Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease

The PETAL Investigators

Title:	**O**utcomes **R**elated to **C**OVID-19 treated with **H**ydroxychloroquine among **I**n-patients with symptomatic **D**isease
Acronym:	ORCHID
Funder:	The National Heart, Lung, and Blood Institute (NHLBI)
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REVISIONS TO THE PROTOCOL

Protocol Version 1
Date: March 27, 2020
Initial protocol

Protocol Version 1.1
Date: March 29, 2020
Substantive protocol changes in Version 1.1:

1. Based on recommendations from FDA, the dose of hydroxychloroquine in the trial was changed from hydroxychloroquine 400 mg every 12 hours for 10 doses (version 1) to hydroxychloroquine 400 mg every 12 hours for 2 doses followed by 200 mg every 12 hours for 8 doses (version 1.1). This change was made before any patients were enrolled and before the trial was posted on clinicaltrials.gov.

Protocol Version 2.0
Date: April 14, 2020
Substantive protocol changes in Version 2.0:

1. Inclusion criterion #4 changed so that only patients with laboratory-confirmed SARS-CoV-2 infection are eligible. Patients with pending SARS-CoV-2 test results with a high clinical suspicion of COVID-19 are no longer eligible. This change was made because SARS-CoV-2 laboratory results are now routinely available within hours of initial hospital presentation at participating hospitals (which was not true early in the COVID-19 pandemic).
2. Exclusion criterion #16 was added. This exclusion criterion states that a patient is excluded if the treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for treatment of this patient.
3. Discussion of potential drug shortages was removed because study drug for all sites will be supplied by the PETAL Network and will not rely on local drug supplies.
4. Language describing consent processes was revised to increase precision.
5. Revised the statistical considerations section (Section 7).
6. Corrected the definition of serious adverse event in section 11.1 to harmonize with section 11.3
7. Added the following statement to Appendix C: “The Medical Monitor will provide to Sandoz Pharmacovigilance any significant safety findings (without disclosing protected health information) during the conduct of the trial.”
8. Added Appendix D: Public Readiness and Emergency Preparedness Act
9. Additional data collection added: Clinically diagnosed deep vein thrombosis (DVT) or pulmonary embolism (PE)
10. Clarification of patient co-morbidities added

Protocol Version 3.0
Date: May 4, 2020
Substantive Changes in Version 3.0:

1. Operationalized the definition of shortness of breath in inclusion criteria #3.
2. Added option for attestation of signature for confirmation of informed consent (section 3.6).
3. Clarified recommendations for stopping guidelines in statistical considerations section, using an odds ratio to suggest futility of 1.1 (section 7.1).

Protocol Version 4.0
Date: June 4, 2020
Substantive Changes in Version 4.0

1. Added language for the DMSB to consider stopping the trial for harm (section 7.1): “If we determine there is >70% probability that the odds ratio is <0.70, the DSMB should consider stopping the trial for harm.”
2. Added language that enrollment will be paused after 510 participants until the DSMB reviews primary outcome data from all 510 participants.
3. Added Appendix E: The ORCHID-BUD Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease – Brain Outcomes and Psychological Distress Ancillary study procedures.

ABBREVIATIONS

ACE-I	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin II receptor blocker
ADR	Adverse drug reaction
AE	Adverse event
DSMB	Data safety monitoring board
eCRF	Electronic case report forms
GFR	Glomerular filtration rate
ICU	Intensive care unit
IV	Intravenous
LAR	Legally authorized representative
LFT	Liver function test
MIC	Minimum inhibitory concentration
NSAIDs	Nonsteroidal anti-inflammatory drug
PI	Principal investigator (a clinician responsible for one site)
RCT	Randomized control trial
SAE	Serious adverse events
S/F	SpO_2/FiO_2 ratio
SOFA	Sequential Organ Failure Assessment
SOP	Standard operating Procedure

1. STUDY SUMMARY

Title	Hydroxychloroquine for the Early Treatment of COVID-19 in Hospitalized Adults: A Multicenter Randomized Clinical Trial
Acronym	ORCHID **O**utcomes **R**elated to **C**OVID-19 treated with **H**ydroxychloroquine among **I**n-patients with symptomatic **D**isease
Background	Effective therapies for COVID-19 are urgently needed. Hydroxychloroquine is an antimicrobial agent with immunomodulatory and antiviral properties that has demonstrated *in vitro* activity against SARS-CoV-2, the virus that causes COVID-19. Preliminary reports suggest potential efficacy in small human studies. Clinical trial data are needed to determine whether hydroxychloroquine is effective in treating COVID-19.
Study Design	Blinded, multicenter, placebo-controlled randomized clinical trial
Intervention group	Hydroxychloroquine 400 mg twice daily for two doses, then 200 mg twice daily for the subsequent eight doses (10 total doses)
Control group	Matched placebo twice daily for 10 total doses
Sample Size	Up to 510 patients
Inclusion Criteria	1. Age ≥18 years 2. Currently hospitalized or in an emergency department with anticipated hospitalization. 3. Symptoms of acute respiratory infection, defined as one or more of the following: a. cough b. fever (> 37.5° C / 99.5° F) c. shortness of breath (operationalized as any of the following: subjective shortness of breath reported by patient or surrogate; tachypnea with respiratory rate ≥22 /minute; hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy). d. sore throat 4. Laboratory-confirmed SARS-CoV-2 infection within the past 10 days prior to randomization.
Exclusion Criteria	1. Prisoner 2. Pregnancy 3. Breast feeding 4. Unable to randomize within 10 days after onset of acute respiratory infection symptoms 5. Unable to randomize within 48 hours after hospital arrival 6. Seizure disorder 7. Porphyria cutanea tarda 8. QTc >500 ms on electrocardiogram within 72 hours prior to enrollment 9. Diagnosis of Long QT syndrome 10. Known allergy to hydroxychloroquine, chloroquine, or amodiaquine

	11. Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol 12. Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment 13. Inability to receive enteral medications 14. Refusal or inability to be contacted on Day 15 for clinical outcome assessment if discharged prior to Day 15 15. Previous enrollment in this trial 16. The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient
Randomization	Eligible participants will be randomized 1:1 to hydroxychloroquine versus placebo. Randomization will be completed in permuted blocks of variable size and stratified by site.
Blinding	Patients, treating clinicians, trial personnel, and outcome assessors will be blinded to group assignment.
Primary Outcome	COVID Ordinal Outcomes Scale on Study Day 15: 1. Death 2. Hospitalized on invasive mechanical ventilation or ECMO 3. Hospitalized on non-invasive ventilation or high flow nasal cannula 4. Hospitalized on supplemental oxygen 5. Hospitalized not on supplemental oxygen 6. Not hospitalized with limitation in activity 7. Not hospitalized without limitation in activity
Secondary Outcomes	• Time to recovery, defined as time to reaching level 5, 6, or 7 on the COVID Outcomes Scale, which is the time to the earlier of final liberation from supplemental oxygen or hospital discharge • All-location, all-cause 14-day mortality (assessed on Study Day 15) • All-location, all-cause 28-day mortality (assessed on Study Day 29) • COVID Ordinal Outcomes Scale on Study Day 3 • COVID Ordinal Outcomes Scale on Study Day 8 • COVID Ordinal Outcomes Scale on Study Day 29 • Composite of death or receipt of ECMO through Day 28 • Oxygen-free days through Day 28 • Ventilator-free days through Day 28 • Vasopressor-free days through Day 28 • ICU-free days through Day 28 • Hospital-free days through Day 28
Safety Outcomes	• Seizure • Atrial or ventricular arrhythmia • Cardiac arrest • Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal • Acute pancreatitis • Acute kidney injury • Receipt of renal replacement therapy

