future clinical trials

A microscopic view of numerous bacteria, appearing as various shapes of rods and spheres, rendered in a light teal color against a darker teal background. The bacteria are scattered across the frame, with some appearing more prominent than others.

GATES MRI OVERVIEW

/ THE GREAT DIVIDE

- 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

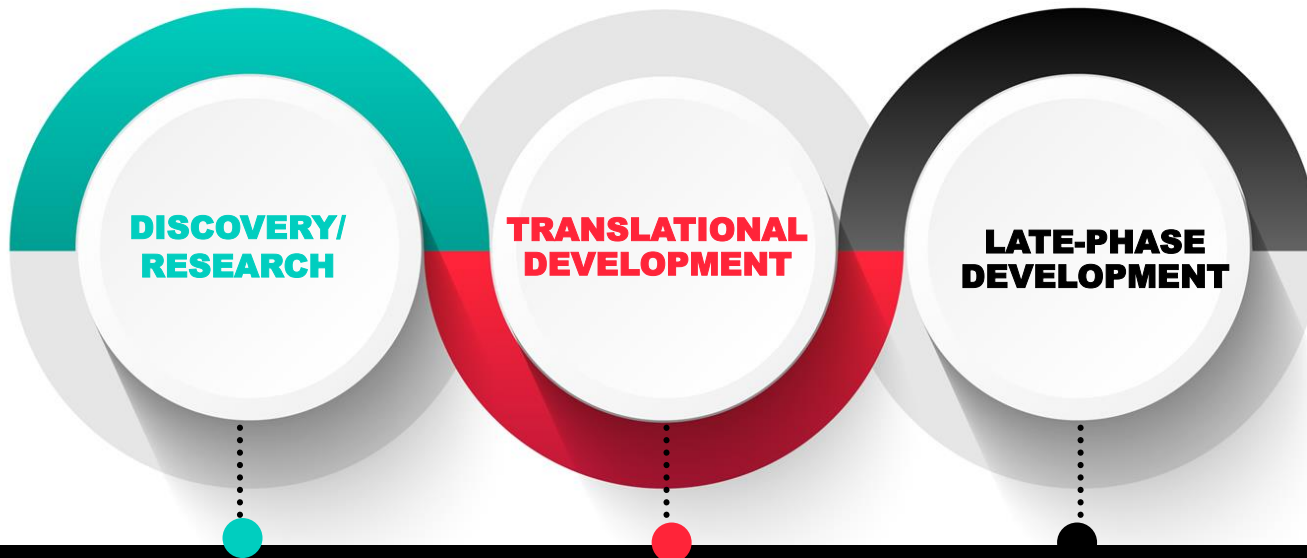


MATERNAL NEONATAL & CHILD HEALTH



Reduce adverse birth outcomes and mortality

/ GATES MRI AT A GLANCE



Lead candidate optimization, pre-clinical development, working with early research partners

GxP studies through clinical POC in the target population, working with translational development partners

Effective handoff to late-phase development partners

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



MADONNA



Zhang Yiming



Contributing Donors

 PrEP / PEP

 Mild

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 Severe

 Recommend for development
with industry partners through
grants...

3 Considering new investigational
compounds and monoclonal antibodies

2 Screening libraries of thousands of
compounds with confirmed safety data

1 Testing approved drugs for
activity against COVID-19

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**



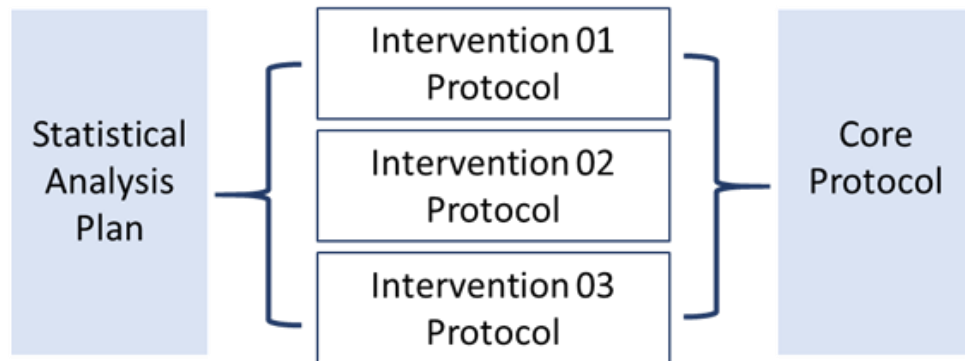
/ PLATFORM CORE PROTOCOL

- **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

/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)

