PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

ORCHID

Outcomes **R**elated to **C**OVID-19 treated with **H**ydroxychloroquine among **I**n-patients with symptomatic **D**isease

The PETAL Investigators

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On the Call
*Wes Self (ORCHID Chair), Todd Rice, Matt Semler, Jon Casey

MGH Coordinating Center: Taylor Thompson, David Schoenfeld
NHLBI: Lora Reineck, Neil Aggarwal
PETAL Steering Committee Chair: Roy Brower
Sam Brown – ORCHID Co-Chair

Why ORCHID?

- PETAL is a publicly funded network for the prevention and early treatment of ARDS

- Hydroxychloroquine (HCQ):
  - Biologically plausible agent for prevention & early treatment of COVID-ARDS
    - Active against SARS-CoV-2 at micromolar concentrations *in vitro*
  - Widespread clinical use and promotion
  - Lack of clinical trial data

- High quality data on the clinical effects of HCQ are urgently needed
- Any trial result is informative
  - Benefit
  - Null
  - Harm

Overview

- **Why Hydroxychloroquine?**
- Brief ORCHID Design
- Unique COVID Challenges and Opportunities
- Study Update

History of (hydroxy)chloroquine

- Chloroquine is a quinine derivative (similar to quinacrine) developed in the 1930s as an antimalarial
- Directly toxic to Plasmodium spp. via multiple mechanisms
- More generally, it increases pH in lysosomes
- In vitro, (hydroxy)chloroquine is toxic to parasites, some bacteria, and inhibits viral replication
- Hints of possible efficacy for *Coxiella burnetti*, HIV, cryptococcus
  - As antimicrobial, only ever approved for malaria prevention and treatment
- Also observed to inhibit IL-1, TNF, IL-6
  - Hence application of hydroxychloroquine in mild auto-immune syndromes

(Hydroxy)chloroquine as an anti-viral

- Extensive *in vitro* efficacy for many viruses
- Studied in HIV
  - Helpful in some studies, harmful in one
- Studied in hepatitis, influenza, Dengue, and Chikungunya
  - No efficacy, suggestion of harm in Chikungunya
- No high quality controlled trials in betacoronaviruses

Clinical data for SARS-CoV-2: Case Series

- Case series (N=20) of hospitalized (non-ICU) patients in France from an investigator who has long advocated HCQ for multiple conditions[1]
  - Potentially biased results, no meaningful controls
  - Report of rapid viral clearance
  - The group who received clinical azithromycin may have cleared virus more quickly
- Small Chinese pilot RCT (N=30)[2]
  - Hospitalized patients with COVID
  - HCQ 400/d x 5d
  - No difference in viral shedding
  - No difference in severity or mortality
- As-yet-unpublished collection of case series (N=120) of apparently mild/moderate hospitalized patients from China.
  - Reportedly rapid viral clearance (”4.4 d after starting CQ”)
  - Reportedly low rate of progression to severe COVID-19 (“none critical”)

1- Gautret – Int J Antimicrob Agents 2020 Mar 20
2- Jun - J of Zhej Univ 2020 March

Overview

- Why Hydroxychloroquine?
- **Brief ORCHID Design**
- Unique COVID Challenges and Opportunities
- Study Update

Design Summary

- Multicenter, blinded, placebo-controlled RCT
- Target population: Hospitalized adults with COVID
- Intervention: Hydroxychloroquine
  - 400 mg BID on day 1
  - 200 mg BID days 2-5
- Control: Matched placebo
- 1° outcome: WHO COVID scale at Day 15

Inclusion Criteria

1. Age ≥18 years
2. Hospitalized (or in ED with anticipated hospitalization)
3. ARI (any of: cough, fever, SOB, sore throat)

4. Laboratory-confirmed SARS-CoV-2 within past 10 days or SARS-CoV-2 test results pending plus high clinical suspicion of COVID by fulfilling all:
   - Cough
   - B pulmonary infiltrates or new SpO2 ≤94% on RA
   - No alternative explanation for acute symptoms

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1° population for analysis: enrolled & COVID (+)

- Enrolled COVID (-) monitored closely; maintain <10%

Exclusion Criteria

- Prisoner
- Pregnancy/breast feeding
- **Unable to randomize within 10 d of ARI symptom onset**
- **Unable to randomize with 48 hr of hospital presentation**
- Seizure disorder
- Porphyria cutanea tarda
- QTc >500 ms on EKG within 72 hr prior to enrollment
- Long QT syndrome
- Allergy
- Need for concurrent medications: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol
- ≥1 dose of hydroxychloroquine or chloroquine in prior 10 days
- Unable to take enteral medications
- Unable to be contacted at Day 15
- Previous enrollment in this trial

Randomization & Study Medication

- 1:1 randomization
  - Hydroxychloroquine
  - Placebo
- Blinded: patient, clinicians, investigators
- Study medication within 4 hours of randomization
- Study Medication BID x 5 days (10 doses)
  - Remaining doses taken at home if discharged prior to Day 5