	• Symptomatic hypoglycemia • Neutropenia, lymphopenia, anemia, or thrombocytopenia • Severe dermatologic reaction
Analysis	The primary analysis will be an intention-to-treat comparison of the primary outcome between patients randomized to hydroxychloroquine versus placebo using a proportional odds model. An odds ratio (OR) >1.0 indicates more favorable outcomes with hydroxychloroquine on the COVID Ordinal Outcome scale, while an OR <1.0 indicates more favorable outcomes with placebo. The trial is designed with a Bayesian monitoring plan and has an anticipated sample size around 510 patients. The suggested stopping boundaries for the DSMB to consider include: >95% probability that the OR is >1.0 with a skeptical prior distribution (stop for efficacy); >90% probability that the OR is <1.1 with a flat prior (stop for futility); or >70% probability that the OR is <0.7 with a flat prior (stop for harm). With 5 interim analyses, a simulation showed that over 90% of trials would show efficacy on or before the fifth interim analysis (510 patients) if the true odds ratio were 1.8. Meanwhile, 6% of trials would show efficacy, and 77% would stop for futility if the odds ratio were 1.0. If the trial enrolls 510 participants, further enrollment will be paused until the DSMB reviews data on the primary outcome from all enrolled participants; a decision to continue enrollment will be made by NHLBI after reviewing DSMB recommendations while the investigators remain blinded.

2. TRIAL DESCRIPTION

2.1 Background

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2).[1,2] Although the epidemiology has not been fully elucidated, most adults with COVID-19 appear to experience fever, cough, and fatigue and then recover within 1-3 weeks. However, a portion of adults with COVID-19 develop severe illness, typically manifesting as pneumonia and hypoxemic respiratory failure, with continued progression to acute respiratory distress syndrome (ARDS) and death in some cases.[1–3] Currently, no therapies have been demonstrated to prevent progression of COVID-19 to severe illness. Based on mechanism of action and early clinical experiences, several agents currently available in the United States (US) have been proposed as potential therapies to prevent progression.[4–6] Among these potential therapies, hydroxychloroquine has generated substantial interest due to its antiviral and immunomodulatory activity and established safety profile. In fact, many US hospitals are currently recommending hydroxychloroquine as first-line therapy for hospitalized patients with COVID-19 despite extremely limited clinical data supporting its effectiveness. Thus, data on the safety and effectiveness of hydroxychloroquine for the treatment of COVID-19 are urgently needed to inform clinical practice. In this trial, we will evaluate the safety and effectiveness of hydroxychloroquine for the treatment of adults hospitalized with COVID-19.

2.1.1 COVID-19 Infection

COVID-19 was first identified as a cluster of cases of pneumonia among a group of workers from a seafood wholesale market in Wuhan, China in December 2019.[7] This observation, along with subsequent viral genotyping showing significant genetic similarities to the bat coronaviruses[8] suggest a zoonotic origin, although the specific reservoir and intermediary species remain unclear.[9] The COVID-19 infection represents the seventh coronavirus known to cause disease in humans.[10] Four of the coronaviruses viruses are known to cause symptoms of the common cold in immunocompetent individuals while two others (SARS-CoV and MERS-CoV) have caused recent outbreaks of severe and sometimes fatal respiratory diseases.[11] SARS-CoV-2 appears to exploit the same cellular receptor as SARS-CoV and MERS-CoV,[12] and its severity may similarly result from a predilection for intrapulmonary epithelial cells over cells of the upper airways.[13,14]

Since the first documented human case, COVID-19 has spread exponentially with 216,846 confirmed cases and 8,908 deaths as of March 18, 2020. While most patients recover after a mild, brief illness with fever and cough, the disease has a clinical spectrum ranging from asymptomatic infection[15] to ARDS and death.[16] The most common reasons for ICU care are respiratory failure and ARDS, with a minority developing shock and possibly cardiomyopathy.[17] The case fatality rate is estimated to be 0.25% to 3.0%.[18]

2.1.2 Hydroxychloroquine as a Therapeutic for COVID-19

Hydroxychloroquine is a medication approved by the US Food and Drug Administration and accounts for millions of US prescriptions annually. It is used both as an antiparasitic agent for malaria and an immunomodulatory agent for rheumatologic diseases. When used for short periods, hydroxychloroquine is generally well-tolerated, with the most common side effects including nausea, vomiting, diarrhea, rash, and headache. Mechanisms of action include: 1) immunomodulation: decreased inflammatory response

via inhibition of IL1, IL6, and tumor necrosis factor and impairment of complement-dependent antigen-antibody reactions; 2) antimalarial: increasing pH of the vacuole within malaria parasites preventing normal growth and replication; and 3) antiviral: increasing endosomal pH, which limits virus-cell fusion and interferes with glycosylation of cell receptors targeted by coronaviruses.[4,5,19,20] Recent laboratory studies demonstrate that hydroxychloroquine is a potent inhibitor of SARS-CoV-2 *in vitro*.[4,5,21] Based on these laboratory data and case series of clinical experiences, hydroxychloroquine has been proposed as a potential therapeutic for treatment of COVID-19.[22]

2.1.3 Rationale for a Randomized Trial among Hospitalized Patients

The initial symptoms of COVID-19 develop approximately 2-10 days after infection with the SARS-CoV-2 virus,[23] with the progression to respiratory failure and ARDS occurring approximately 7-10 days after the onset of symptoms.[24] While most adults with COVID-19 recover without complications, patients who require hospitalization experience high rates of complications. In case series of hospitalized patients with COVID-19, up to 26% require ICU admission and up to 17% die in the hospital.[24,25] The period between onset of symptoms and development of severe respiratory failure represents a potential window for treatment of hospitalized patients to prevent disease progression.

Given the unprecedented public health crisis caused by COVID-19, there is significant interest in finding effective therapies and, specifically, in repurposing approved medications with widespread availability and known safety profiles.[3,26] Potential therapies that are being considered include hydroxychloroquine, chloroquine, lopinavir/ritonavir, interferon β, and corticosteroids. Despite extremely limited clinical data, hydroxychloroquine has been adopted into treatment guidelines in China[27] and has been proposed as first-line therapy for hospitalized patients in institutional protocols for COVID-19 at some hospitals in the US.

Data on the safety and efficacy of hydroxychloroquine from randomized trials is urgently needed. A randomized clinical trial demonstrating that hydroxychloroquine prevents disease progression in hospitalized patients with COVID-19 would provide evidence-based therapy for an ongoing pandemic. A randomized clinical trial demonstrating that hydroxychloroquine is ineffective against COVID-19 would also have important public health impacts. Hydroxychloroquine is known to be associated with a risk of QT prolongation, seizure, bone marrow suppression, and neuromyopathy. Risks of hydroxychloroquine may increase in patients with decreased renal function and critical illness, as may occur in COVID-19. It also interacts with many medications commonly administered to hospitalized and critically ill patients. If hydroxychloroquine is not effective at treating COVID-19, patients should not be exposed to these potential toxicities. Additionally, prior trials have suggested that hydroxychloroquine may worsen outcomes for some viral infections. In a placebo-controlled trial of hydroxychloroquine for HIV treatment, it caused significantly higher HIV viral loads and lower CD4 counts.[28] A related drug, chloroquine, was shown to delay the immune response to Chikungunya infection and lead to higher viral loads and more lymphopenia in a non-human primate model.[29]

Given the need for effective treatments of COVID-19, the unclear efficacy and safety of hydroxychloroquine as a treatment of COVID-19, and the widespread clinical use of hydroxychloroquine during the current pandemic, a randomized clinical trial is urgently needed.