Scale	Category	Endpoint definition
1	Asymptomatic/symptoms similar to pre-COVID status	<ul style="list-style-type: none"> • No symptoms and signs AND • No limitation of daily activities
2	Mild	<ul style="list-style-type: none"> • Symptomatic AND • No shortness of breath AND • No hypoxemia (O2 saturation \geq94% in ambient air)
3	Moderate or severe	<ul style="list-style-type: none"> • Symptomatic AND • Shortness of breath OR tachypnea (respiratory rate \geq 20 min)* OR hypoxemia (<94% in ambient air)*
4	Critically ill	<ul style="list-style-type: none"> • Symptomatic AND • Receiving high flow oxygen OR non-invasive mechanical ventilation
5	Critically ill with invasive mechanical ventilation or extrapulmonary complication	<ul style="list-style-type: none"> • Symptomatic AND • Receiving invasive mechanical ventilation OR Life threatening or debilitating extrapulmonary complications
6	Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO)	<ul style="list-style-type: none"> • Symptomatic AND • Receiving ECMO
7	Death	<ul style="list-style-type: none"> • Death

PRIMARY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<p>To characterize safety of study intervention</p>	<p>Through end of study</p> <ul style="list-style-type: none"> • Frequencies of grade 3 AEs and grade 4 AEs • AEs resulting in treatment discontinuation • All SAEs
<p>To assess efficacy of study intervention</p>	<p>Through Day 28</p> <ul style="list-style-type: none"> • Options for primary efficacy endpoint (selection is based on the intervention) • Time to disease resolution defined by viral clearance AND symptoms resolution • Time to disease resolution, defined as symptoms resolution • Progression to moderate disease or severe category or greater (Gates MRI ordinal scale ≥ 3)

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**

SCHEDULE OF PROCEDURES

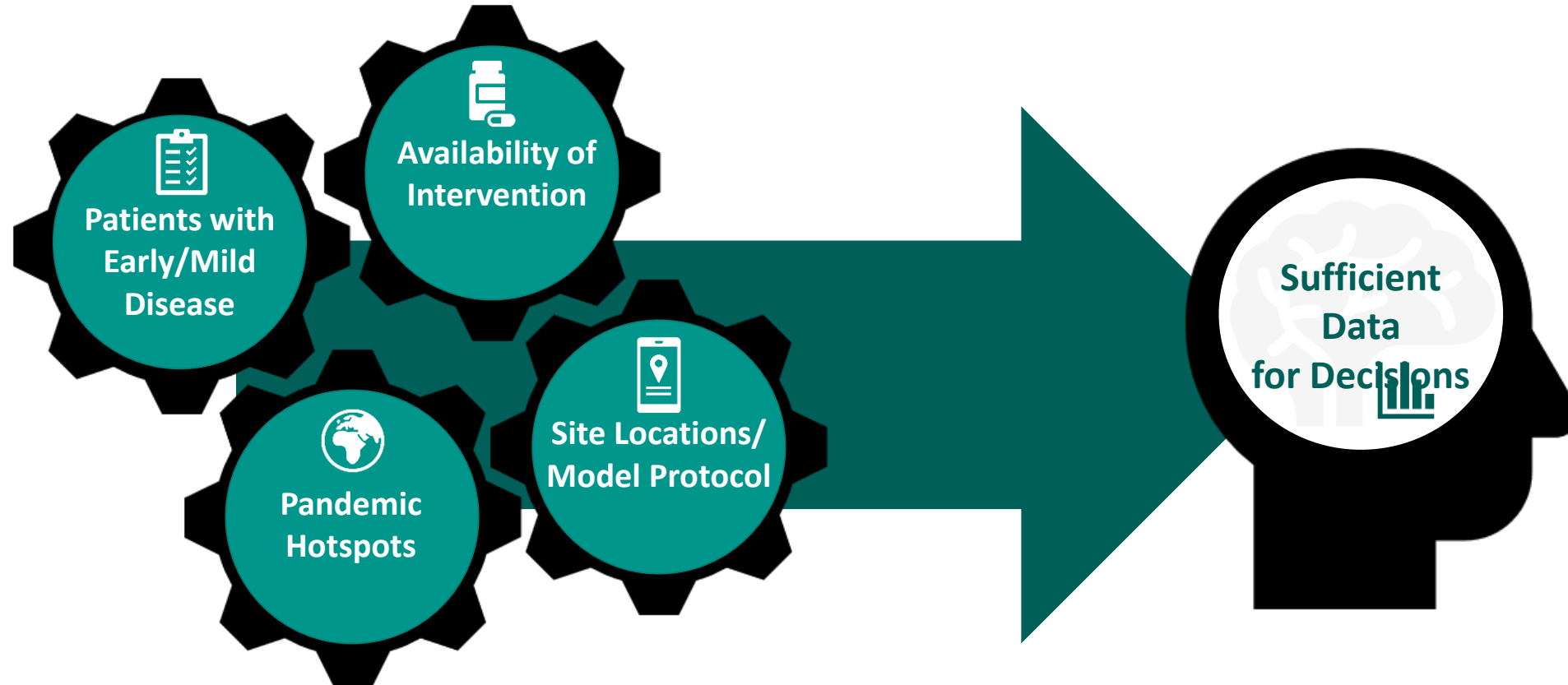
(USED IN FIRST INTERVENTION TRIAL OF RIVAROXABAN)