Hydroxychloroquine Dose

- ORCHID Dose: 400 mg BID x 2 doses then 200 mg BID x 8 doses
  - FDA Supported

- Common malaria dosing
  - 1200 mg Day 1
  - 400 mg Day 2 and Day 3

- HCQ regimens used for COVID vary somewhat:
  - 400 mg QD x 5 days [Shanghai protocol]
  - 400 mg BID Day 1, then 200 mg BID Days 2-5 [MGH, Vanderbilt protocols]
  - 400 mg TID Days 1-3, then 200 mg BID Days 4-10 [ASCOT protocol]

ORCHID →

Hydroxychloroquine – *in vitro*

Clinical Infectious Diseases (2020), Mar 9

In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Xueting Yao[1,#], Fei Ye[2,#], Miao Zhang[1,#], Cheng Cui[1,#], Baoying Huang[2,#], Peihua Niu[2], Xu Liu[1], Li Zhao[2], Erdan Dong[3], Chunli Song[4], Siyan Zhan[5], Roujian Lu[2], Haiyan Li[1,3,*], Wenjie Tan[2,*], Dongyang Liu[1,*]

[1] Drug Clinical Trial Center, Peking University Third Hospital, Beijing, 100191, China.

- Physiologically-based pharmacokinetic models
- In-vitro HCQ PK
- Supports
  - Day 1 400 mg BID “load”
  - Then 200 mg BID maintenance
  - 5-day treatment course
  - Maintains therapeutic lung concentrations for 10 days

Safety Monitoring

- EKG prior to enrollment (QTc must be <500 ms)
- EKG/rhythm strip 24-48 hrs after 1st dose (QTc must be <500 ms)

- Day 1 – 5 monitoring of concomitant medications
  - A. Study drug or concomitant med must be stopped (e.g. amiodarone)
  - B. Discussion with clinical team on risk/benefits (e.g. flecainide)

Primary Outcome

WHO COVID Ordinal Scale at Day 15

Level	Description
1	Death
2	Hospitalized on IMV or ECMO
3	Hospitalized on NIV or HFNC
4	Hospitalized on supplemental O2
5	Hospitalized not on supplemental O2
6	Not hospitalized with limitation in activity
7	Not hospitalized without limitation in activity

- Patient important
- Collectable in pandemic
- Widely used for COVID trials
- Enhanced power compared with binary outcome

Secondary Outcomes

- Mortality
  - 15 day all-cause all-location
  - 28 day all-cause all-location
- COVID Outcomes Scale
  - Day 3, Day 8, Day 29
- Free-Days
  - Oxygen
  - Ventilator
  - Vasopressor
  - ICU
  - Hospital

Analysis

- Proportional odds model for COVID Outcome Scale

- Sample size 510 patients enrolled
  - Outcomes predicted based on VIOLET[1] Day 15 outcomes
  - 90% power (alpha=0.05) to detect OR=1.82 from primary model

1- Ginde, et al *NEJM* 2019 Dec 26;381(26)

Illustrative Effect Sizes with OR=1.82

	Death	Death/IMV	Death/IMV/Hospitalization
HCQ	6.7%	10.3%	26.3%
Placebo	11.5%	17.3%	39.3%

COVID **Challenges**/Opportunities

- **Equipoise at sites – FDA EUA issued**
- Consent and Data Collection- minimize staff exposure & paper consent cannot leave room
- Rapid progress through cIRB, FDA, PRC, DSMB, database build

FDA U.S. FOOD & DRUG ADMINISTRATION

March 28, 2020

Re: Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease

Based upon limited in-vitro and anecdotal clinical data in case series, chloroquine phosphate and hydroxychloroquine sulfate are currently recommended for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines report incorporating recommendations regarding use of chloroquine phosphate or hydroxychloroquine sulfate in the setting of COVID-19. FDA encourages the conduct and participation in randomized controlled clinical trials that may produce evidence concerning the effectiveness of these products in treating COVID-19. FDA is issuing this EUA to facilitate the availability of chloroquine phosphate and hydroxychloroquine sulfate during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.

Vanderbilt COVID-19 Guidelines

Clinical Recommendations for Treatment of COVID-19 Adult Patients

Written by: Faculty in Infectious Diseases, Emergency Medicine, Pulmonary/Critical Care, Hospital/General Medicine, Cardiology, & Radiology

Approved by: ACPC

Date: **March 27, 2020**

For patients who do not/will not meet trial criteria, treating clinicians may choose to administer **hydroxychloroquine** as a medication for COVID-19 based on emerging early observations, but keeping in mind the known adverse events (QT prolongation, bone marrow suppression, neuropathy, and many drug-drug interactions). Some prior trials in HIV and Chikungunya infection have suggested that hydroxychloroquine may worsen outcomes in those infections by increasing viral load.