2.1.4. Rationale for Evaluating Hydroxychloroquine Monotherapy

In addition to hydroxychloroquine, several other medications have been proposed as potential therapies for COVID-19, including remdesivir and azithromycin. Remdesivir treatment for COVID-19 is being studied in a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) [NCT04280705]. Azithromycin is a macrolide antibiotic that is commonly used in the US for treatment of respiratory infections. During the design of this protocol, the investigators considered studying combination therapy of hydroxychloroquine plus remdesivir and hydroxychloroquine plus azithromycin. The investigators noted that combination therapy would likely increase the risk of toxicities. With no preliminary data suggesting combination therapy is likely to be more effective than hydroxychloroquine monotherapy, the investigators believe the risks of studying combination therapy likely outweigh the benefits at this time. Additionally, results of a trial evaluating combination therapy may be difficult to interpret. Trial results suggesting effectiveness would probably not be attributable to a single agent and would leave uncertainty about whether treatment with combination therapy is preferable to monotherapy. Furthermore, null results of a trial evaluating combination therapy could occur if neither agent is effective, if one is effective and one is detrimental, or if both are effective but there are unfavorable drug-drug interactions. Interpretation of a trial of one agent will be straightforward and may provide the basis for subsequent trials of combination therapy. The investigators note that two distinct, simultaneously conducted placebo-controlled randomized trials evaluating remdesivir and hydroxychloroquine separately will provide high quality data on the effectiveness and safety of each agent versus placebo.

2.2 Study Aims

2.2.1 Study aim

To compare the effect of hydroxychloroquine versus placebo on clinical outcomes, measured using the COVID Ordinal Outcomes Scale at Day 15, among adults with COVID-19 requiring hospitalization.

2.2.2 Study hypothesis

Among adults hospitalized with COVID-19, administration of hydroxychloroquine will improve clinical outcomes at Day 15.

2.3 Study Design

We will conduct an investigator-initiated, multicenter, blinded, placebo-controlled, randomized clinical trial evaluating hydroxychloroquine for the treatment of adults hospitalized with COVID-19. Patients, treating clinicians, and study personnel will all be blinded to study group assignment.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria

1. Age ≥18 years
2. Currently hospitalized or in an emergency department with anticipated hospitalization.

3. Symptoms of acute respiratory infection, defined as one or more of the following:
    a. Cough
    b. fever (> 37.5° C / 99.5° F)
    c. shortness of breath (operationalized as any of the following: subjective shortness of breath reported by patient or surrogate; tachypnea with respiratory rate ≥22 /minute; hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy).
    d. sore throat
4. Laboratory-confirmed SARS-CoV-2 infection within the past 10 days prior to randomization

3.2 Exclusion Criteria

1. Prisoner
2. Pregnancy
3. Breast feeding
4. Unable to randomize within 10 days after onset of acute respiratory infection symptoms
5. Unable to randomize within 48 hours after hospital arrival
6. Seizure disorder
7. Porphyria cutanea tarda
8. QTc >500 ms on electrocardiogram within 72 hours prior to enrollment
9. Diagnosis of Long QT syndrome
10. Known allergy to hydroxychloroquine, chloroquine, or amodiaquine
11. Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol
12. Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment
13. Inability to receive enteral medications
14. Refusal or inability to be contacted on Day 15 for clinical outcome assessment if discharged prior to Day 15
15. Previous enrollment in this trial
16. The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient

3.3 Justification of Exclusion Criteria

The exclusion criteria are primarily designed for patient safety. In addition to excluding specific vulnerable populations (e.g., prisoners), these criteria are designed to exclude patients for whom receipt of hydroxychloroquine might increase the risk of serious adverse events. For example, patients who have a prolonged QTc or are taking medications that would increase the risk of experiencing a prolonged QTc when combined with hydroxychloroquine are excluded to minimize the risk of Torsades de Pointes.

3.4 Screening

The site investigator or delegate will screen for hospitalized patients with laboratory confirmed COVID-19 (that is, a positive laboratory test for SARS-CoV-2) or a pending SARS-CoV-2 test. Treating clinicians will also be instructed to contact the site investigator or delegate for patients with a high clinical suspicion of COVID-19.

3.5 Assessment of Eligibility and Exclusion Tracking

For patients who appear to meet inclusion criteria during screening, an electronic case report form will be completed to determine eligibility and track exclusions. The electronic case report form will be accessed and stored in the electronic database. At the time of entry into the screening database, the patient will be assigned a screening number.

If a patient appears to meet all eligibility criteria, the site investigator or delegate will approach the treating clinician to ask permission to approach the patient or Legally Authorized Representative (LAR) to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

For all excluded patients, including refusal by the treating clinician or patient/surrogate, a small number of de-identified variables will be collected including month and year the patient met screening criteria, age, sex, ethnicity, patient location, and reason(s) patient was excluded. For the safety of research personnel and conservation of personal protective equipment, these encounters may occur via telephone or videophone.

3.6 Process of Obtaining Informed Consent

Informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity.

In some instances, bringing a paper consent form and pen to the bedside of a patient with known or suspected COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), there is a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. The current epidemic also presents unique challenges to obtaining consent from participant's legally authorized representative (LAR). To minimize infectious risk, many institutions are not allowing visitors to enter the hospital. Furthermore, the LAR is likely to have been exposed to the patient and may therefore be under self-quarantine at the time of the informed consent discussion.

Therefore, in addition to the traditional approach of an in-person consent discussion and signed paper informed consent document, we will allow use of "no-touch" consent procedures for this trial. Below, we outline three examples of no-touch consent procedures that may be used: (a) a paper-based approach; (b) an electronic/e-consent approach; and (c) attestation of informed consent.

3.6.1 Paper-based approach

1. The informed consent document is delivered to the patient or LAR.
    a. If the patient or LAR is on-site, the informed consent document many be delivered to the patient or LAR either by research staff or by clinical staff
    b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy)
2. Research staff discuss the informed consent document with the patient or LAR either in-person or by telephone or videophone. *This step confirms subject/LAR identity*.

3. If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document.
4. A photograph is taken of the signature page of the informed consent document and uploaded into the electronic database (e.g. REDCap).
    a. If using the patient's device (such as a patient's personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g. REDCap).
    b. If using a staff device, it must be approved to store PHI by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document either directly or through the window or glass door leading into the patient's room. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a photograph it must be able to be disinfected according to local institutional practices.
5. Research staff and witness provide signatures within the electronic database (e.g. REDCap) confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

3.6.2 Electronic/e-consent approach

1. The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
2. Research staff discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate the patient or LAR signs the electronic informed consent document. This signature may be either:
    a. an actual signature (often tracing a finger on the screen) OR
    b. a username and password specific to the individual signing
4. Research staff and witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
5. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols and removed by research staff or clinical staff during the next entry into the patient's room.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

The information for the informed consent discussion will be provided in a formal document (or electronic equivalent) that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any

potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient does not speak English, a short-form consent and qualified interpreter will be employed, using similar "no-touch" principles. Use of an interpreter and the interpreter's identity will be documented on the electronic consent.

3.6.3 Attestation of informed consent

If none of the options outlined above (traditional signature and storage of a paper consent form, electronic photographs of a signed consent page, or e-consent) are available, study personnel may attest to completion of the informed consent process using the procedures outlined below. Importantly, the process of informed consent using this attestation option should not change compared with the traditional method of obtaining informed consent for trial participation except for the method of documenting the consent process in the research record. Rather than storing a paper document with the participant's signature, a member of the research team and an impartial witness will attest to completion of the informed consent process and that the participant signed the informed consent document. This option of attestation of informed consent is not available when obtaining consent through an LAR.

Procedures for attestation of informed consent:

1. An unsigned paper consent form is provided to the patient by a heath care worker or study member.
2. The study member obtaining consent arranges an in-person meeting or three-way call or video conference with himself/herself, the patient, and an impartial witness. If desired and feasible, additional people requested by the patient (e.g., next of kin) may also join this discussion.
3. Study member reviews consent and answers questions in the presence of the impartial witness.
4. Patient signs the paper informed consent document while the witness is listening on the phone or directly observing.
5. Patient provides verbal confirmation that he/she would like to participate in the trial and he/she has signed and dated the informed consent document. This signed informed consent document stays with the patient due to the risk of spreading the virus.
6. Study member and witness attest that other techniques for documenting informed consent were not available for this participant and that the participant provided written informed consent for trial participation by signing a paper informed consent document. An attestation form is available in the ORCHID REDCap toolkit for documenting this attestation. This attestation page with signatures from the study member and witness will be save as evidence of the informed consent process. A signature from the participant will not be saved in the research record.