Visits	Screening (≤ 5 days of Day 1)	Day 1	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14	Day 18	Day 21	Day 24	Day 28	Day 35
Obtain consent	X												
Demographics, past and current medical history including known pregnancy/lactation status, and medication history	X												
Lab-confirmed SARS-CoV-2 positive diagnostic test	X												
Inclusion and exclusion criteria	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X												
Study intervention dose (rivaroxaban vs. placebo-equivalent)		X	X	X	X	X	X	X	X	X			
Clinical status assessment using ordinal scales for Gates MRI and WHO		X	X	X	X	X	X	X	X	X	X	X	
COVID-19 signs and symptoms, temperature, oxygen saturation		X	X	X	X	X	X	X	X	X	X	X	
AEs assessment (including bleeding events)	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-collection of nasal SARS-CoV-2 diagnostic test	(X)	X	X		X			X		X		X	

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...

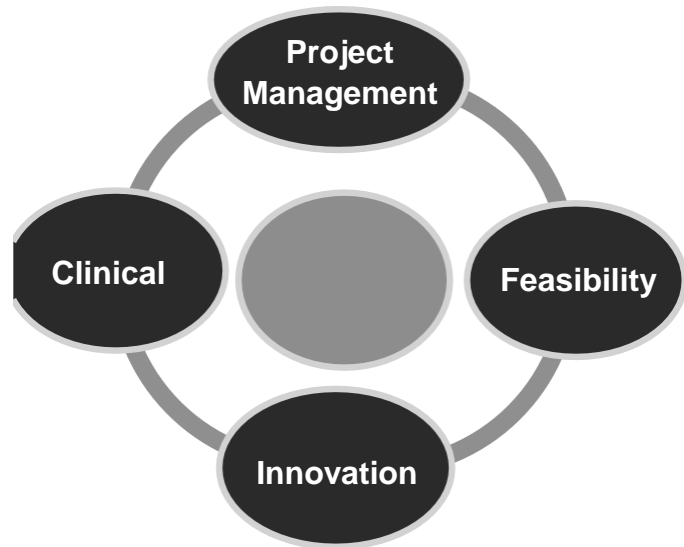


“I skate to where the puck will be, not where it has been” - *Wayne Gretzky*



PROACTIVE STRATEGY TO NEW PRODUCTS

Product Risk Assessment



Site + Operational Strategy

Fully Decentralized Metasite Model

Science 37



Supplemented with home health care professional

Why

- 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

Bricks & Mortar + (Metasite) Model

Science 37



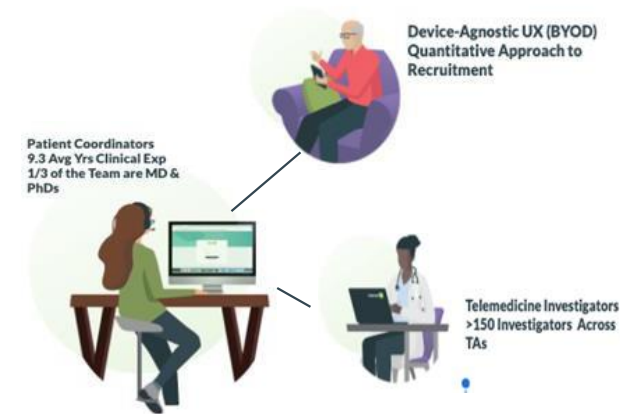
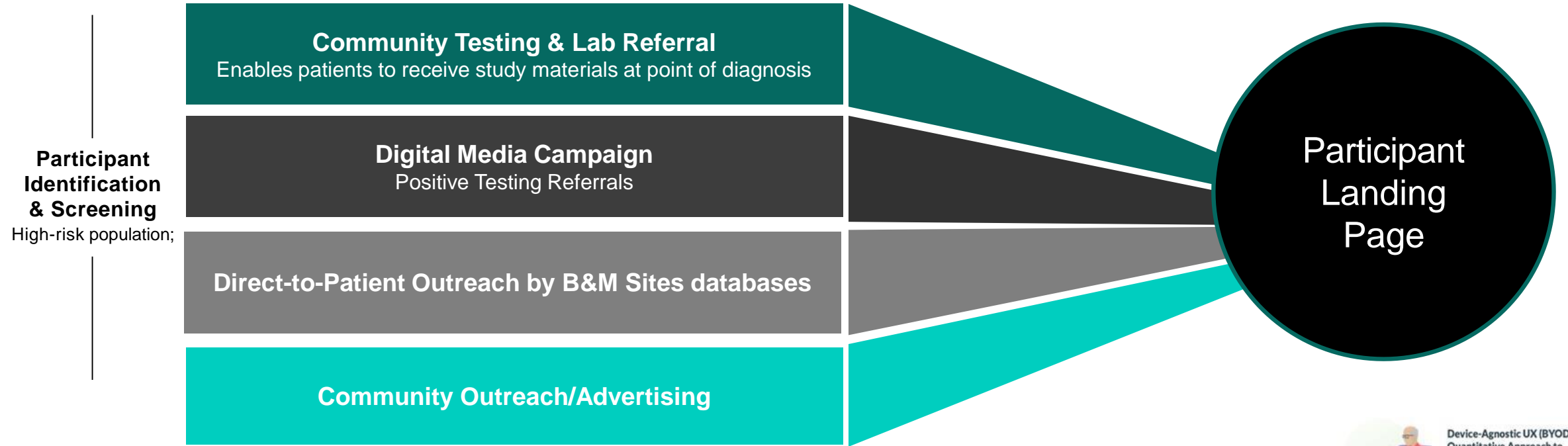
Why

- Maintain brick and mortar sites for in clinic requirements
- Maintain KOL engagement
- Allow for patient recruitment at point of care