COVID **Challenges**/Opportunities

- Equipoise at sites – FDA EUA issued
- **Consent and Data Collection- minimize staff exposure & paper consent**
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Informed Consent

- Individual informed consent from patient or Legally Auth. Representative

- No-touch system
  - Paper approach
    - Paper consent form provided, consent discussion, sign paper
    - Photo of consent signature page uploaded to REDCAP
    - Paper remains with patient
  - Electronic approach
    - Electronic link used in room with participant/sent to LAR, consent discussion
    - Electronic signature in REDCap

E-Consent Process

- Bring paper consent form into room with patient to review (stays there)
- 2 study personnel (or 1 personnel and bedside nurse as witness) in PPE go into room
- iPad or bedside computer in room to sign e-consent

E Consent - Step 1

Remember to open the eConsent as a survey before handing to the participant

Consent Part 1

PART 1 OF 2: MAIN CONSENT FOR ALL SITES

Institutional Review Board
Informed Consent Document for Research

Study Title: Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease
Revision Date: 3/30/2020

This informed consent applies to adults

Name of Participant:
* must provide value
First Last

Age of Participant:
* must provide value

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several differ locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Con and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

KEY INFORMATION:

The first section of this document contains some key points that the research team thought you would find important. The st is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

You are being asked to take part in this research study because you have signs and symptoms that may be caused by Coronav Disease 2019 (COVID-19). These include fevers, cough, difficulty breathing and fatigue. In this study, we are trying to understar whether a medication called hydroxychloroquine improves recovery from COVID-19 in patients admitted to the hospital. Hydroxychloroquine is used to treat malaria and some joint (rheumatologic) diseases, but it is unknown if it helps patients rec from COVID-19. In this study hydroxychloroquine is considered investigational which means it has not been approved for use COVID-19 by the U.S. Food and Drug Administration (FDA). While you are in this study, you will receive a study medication for 5 days. This medication could be either hydroxychloroquine or placebo (that means a pill with no medicine in it). The identity of

50 hospitals in the United States.

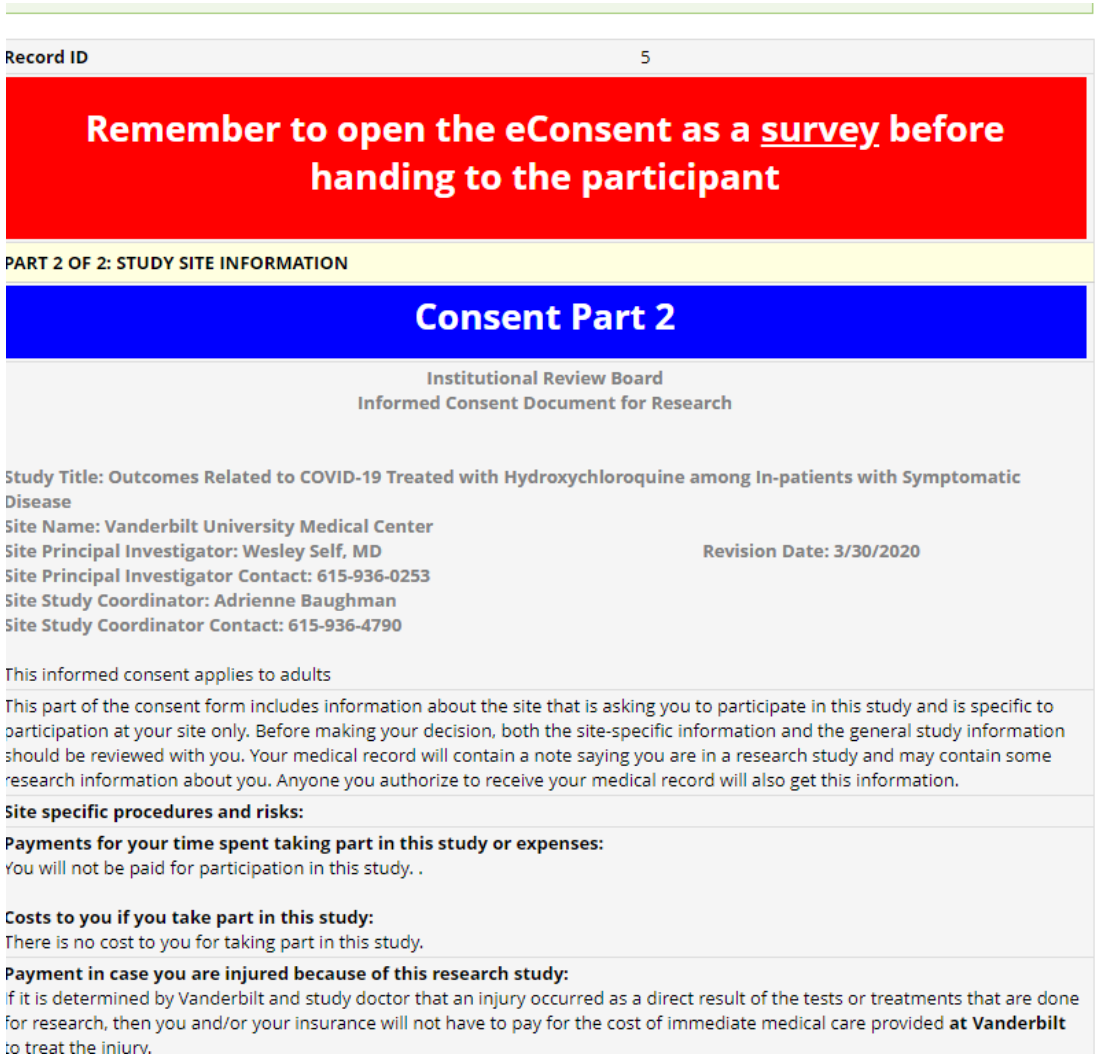
What will happen during the study?
If you agree to be in the study, you will be in the study for about 30 days. The tables below outline each component of the study.