3.7 Randomization and Blinding

Participants confirmed to meet all eligibility criteria who have provided informed consent will be randomized 1:1 to hydroxychloroquine versus placebo. A randomization code will be provided to the site investigator or delegate from a centralized, web-based platform. Randomization will require provision of the screening number and confirmation of patient eligibility.

Randomization will be completed in permuted blocks of varying size and stratified by site. The randomized sequence allocation will be stored on a secure server and will not be available to site study personnel. Site research personnel will have a unique Personal Identification Number (PIN) to access the

randomization system. Each subject will receive a computer-generated randomization ID number. The computer-generated randomization ID number will be provided to the pharmacy who will provide a dose pack containing hydroxychloroquine or placebo. The participant, treating clinicians, study personnel, and outcome assessors will all remain blinded to group assignment until after the database is locked and blinded analysis is completed.

3.8 Minorities and Women

No patients will be excluded on the basis of race, ethnicity, or sex. The clinical coordinating center will monitor recruitment of minorities and women. If necessary, additional recruitment efforts will be made to ensure that the aggregate patient sample contains representative race/ethnicity and sex subsets.

4. STUDY INTERVENTIONS

4.1 Treatment of Study Participants

A summary of the trial's schedule of events is included in Appendix A.

Timing of study procedures is based on the time of randomization, which is defined as "Time 0". The primary outcome will be assessed on Study Day 15, which corresponds to 14 days (2 weeks) after randomization.

Study medications will be administered by clinical or research personnel while the patient is hospitalized. The first dose of study medications will be administered within 4 hours of randomization. In the hospital, medication delivery after the first dose will correspond to the timing of morning and evening medication delivery for the hospital/unit. If the patient is discharged prior to completion of the study medication, the patient will be discharged with the study medication packet to complete the course after discharge. At home, the patient will be instructed to take the morning dose upon awakening and the evening dose approximately 12 hours later.

On Study Days 1-5, study personnel will review patient records to confirm administration of study drug and document the number and reason for any missed doses. For patients who are discharged prior to Day 5, study personnel will obtain data on study drug adherence and safety outcomes from the patient or surrogate at via telephone follow-up scheduled at Day 8. Research personnel will also assess patients at Day 15 and Day 29; these assessments will be completed by phone if the patient has been discharged from the hospital.

4.2 Hydroxychloroquine Group

Participants assigned to the hydroxychloroquine arm will receive hydroxychloroquine sulfate 400 mg enterally twice daily for the first two doses and then 200 mg twice daily for the subsequent eight doses ("Days 2 – 5"). This dosing regimen is a total of 10 doses over 5 days with an 800 mg load in the first 24 hours divided into two doses followed by 400 mg daily divided into two doses over the following 4 days. Medication dose packs containing all 10 doses will be provided at randomization by the investigational pharmacy.

Hydroxychloroquine is available in 200 mg oral tablets of hydroxychloroquine sulfate. Common hydroxychloroquine dosing for treatment of uncomplicated malaria is 800 mg followed by 400 mg at 6 hours, 24 hours, and 48 hours. Common initial dosing for rheumatoid arthritis is 400 mg to 600 mg daily. For this COVID-19 trial, we selected a dose of hydroxychloroquine (400 mg twice daily for the first two doses followed by 200 mg twice daily for next 8 doses) based on similar doses being well tolerated in the treatment of other conditions and *in vitro* studies suggesting that SARS-CoV-2 inhibition is achieved by a dose of 800 mg on the first day followed by 400 mg for the following 4 days.[5] This dose and duration is comparable to the dose and duration being administered empirically to patients with COVID-19 as a part of clinical care during the current epidemic.

4.3 Control Group

Participants randomized to the control group will receive matching placebo enterally twice daily matching the dosing regimen described above for hydroxychloroquine. Medication dose packs containing all 10 doses will be provided at randomization by the Investigational Pharmacy. The placebo pills will be as similar as possible to the hydroxychloroquine pills to ensure blinding.

4.4 Co-Interventions

This trial will control the use of hydroxychloroquine vs placebo during the 5-day intervention period. Enrolled participants will not receive open-label hydroxychloroquine or chloroquine during the 5-day intervention period. All other treatment decisions will be made by treating clinicians without influence from the protocol. Administration of other antiviral medications ("rescue therapy") will be allowed. The decision to administer other antiviral medications will be made by treating clinicians and will be recorded in the case report form. The decision to administer immunomodulating medications, including corticosteroids, will be made by treating clinicians and will be recorded in the case report from.

4.5 On-Study Monitoring

All patients enrolled in the study will be initially hospitalized and will therefore receive monitoring as a part of routine clinical care, including monitoring by their physicians, nurses, respiratory therapists, and ancillary staff.

In addition to routine clinical monitoring, enrolled patients will have an assessment of the QTc with an electrocardiogram (EKG) or rhythm strip performed 24-48 hours after administration of the first study medication. If an EKG or rhythm strip has been performed as a part of clinical care during this window, study personnel will assess the QTc on these clinically performed tracings. If an EKG or rhythm strip has not been performed as a part of clinical care during this window, an EKG or rhythm strip will be ordered and performed as a part of study procedures. This QTc will be used to monitor patient safety and inform stopping of the study drug as described below. If a patient is discharged from the hospital before the QTc is evaluated at 24-48 hours, the study drug may be continued after discharge without this assessment.

Between randomization and Day 5, study personnel will review the electronic health record daily for potential medication interactions with hydroxychloroquine (see Appendix B). If a medication that is considered to be contraindicated with hydroxychloroquine is discovered, treating clinicians will be contacted to discuss if stopping study drug is appropriate or if the medication in question can be stopped or substituted. If a medication with a potential interaction with hydroxychloroquine is identified, study

personnel will contact treating clinicians to ensure they are aware of the potential interaction. Treating clinicians will determine whether an alternative medication would be appropriate or whether the risk-benefit ratio favors continuing the medication with the known potential interaction. If a patient is started on a medication listed in Appendix B that potentially prolongs the QTc, study personnel will recommend to treating clinicians use of continuous cardiac monitoring when available during the study drug treatment period.

In addition to manual monitoring by study personnel for medication interactions, many electronic health records contain tools within the electronic order entry system to automatically screen for medication interactions with hydroxychloroquine and notify ordering providers of the potential interaction at the time of order entry.

4.6 Criteria for Stopping Study Drug

Administration of the blinded study drug may be stopped temporarily or permanently for (a) adverse events, (b) results of on-study monitoring, (c) clinical deterioration, or (d) evidence of an alternative cause to the patient's symptoms.

If a patient experiences an adverse event that the patient (or legally authorized representative), treating clinicians, or investigators feel merits temporarily or permanently stopping the study drug, the study drug will be stopped. The explanation for stopping the study drug will be recorded in the case report form, and the adverse event will be recorded and reported according to the adverse event guidelines below. If the adverse event resolves to the extent that the patient (or legally authorized representative), treating clinicians, and investigators feel that resuming the study drug is appropriate, the study drug will be resumed, and this information will be recorded in the case report form.