Deliverables

Consistent pull through of data and aggregation in a central location

MULTIPLE TACTICS FOR PARTICIPANT IDENTIFICATION & OUTREACH



ENROLL THROUGH A VIRTUAL SITE

Pre-screening

Pre-screening questionnaire



Pre-screening e-Consent & eligibility



Daily check for symptoms



High touch, concierge level experience

Screening



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



Confirmed test result

Study Visits



Multi-channel, data driven approach

VIRTUAL SITE

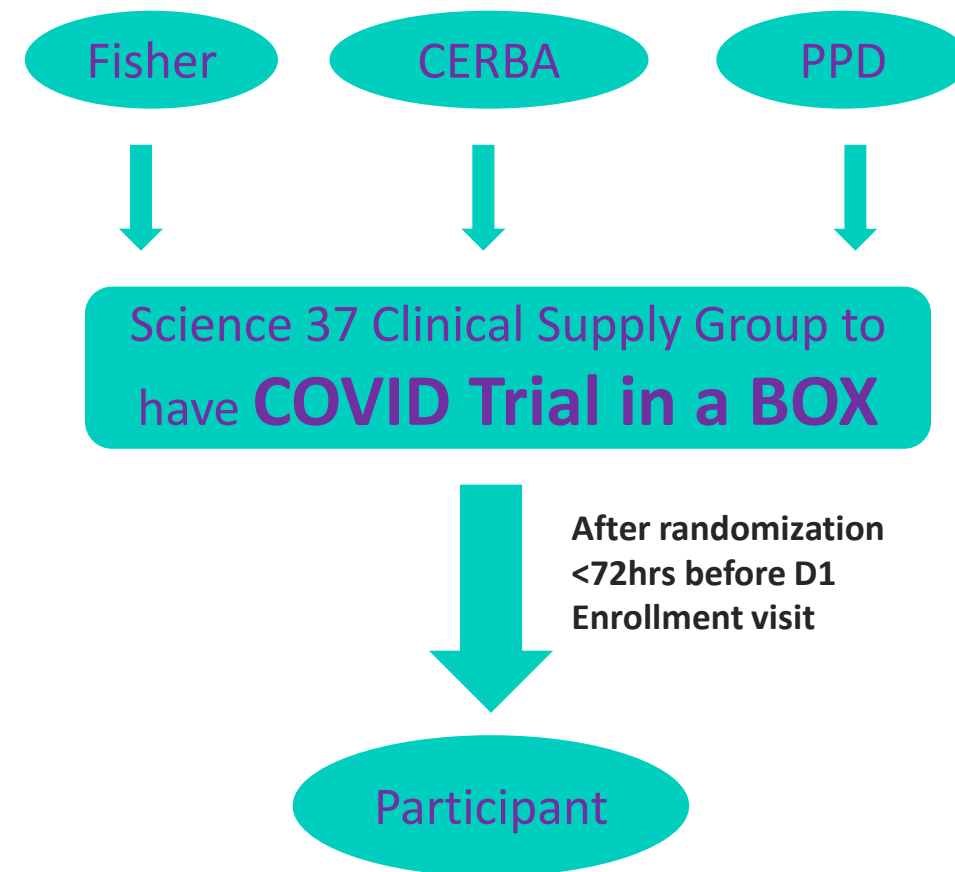
Enables us to reach any participant, anywhere, from the comfort of their own home

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.