Study Procedure 1: Consent for Study Participation	
Timing	**Today**
Explanation	**Consent includes reading through this form, asking questions, and receiving answers.**
Risks or Discomforts	**You may not understand all the information in this form. Please be sure to ask questions so you understand.**
What you will do	**After reading this form and asking questions, if you agree to be in this research study, you will sign this form.**
What we will do	**We will go through this form with you, answer any questions you have, and give you a copy of the consent form.**

Study Procedure 2: Randomization	
Timing	**Today (following signing of the consent)**
Explanation	**If you agree to be in this study, you would be assigned to one of two groups: the Hydroxycloroquine Group or the Placebo Group. You would be assigned randomly, like the flip of the coin. This is called randomization and is done by a computer program.**
Risks or Discomforts	**You will recieve Hydroxychloroquine or Placebo. Both are explained below.**
What you will do	**Agreeing to be in this study includes knowing that you will be assigned to one group or to the other. You will not be able to pick which group you are in. You will not be able to change groups and will not know which group you are assigned to.**
What we will do	**We will get the medicines for you that you will take as part of the study for the next 5 days. Your doctors, nurses, and study personnel will not know if you are taking Hydroxchloroquine or Placebo. If it becomes necessary for your doctors to know if you are taking Hydroxchloroquine or Placebo, they can find out which one you are taking.**

Study Procedure 3: Study Medication	
Timing	**Today and then 24-48 hours after starting study treatment.**
Explanation	**You will be given medications as part of the study twice a day for the next 5 days (10 doses). These medications will be given as pills that can be swallowed or placed down feeding tubes. The study medication will either be hydroxychloroquine (the medication we are studying to**

E Consent - Step 2



Record ID 5

Remember to open the eConsent as a survey before handing to the participant

PART 2 OF 2: STUDY SITE INFORMATION

Consent Part 2

Institutional Review Board
Informed Consent Document for Research

Study Title: Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease
Site Name: Vanderbilt University Medical Center
Site Principal Investigator: Wesley Self, MD
Site Principal Investigator Contact: 615-936-0253
Site Study Coordinator: Adrienne Baughman
Site Study Coordinator Contact: 615-936-4790
Revision Date: 3/30/2020

This informed consent applies to adults

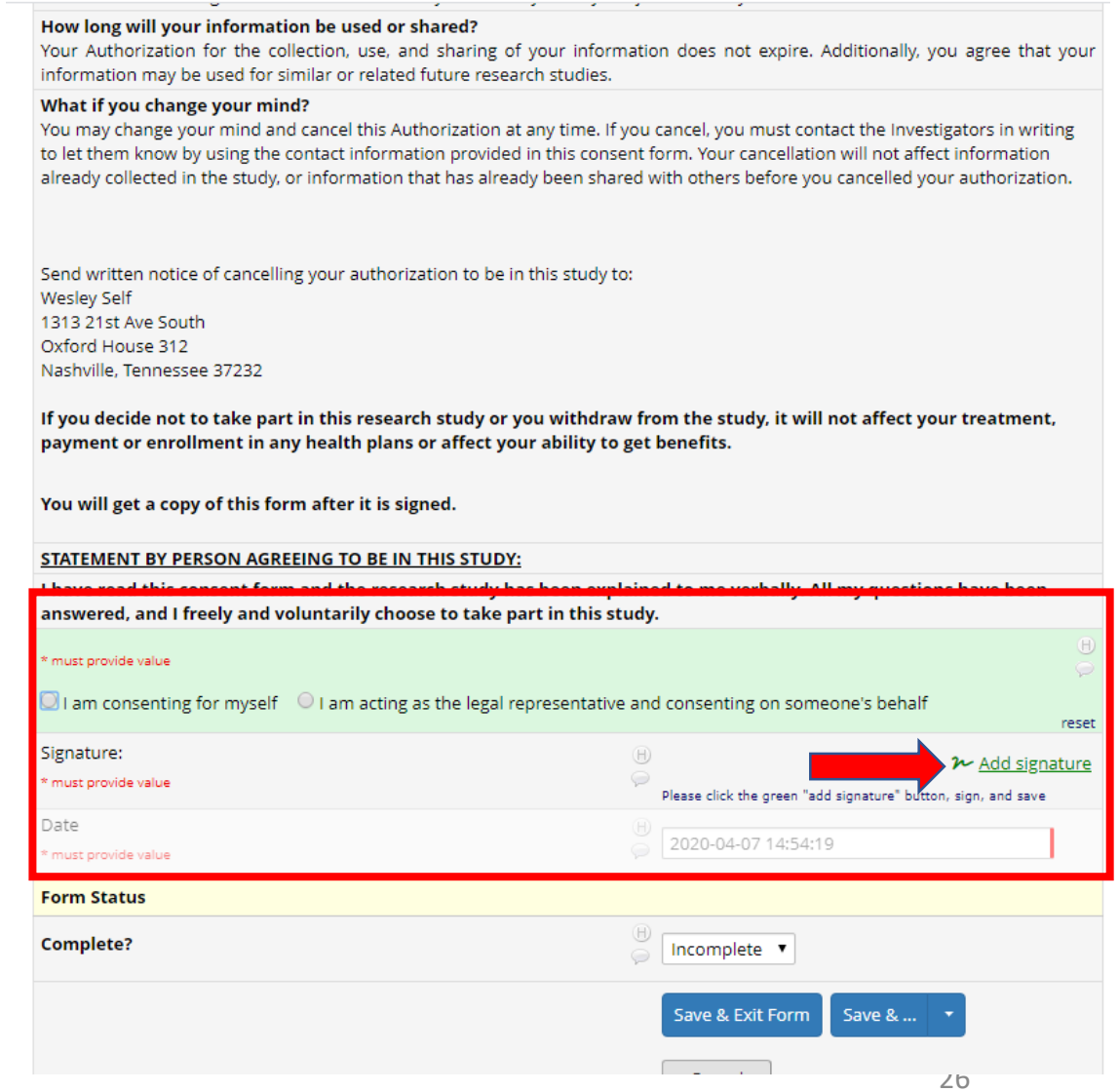
This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Site specific procedures and risks:

Payments for your time spent taking part in this study or expenses:
You will not be paid for participation in this study. .

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and study doctor that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.



How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Investigators in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Send written notice of cancelling your authorization to be in this study to:
Wesley Self
1313 21st Ave South
Oxford House 312
Nashville, Tennessee 37232

If you decide not to take part in this research study or you withdraw from the study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits.

You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY:

answered, and I freely and voluntarily choose to take part in this study.

* must provide value

I am consenting for myself I am acting as the legal representative and consenting on someone's behalf

reset

Signature:
* must provide value
Add signature
Please click the green "add signature" button, sign, and save

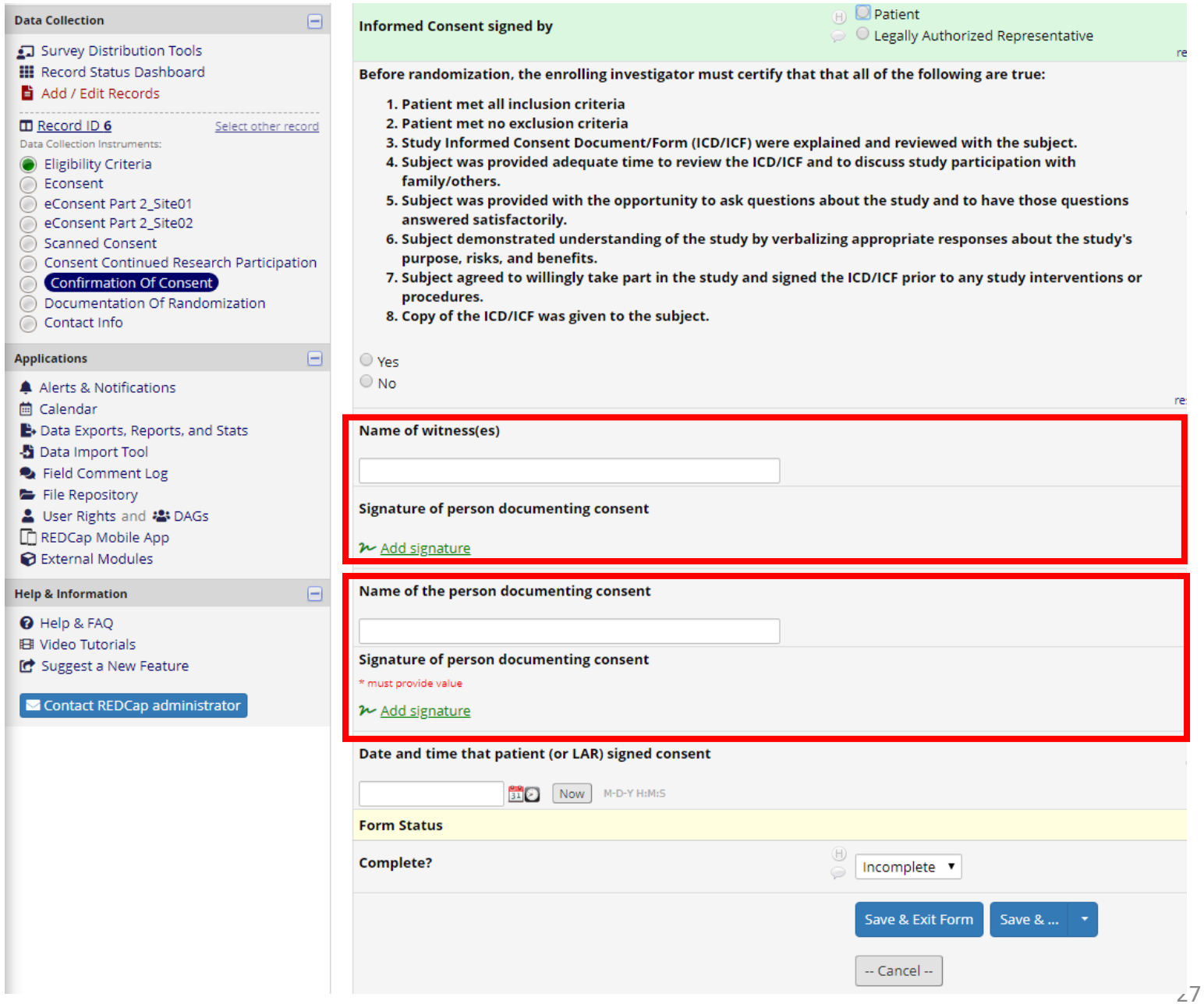
Date
* must provide value
2020-04-07 14:54:19