If a QTc assessed after randomization is >500 ms, the study drug will be discontinued for 24 hours and a repeat EKG will be performed daily until either the QTc is less than 500 ms, at which time study drug is resumed until 5 days after randomization with daily QTc assessments, or until 5 days after randomization is reached without resumption of study drug. Both the value for the QTc and the decision to continue or stop the study drug will be recorded in the case report form. If the QTc in hospitalized patients cannot be assessed at 24-48 hours, study drug will be discontinued until the QTc can be assessed. If the daily on-study monitoring by study personnel for medication interactions indicates a potential interaction with a medication that treating clinicians feel is required for the optimal treatment of the patient and with which treating clinicians and the investigator feel it would be unsafe to administer hydroxychloroquine (including but not limited to: amiodarone; cimetidine; chloroquine; dofetilide; phenobarbital; phenytoin; sotalol), the study drug will be stopped and the reason will be recorded in the case report form.

Patients on study may experience clinical deterioration due to their illness. Clinical deterioration will be defined as a decrease of 1 point or more on the ordinal scale for the primary outcome (e.g., patient transitions from "hospitalized on supplemental oxygen" to "hospitalized on non-invasive ventilation or high flow nasal cannula"). Patients who experience clinical deterioration in either group may be administered other antivirals or immunomodulators as "rescue therapy". For patients who experience clinical deterioration for which treating clinicians feel optimal care would be to stop the study drug, unblind group assignment, and administer hydroxychloroquine to patients in the placebo group, the study drug will be stopped, the site investigator will contact the coordinating center to receive the unblinded

study group assignment, and any additional treatment will be deferred to treating clinicians. In this situation, the following data will be recorded in the case report form: the criteria met for clinical deterioration; the reason for stopping study drug and unblinding; use of hydroxychloroquine, other antivirals, and immunomodulators; and study outcomes. Crossovers from placebo to open-label hydroxychloroquine will be recorded and reported to the DSMB at DSMB reviews and interim analyses.

Before implementation of protocol version 2.0, patients could be enrolled with a pending SARS-CoV-2 test result if clinical criterial were present suggesting a high likelihood of COVID-19. In these patients, if SARS-CoV-2 results returned negative and the clinical team identified a likely alternative cause of the patient's clinical syndrome, the clinical team could elect to stop administration of the study drug. If the study drug was stopped for this reason, the timing and reason for study drug discontinuation was recorded. After implementation of protocol version 2.0, only patients with laboratory-confirmed SARS-CoV-2 infection are eligible.

5. OUTCOMES

5.1 Primary Outcome

COVID Ordinal Outcomes Scale on Study Day 15:

1. Death
2. Hospitalized on invasive mechanical ventilation or ECMO
3. Hospitalized on non-invasive ventilation or high flow nasal cannula
4. Hospitalized on supplemental oxygen
5. Hospitalized not on supplemental oxygen
6. Not hospitalized with limitation in activity
7. Not hospitalized without limitation in activity

5.2 Secondary Outcomes

- Time to recovery, defined as time to reaching level 5, 6, or 7 on the COVID Outcomes Scale, which is the time to the earlier of final liberation from supplemental oxygen or hospital discharge
- All-location, all-cause 14-day mortality (assessed on Study Day 15)
- All-location, all-cause 28-day mortality (assessed on Study Day 29)
- COVID Ordinal Outcomes Scale on Study Day 3
- COVID Ordinal Outcomes Scale on Study Day 8
- COVID Ordinal Outcomes Scale on Study Day 29
- Composite of death or receipt of ECMO through Day 28
- Oxygen-free days through Day 28
- Ventilator-free days through Day 28
- Vasopressor-free days through Day 28
- ICU-free days through Day 28
- Hospital-free days through Day 28

5.3 Safety outcomes

- Seizure
- Atrial or ventricular arrhythmia
- Cardiac arrest

- Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal
- Acute pancreatitis
- Acute kidney injury
- Receipt of renal replacement therapy
- Symptomatic hypoglycemia
- Neutropenia, lymphopenia, anemia, or thrombocytopenia
- Severe dermatologic reaction

5.4 Rationale for Primary Outcome

COVID-19 has a broad spectrum of clinical severity. Even among hospitalized patients, most recover without experiencing critical illness.[30] Designing a trial with statistical power to detect a meaningful difference in ICU-free days or mortality might require an unfeasibly large sample size and could miss significant morbidity experienced by the majority of hospitalized patients. Since the majority of morbidity from COVID-19 relates to hypoxemia, the fact that this outcome is tied to degree of hypoxemic respiratory failure increases its face validity and relevance. For similar reasons, previous trials of severe influenza have employed a similar ordinal outcome.[31] This ordinal scale has been selected as an outcome in multiple ongoing COVID-19 trials and is a preferred outcome by the World Health Organization Research and Development Blueprint for COVID-19.[32] Use of this standardized outcome will increase the potential to compare the results of this trial with other trials and perform meta-analyses.

6. DATA COLLECTION

Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), we will minimize face-to-face contact between patients and non-clinical staff. Additionally, minimizing research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of strained clinical and research resources during the COVID-19 pandemic. We will emphasize data that can be collected from the electronic health record, radiographs obtained as part of routine clinical care, and assessments that can be completed over the telephone as needed.

Biological specimens will not be collected as part of this trial. To further elucidate the pathophysiology of COVID-19 and the effects of hydroxychloroquine, we encourage ancillary studies and co-enrollment in observational studies that collect biological specimens and more detailed data.

6.1 Baseline Variable Collection

- Presence or absence of inclusion and exclusion criteria
- Date and time of randomization
- Date of symptom onset
- Admission data: date and time of presentation, origin (home, skilled nursing facility, rehabilitation/LTACH, nursing home, outside hospital, outside ICU), location at enrollment (ED, hospital ward, ICU)
- Demographics (age, sex, race, ethnicity, height, weight)

- Comorbidities: AIDS, Leukemia, Malignant Lymphoma, Hemiplegia, Cerebrovascular Disease, A prior myocardial infarction, Congestive Heart Failure, Peripheral vascular disease, Dementia, COPD, Connective tissue disease, Peptic ulcer disease, History of hypertension, HIV positive (without AIDS), Alcoholism, Coronary artery disease, Rapidly fatal disease, Solid tumor, Liver disease, Diabetes mellitus, Moderate to severe kidney disease
- Acute signs and symptoms: altered mental status, acute hypoxemic respiratory failure, liver function tests, renal function, coagulation studies, chest imaging results
- Sequential Organ Failure Assessment (SOFA)[33] at enrollment
- Chronic use of medication: corticosteroids, ACE inhibitors, angiotensin receptor blockers, non-steroids anti-inflammatory drugs, other
- Receipt of open label antivirals between hospital presentation and enrollment: chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, other
- Receipt of open label immunomodulators between hospital presentation and enrollment: corticosteroids, tocilizumab, sarilumab, interferon β, other
- Receipt of convalescent plasma between hospital presentation and enrollment
- Receipt of azithromycin between hospital presentation and enrollment
- Receipt of invasive mechanical ventilation, non-invasive ventilation, high-flow nasal cannula, vasopressors, and oxygen therapy at enrollment
- Highest fraction of inspired oxygen, lowest arterial oxygen saturation, highest respiratory rate, lowest systolic blood pressure, highest heart rate in the 12 hours prior to enrollment
- Diagnosis of Acute Respiratory Distress Syndrome (ARDS) by Berlin Criteria[33] at enrollment
- COVID Ordinal Outcomes Scale at enrollment

6.2 Assessments between Hospital Presentation and Hospital Discharge

- Specimen type, date, and result of SARS-CoV-2 testing conducted clinically
- Specimen type, date, and result of viral testing conducted clinically
- Specimen type, date, and result of bacterial testing conducted clinically
- Date and time of study drug administration and reason for missed doses
- COVID Ordinal Outcomes Scale on Days 2, 3, 4, 5, 8, 15, and 29
- SOFA on Day 3
- S/F ratio on Day 3
- Receipt of open label antivirals between randomization and hospital discharge: chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, other
- Receipt of open label immunomodulators between randomization and hospital discharge: corticosteroids, tocilizumab, sarilumab, interferon β, other
- Receipt of convalescent plasma between hospital presentation and enrollment
- Receipt of azithromycin and other antibiotics between randomization and Day 8
- Clinically diagnosed deep vein thrombosis (DVT) or pulmonary embolism (PE) between hospital presentation and hospital discharge.
- Date and time of first receipt of supplemental oxygen (if applicable)
- Date and time of final receipt of supplemental oxygen (if applicable)
- Date and time of first receipt of high flow nasal cannula (if applicable)