PARTICIPANT JOURNEY



COVID-19 Symptoms start

Prior to screening within ≤ 7 days to Randomization

Participant seeks testing to confirm Diagnosis

SARS COV-2 Test ≤ 10 days

Participant screened for Eligibility

High Risk group

COVID Trial in A box is shipped DTP



Nasal Swabs self collected and shipped to Lab



Site investigator schedule Day 1 visit

Re-confirm Eligibility



Thinking of possible treatments

Participant interested in clinical trial



Social Media

Participant sees the study Ads and signs up

Call center Science 37



Participant contacted for Pre-screening

IRT System

Participant randomized to either Xarelto or Placebo

HOME

COVID Trial in a Box is ready



HOME

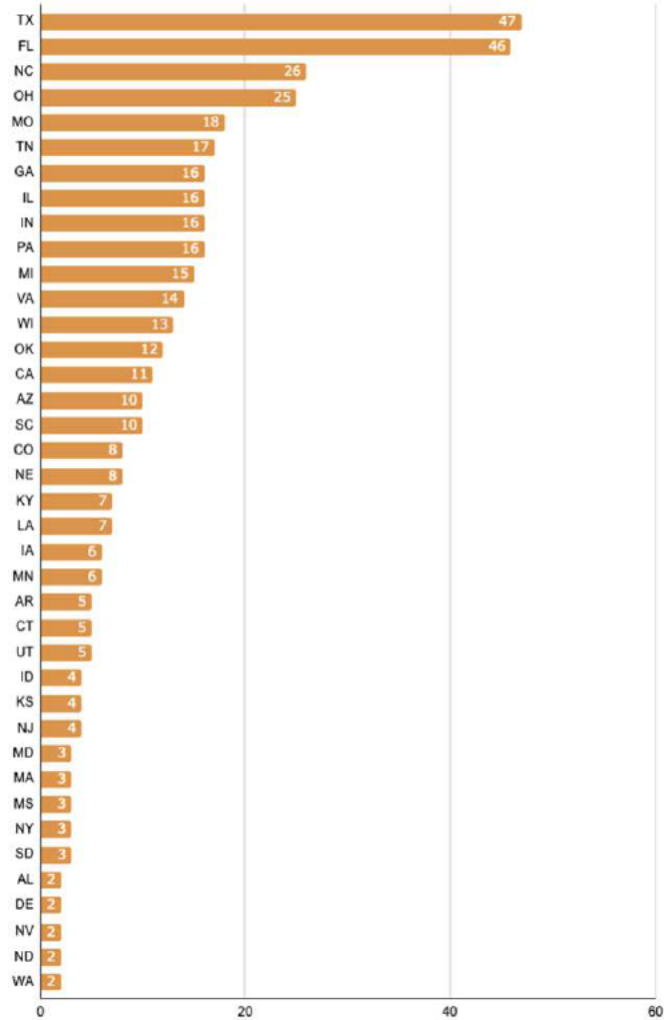
First Dose of Study IP



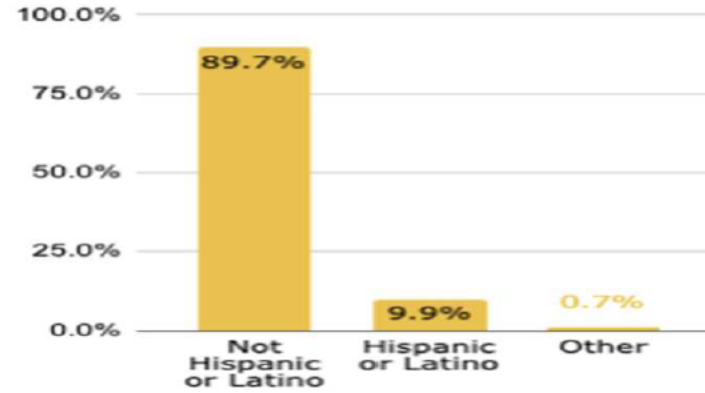
E-Source to EDC

Participant Demographics

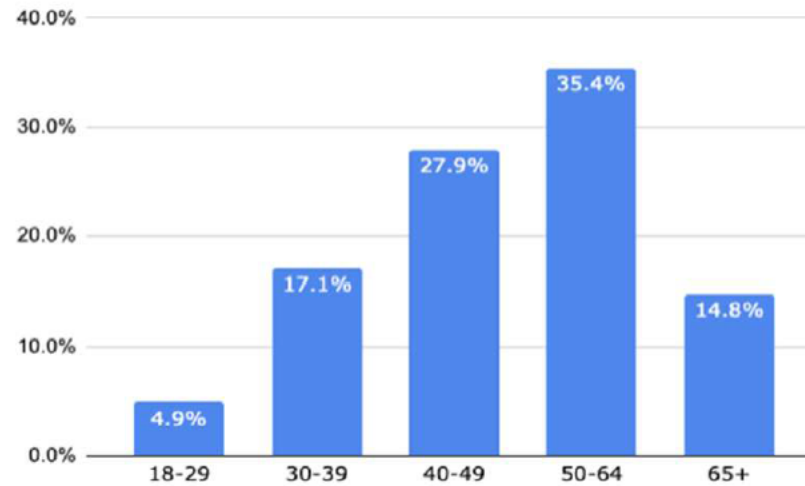
States



Ethnicity



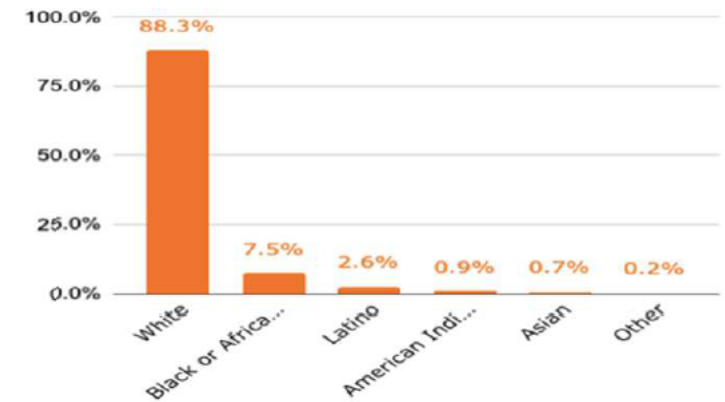
Age



SEX



Race



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

PPD Biotech

PPD



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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**

QUESTIONS/DISCUSSION