Form Status

Complete? Incomplete

Save & Exit Form Save & ...

E Consent - Confirmation of Consent



Data Collection - Takeaways

- After consent, all data is remote
- No specimen collection (initially)
- Phone follow-up & chart review for primary outcome

Data Collection Schedule

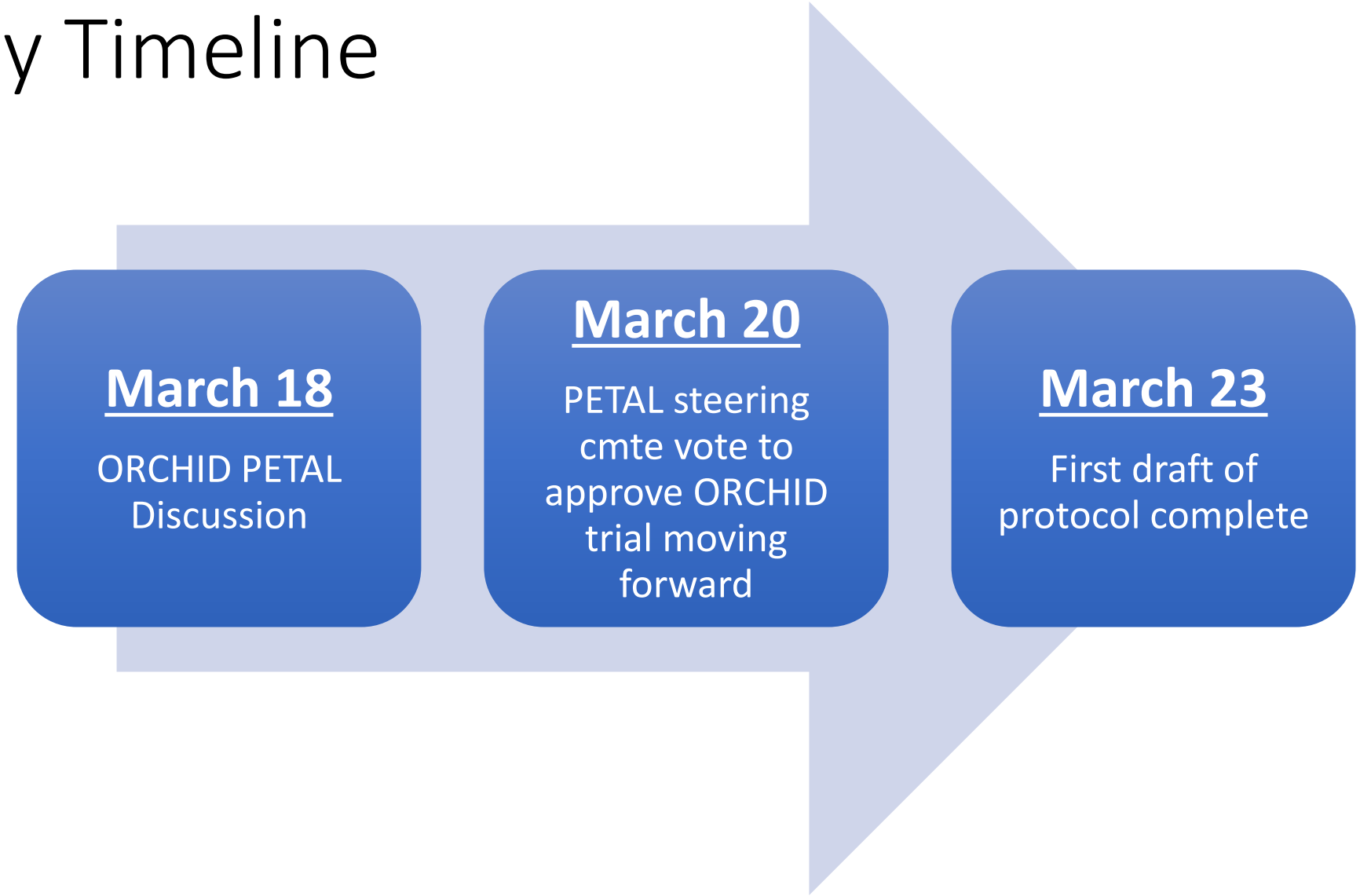
Study Activity	Pre-Enrollment Day 1	Post-Enrollment Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 15	Day 28
Screening log	X								
Enrollment/Baseline									
Documentation of eligibility	X								
Documentation of informed consent	X								
Contact information	X								
Demographics	X								
Vital signs	X								
SOFA score	X								
Chest imaging	X								
Medications	X								
On-study									
Study drug log		X	A*	A*	A*	A*	*		
Documentation of medication review									
Documentation of AE review			X	X	X	X			
SOFA score				A					
QTc				A					
Final clinical outcomes assessment									
Concomitant medications									X
Microbiology									X
In-hospital outcomes									X
Safety outcomes									X
Chest imaging									X
Adverse Event Assessment		X	X	X	X	X	X		
WHO COVID ordinal scale	X		A	A	A	A	X	X	X