- Date and time of final receipt of high flow nasal cannula (if applicable)
- Date and time of first receipt of non-invasive ventilation (if applicable)
- Date and time of final receipt of non-invasive ventilation (if applicable)
- Date and time of first receipt of invasive mechanical ventilation (if applicable)
- Date and time of final receipt of invasive mechanical ventilation (if applicable)
- Date and time of first receipt of extracorporeal membrane oxygenation (if applicable)
- Date and time of final receipt of extracorporeal membrane oxygenation (if applicable)
- Date and time of first receipt of vasopressors (if applicable)
- Date and time of final receipt of vasopressor (if applicable)
- Date and time of first meeting the Berlin Diagnostic Criteria for ARDS[33] (if applicable)
- Date and time of first ICU admission (if applicable)
- Date and time of final ICU discharge (if applicable)
- Date and time of hospital discharge (if applicable)
- Date of death (if applicable)
- Safety Outcomes: seizure, atrial or ventricular arrhythmia, cardiomyopathy, cardiac arrest, aspartate aminotransferase or alanine aminotransferase levels that are greater than twice the local upper limit of normal, acute pancreatitis (defined by a clinically obtained lipase level above the local upper limit of normal), stage II or greater acute kidney injury according to KDIGO criteria[34], receipt of new renal replacement therapy, symptomatic hypoglycemia, neutropenia, lymphopenia, anemia, thrombocytopenia, or severe dermatologic reaction (e.g., Steven's Johnson Syndrome)
- Patient destination at discharge

6.3 Assessments following Hospital Discharge

6.3.1 Acute Care Follow-up

For participants discharged from the study hospital prior to the Day 8, Day 15 or Day 29 assessment, we will perform these assessments via telephone follow-up. The Day 8 call window will be Day 8 through 14. The Day 15 call window will be Day 15 through 22. The Day 29 call window will be Day 29 through 36. During these telephone calls, we will interview the patient, LAR, or facility staff to assess:

- Number and reason for missed doses of study drug (only for those discharged prior to completing study drug)
- Date of death (if applicable)
- ED visits, hospital readmissions, and use of supplemental oxygen after hospital discharge
- Non-laboratory safety outcomes after hospital discharge and adverse events
- Symptoms of acute respiratory infection
- COVID Ordinal Outcomes Scale

6.3.2 Long-term Follow-up

We will follow-up selected patients at 3, 6, and 12 months to assess vital status, cognition, basic and instrumental activities of daily living, quality of life, employment status, physical disability, and psychological distress (i.e., depression, post-traumatic stress disorder, etc.), place of residence, and rehospitalizations. These assessments may occur by phone, in-person, or videoconferencing.

Follow-up procedures in ORCHID are further specified by the Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease – Brain Outcomes and Psychological Distress (ORCHID-BUD) ancillary study. In summary, ORCHID-BUD will perform a phone battery at 12-months to determine cognition, post-traumatic stress disorder, and depression. In order to determine incident cases of cognitive impairment, post-traumatic stress disorder, and depression, baseline data will be collected from the subject's family member or friend or the subject him/herself. Details of ORCHID-BUD study procedures are described in **Appendix E.**

7. STATISTICAL CONSIDERATIONS

7.1 Statistical Approach

The primary analysis will be an intention-to-treat comparison of the Day 15 COVID Ordinal Outcome score between patients randomized to hydroxychloroquine versus placebo. This analysis will be conducted with a proportional odds model using the Day 15 COVID Ordinal Outcome score as the dependent variable, randomized group assignment as the primary independent variable, and the following co-variables: age, sex, baseline COVID Ordinal Outcome score, baseline SOFA score, and duration of acute respiratory infection symptoms prior to randomization. An odds ratio >1.0 indicates more favorable outcomes with hydroxychloroquine on the COVID Ordinal Outcome scale, while an odds ratio <1.0 indicates more favorable outcomes with placebo.

Patients enrolled prior to implementation of protocol version 2.0 who did not have laboratory confirmed SARS-CoV-2 infection will be included in the primary intention to treat analysis. In additional to reporting data for the full trial population we will also report data separately for patients randomized in the ICU (who tend to be more severely ill) and those randomized outside the ICU (who tend to be less severely ill) as well as those with duration of symptoms ≤5 days prior to randomization and those with >5 days of symptoms prior to randomization.

The anticipated study size is about 510 patients. We calculated the sample size under the assumption that we would have an interim analysis after approximately each 102 patients. We calculated the standard error of the log(odds-ratio) statistic with 51 patients per arm based on data from a recently completed trial within the PETAL Network that enrolled patients early in the course of critical illness, the *Vitamin D to Improve Outcomes by Leveraging Early Treatment* (VIOLET) trial.[35] In the VIOLET trial at Day 15, 11.5% of patients had died, 5.8% were on invasive mechanical ventilation, 22.9% remained in the hospital, and the remaining had been discharged from the hospital (Table 1). We used these outcomes in VIOLET to approximate Day 15 outcomes on the COVID Ordinal Outcome scale that we may observe in this trial.

Table 1. Patient status 14 days ("Day 15") after randomization in the VIOLET trial.[35]

Patient Status	Percentage of patients
Dead	11.5%
Invasive mechanical ventilation	5.8%
Hospitalized, not on invasive mechanical ventilation	21.9%
Discharged from the hospital	60.8%

We plan to use a Bayesian analysis of the evolving data which allows flexibility in the number and timing of the interim analyses. If we determine there is >95% probability of the odds ratio being >1.0, the DSMB should consider stopping the trial for efficacy. If we determine there is >90% probability that the odds ratio is <1.1, the DSMB should consider stopping the trial for futility. If we determine there is >70% probability that the odds ratio is <0.70, the DSMB should consider stopping the trial for harm. We will use a prior odds ratio of 1.0 (equal chance of harm and benefit; mean log OR of 0.0) and a prior distribution of the standard error for its log set at 0.352 for tests of efficacy and a non-informative prior for tests of futility and harm. The results will be reported in a similar manner to those published by Goligher et al.[36] One advantage of Bayesian analysis is that stopping guidelines are not binding and the DSMB is charged with using judgement and data both internal and external to the trial to make any irrevocable decision.

If the trial enrolls 510 participants, further enrollment will be paused until the DSMB reviews data on the primary outcome from all enrolled participants; a decision to continue enrollment will be made by NHLBI after reviewing DSMB recommendations while the investigators remain blinded.

We calculated probabilities that this trial would stop for efficacy or futility based on several fixed scenarios assuming we had an interim analysis after each 102 patients. The probabilities for continuing, stopping for efficacy, and stopping for futility based on a true odds ratio of 1.0 (no difference between the hydroxychloroquine and placebo groups) and 1.8 (substantially better outcomes in the hydroxychloroquine group) are show in Table 2 and Table 3.

Table 2. Probabilities of continuing or stopping the trial before or at the time 510 patients analysed based on a true odds ratio of 1.0 and 1.8.

	Odds Ratio = 1.0 Probability	Odd Ratio = 1.8 Probability
Continue	0.556	0.057
Stop for Efficacy	0.061	0.937
Stop for Futility	0.383	0.007

Table 3. Probabilities of continuing or stopping the trial on or before the n^{th} interim analysis based on a true odds ratio of 1.0 and 1.8.

	Odds Ratio = 1.0				Odds Ratio = 1.8		
Interim Analysis	Continue	Stop for Efficacy	Stop for Futility		Continue	Stop for Efficacy	Stop for Futility
1	0.844	0.006	0.150		0.840	0.154	0.006
2	0.744	0.021	0.235		0.494	0.500	0.007
3	0.667	0.036	0.297		0.254	0.740	0.007
4	0.606	0.0509	0.344		0.122	0.871	0.007
5	0.556	0.061	0.383		0.056	0.937	0.007

To illustrate frequentist properties of these tests, we plotted the p-values at each interim analysis where the interim stopped for futility or efficacy or continued based on an odds ratio of 1.0 (Figure 1) and 1.8 (Figure 2)

FIGURE 1

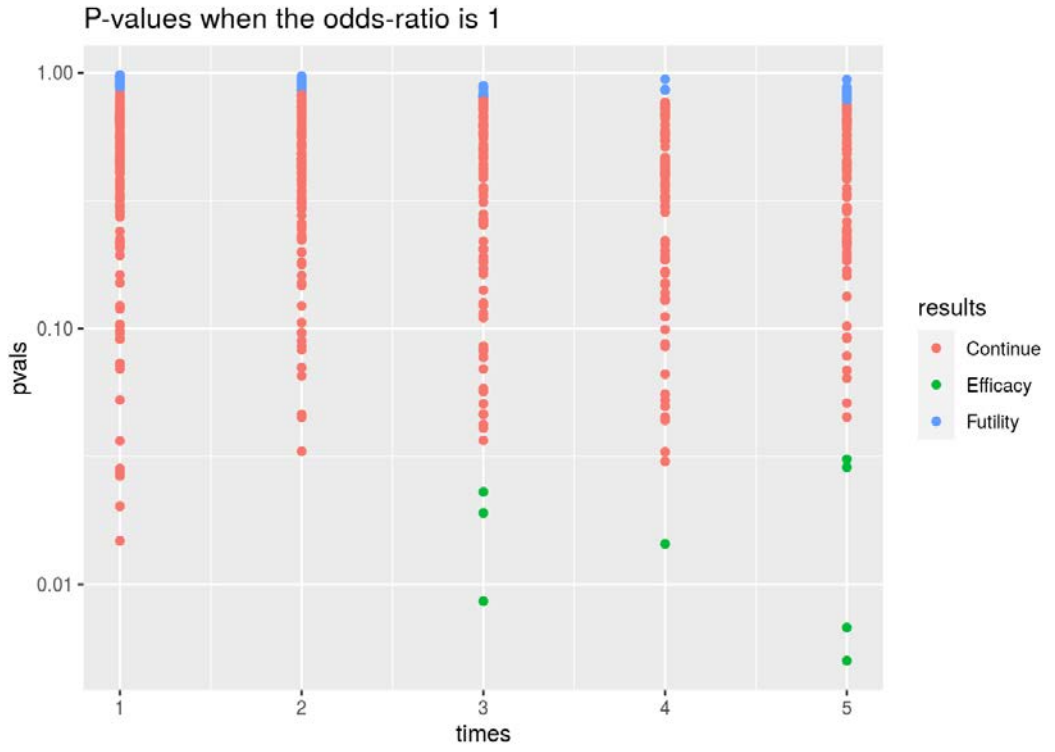
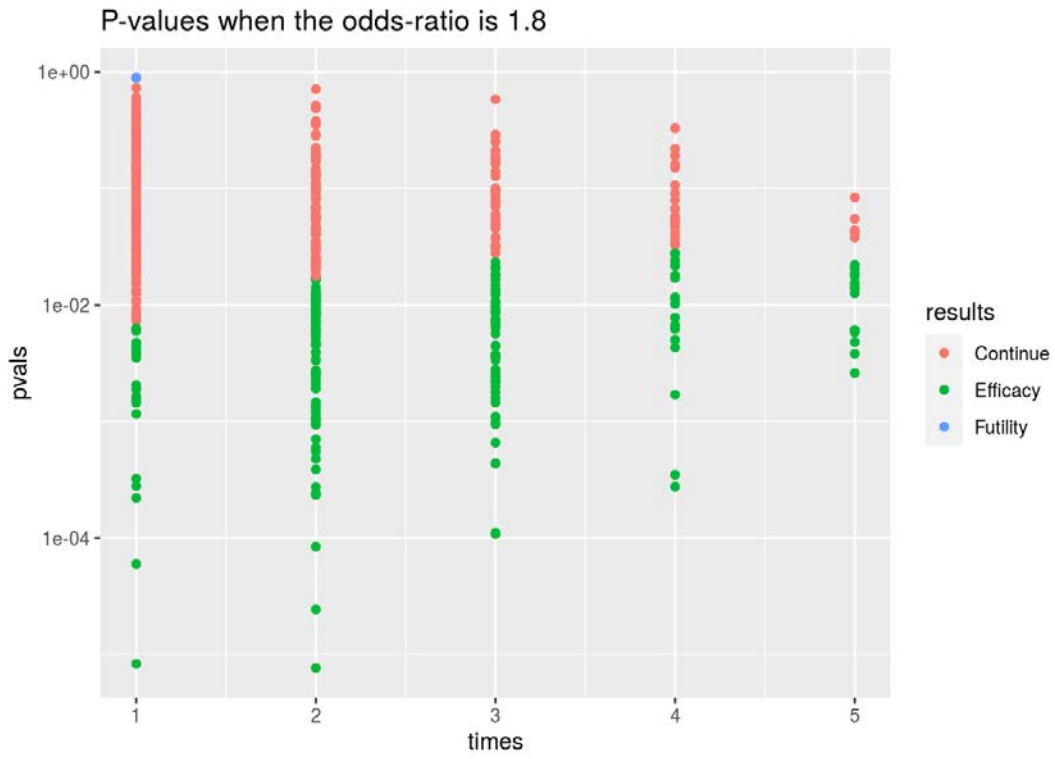


FIGURE 2



7.2 Planned deviations from this design

This trial is being conducted in a rapidly evolving pandemic of a novel disease. Thus, we have developed a statistical plan with flexibility to be modified based on results from other concurrently conducted trials and emerging data on the clinical epidemiology of COVID-19. The primary advantage of a Bayesian monitoring plan is that whenever the trial is stopped the inference only depends on the data and not the original statistical plan that was developed at a time when less was known about COVID-19 and potentially effective treatments.

We suspect multiple trials of hydroxychloroquine for COVID-19 will be conducted simultaneously. We will be receiving reports of completed studies and may be receiving interim reports of ongoing ones as well. We will incorporate this information using Bayesian methods, which allows us to calculate posterior probabilities that use this information.[37] This method weights the external data based on their relevance to the trial we are conducting. In addition, there may be reasons to continue this trial past the 510 patients initially planned. For instance, if the trial reaches the 510 patient interim analysis, the posterior probabilities indicate a reasonable chance of efficacy, and the question of hydroxychloroquine's efficacy is still relevant, the current design can be continued with the same stopping rules.

8. DATA QUALITY MONITORING AND STORAGE

8.1 Data Quality Monitoring

Data quality will be reviewed remotely using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools connecting the online database to statistical software to generate data reports. Patient records and case report forms will also be examined by site personnel for a randomly selected 5-10% sample to evaluate the accuracy and completeness of the data entered into the database and monitor for protocol compliance. The coordinating center will perform remote monitoring of each study site to examine the completeness and accuracy of informed consent documents for study participants, documentation of eligibility criteria, and the completeness of study outcome collection.

8.2 Data Storage

Data will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

9. RISK ASSESSMENT

9.1 Potential Risk to Participants

Although hydroxychloroquine is an FDA approved medication with an established safety profile (described as "among the safest medications used for the treatment of systematic rheumatic disease"),[38]

potential risks exist to participating in this study of hydroxychloroquine versus placebo for the treatment of COVID-19.