X = mandatory assessments for all participants
A = mandatory assessments for admitted participants
* participants discharge before Day 5 will have doses of study drug assessed on Day 7 telephone call

COVID Challenges/**Opportunities**

- Equipoise at sites – FDA EUA waiver issued
- No use of paper consent
- **Rapid progress through PETAL, MGH CCC/DCC, NHLBI, cIRB, FDA, & DSMB**
  - **Synergy across many groups**

Study Timeline



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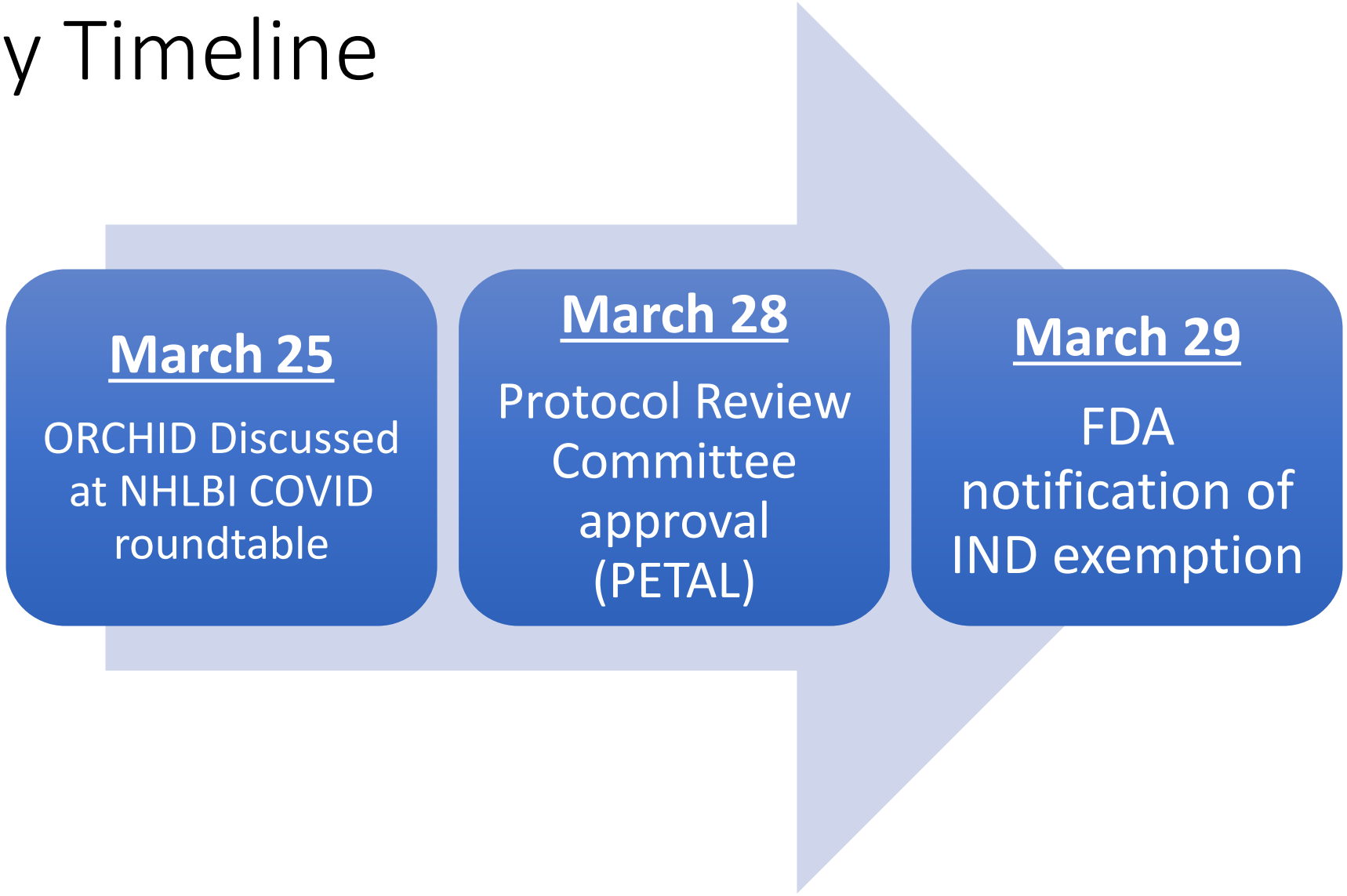
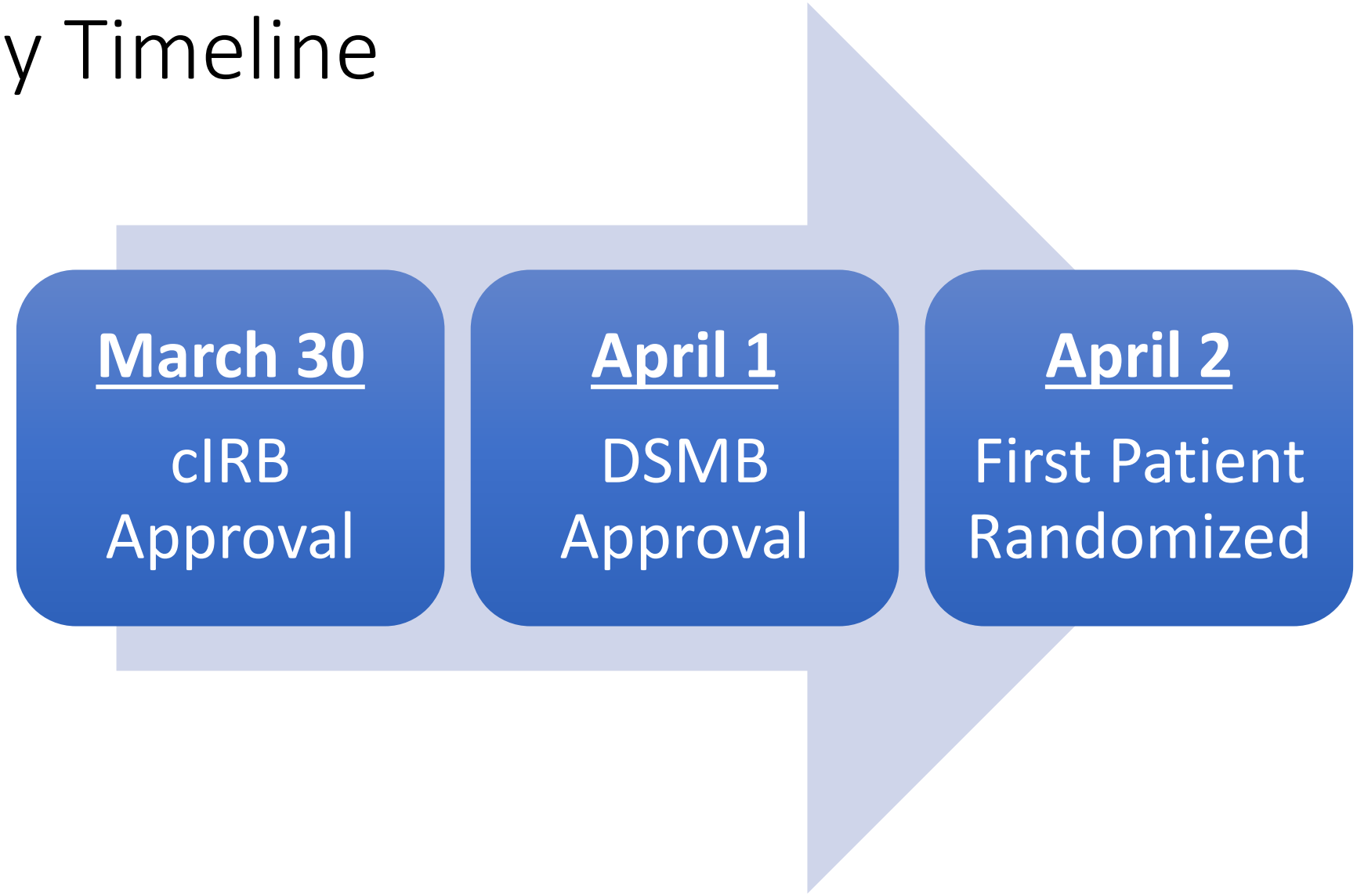


Study Timeline



Timeline Summary

- PETAL SC approval of ORCHID to first patient enrolled = 13 days
- PETAL, NHLBI, MGH CCC/DCC, VCC, Novartis, cIRB (consent process), PRC, DSMB, VUMC cardiology (Roden), Database build and testing (VUMC Biostats)
- Normal process 12 months or more

Study Update

- VUMC – 12 patients enrolled as of 4/9
- Study drug- shipping to other PETAL sites in the next few days
- Goal- open other sites next week

Thank You