9.1.1 Potential risks of receiving hydroxychloroquine

Potential risks of receiving hydroxychloroquine can be classified based on their severity as Major or Minor. Major potential risks of receiving hydroxychloroquine include:

1) Neurological System
   a) Seizure – Hydroxychloroquine can lower the seizure threshold and co-administration of hydroxychloroquine with other medications known to lower the seizure threshold has been reported to increase the risk of seizures. This trial protocol excludes patients with a seizure disorder.
   b) Psychosis – A small number of case reports describe psychosis in patients on long-term treatment with hydroxychloroquine,[39] but has not been described with short-term treatment.
   c) Suicidal behavior - Suicidal behavior has been rarely reported in patients on long-term treatment with hydroxychloroquine for rheumatologic disorders,[40] but not with short-term therapy.
2) Circulatory system
   a) Cardiac arrhythmias
      i) Ventricular arrhythmias and torsades de pointes – Hydroxychloroquine can prolong the QT interval and ventricular arrhythmias and torsades de points have been reported in patients taking hydroxychloroquine. This trial protocol excludes patients with a prolonged QTc on baseline EKG and history of prolonged QTc syndromes, assesses the QTc after receipt of study drug, monitors daily for co-administration of medications that prolong the QTc and specifies criteria for stopping the study drug based on prolonged QTc.
      ii) Cardiomyopathy, sick sinus syndrome, atrioventricular block, or bundle branch block – Cardiomyopathy and conduction system disease have rarely been reported among patients on long-term hydroxychloroquine,[41] but have not been reported among patients receiving less than 3 months of therapy.
3) Digestive system
   a) Liver injury – Fulminant hepatic failure has been reported in at least two cases from long-term administration of hydroxychloroquine.[42] Porphyria cutanea tarda appears to be a risk factor for liver injury from hydroxychloroquine. This trial protocol excludes patients with porphyria cutanea tarda.
   b) Increased cyclosporine or digoxin levels – hydroxychloroquine can increase levels of cyclosporine or digoxin for patients being co-administered these medications. This trial protocol monitors daily for receipt of medications that interact with hydroxychloroquine and notifies treating clinicians about potential medication interactions.
4) Endocrine system
   a) Symptomatic hypoglycemia – hydroxychloroquine can increase risk of hypoglycemia, especially when co-administered with antidiabetic agents, although this is rarely observed in clinical practice.[43]
5) Integumentary system
   a) Severe dermatologic reactions – A mild dermatologic reaction occurs in approximately 10 percent of patients treated with hydroxychloroquine, but severe dermatologic reactions such as Steven’s

Johnson Syndrome or Toxic Epidermal Necrolysis are rare. For example, in one recent case series of patients on hydroxychloroquine with dermatologic reactions, none of the reported reactions were severe.[44]

6) Hematological system
   a) Neutropenic, leukopenia, anemia, thrombocytopenia – Rare toxicities of hydroxychloroquine include agranulocytosis[45] and aplastic anemia, but there has never been a report of this occurring with hydroxychloroquine in doses less than 7 mg/kg/day or during short-term use.

Minor potential risks of receiving hydroxychloroquine include: retinopathy or corneal deposits (with months-to-years of therapy); vertigo, tinnitus, or deafness; headache; light-headedness; insomnia; tremor or dyskinesia; peripheral neuropathy (with months-to-years of therapy); nausea, vomiting, or diarrhea; mild dermatologic reaction; and muscle weakness (with months-to-years of therapy).

9.1.2 Potential risks of receiving placebo with COVID-19

One potential risk to participating in this study is receiving placebo rather than hydroxychloroquine. This risk is only relevant if hydroxychloroquine is ultimately found to be an effective therapy for COVID-19 and is not relevant if hydroxychloroquine is ultimately found to be an ineffective therapy for COVID-19. This trial protocol minimizes this risk through rigorous design to minimize the number of patients who must be enrolled to determine whether hydroxychloroquine is an effective therapy for COVID-19, excluding patients who decline to participate because they feel their optimal care requires hydroxychloroquine, excluding patients whose treating clinicians declines to allow enrollment because they feel the patient's optimal care requires treatment with hydroxychloroquine, and specifying procedures for stopping the study drug, unblinding, and allowing open-label administration of hydroxychloroquine for patients who experience clinical deterioration during the study period.

9.1.3 Potential risks of receiving an EKG.

EKGs are a safe, noninvasive, painless test and have no major risks. Patients may develop a mild rash or skin irritation where the electrodes were attached. If any paste or gel was used to attach the electrodes, patients may have an allergic reaction to it. This irritation usually goes away once the patches are removed, without requiring treatment.

9.2 Minimization of Risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with sound research design. This trial protocol incorporates numerous design elements to minimize risk to patients that meet this human subject protection requirement. Hydroxychloroquine has been approved by the Food and Drug Administration and has been used in clinical practice for decades in a number of patient populations with an established safety profile. The dose and route of administration of hydroxychloroquine in this trial are comparable to the dose and route of administration approved for the treatment of other acute infections, such as malaria. The duration of treatment in this trial of 5 days is significantly shorter than for treatment of rheumatologic conditions, for which the drug is frequently administered for multiple years. To further mitigate risk, we will exclude patients with specific risk factors for adverse events from hydroxychloroquine including patients with prolonged QTc, patients receiving medications that may interact with hydroxychloroquine to prolong the QTc, patients with seizure disorder, and patients with porphyria cutanea tarda. The trial protocol includes

on-study monitoring to minimize the risk to patients during therapy. This monitoring includes assessment of QTc after receipt of study drug with specific criteria at which the study drug would be stopped. This monitoring also includes both automated electronic health record and manual study personnel review for medications with potential interactions with hydroxychloroquine during the 5-day study period. The trial protocol includes monitoring of adverse events, clinical outcomes, and interim analyses by an independent data and safety monitoring board empowered to stop or modify the trial at any time.

9.3 Potential Benefit

Study participants may or may not receive any direct benefits from their participation in this study. Administration of hydroxychloroquine may improve clinical outcomes among adults hospitalized for COVID-19 infection.

9.4 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. Hydroxychloroquine has been used in clinical practice for decades and previously evaluated for the treatment of patients acutely ill from infection with substantial data to support its safety and potential efficacy.

10. HUMAN SUBJECTS PROTECTIONS

Each study participant or a LAR must sign and date an informed consent form. Approval of the central institutional review board will be required before any participant is entered into the study.

10.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The emergency departments, hospital wards, and ICUs of participating sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine clinical care of the patient will be reviewed to determine eligibility. If any patient meets criteria for study enrollment, then the attending physician responsible for his or her care will be asked for permission to approach the patient or his or her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of participants conforms to the principle of distributive justice.

10.2 Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of hydroxychloroquine for the treatment of patients with COVID-19 who are at high risk for respiratory failure and mortality. Due to the nature of this patient population, many of these patients will have impaired decision-making capabilities. Moreover, those with intact decision-making capacities probably have milder disease than those with impaired capacity. Therefore, the validity of the study and its generalizability to severely ill patients would be compromised by enrolling only those participants with retained decision-making capacity.

Hence, participants recruited for this trial are not being unfairly burdened with involvement in this research.

10.3 Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each patient or the patient's LAR. Study personnel obtaining informed consent are responsible for ensuring that the patient or LAR understands the risks and benefits of participating in the study, answering any questions the patient or LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's or LAR's willingness to permit the patient's continued participation in the trial. The study personnel obtaining informed consent will make every effort to minimize coercion. All patients or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the patient or LAR in simple terms before the patient is entered into the study, and to confirm that the patient or LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each patient or LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including administration of study agent.

For additional details, see Section 3.

10.4 Continuing Consent

Patients for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained. The process for obtaining consent from these patients will be the same as that outlined in section 3.

10.5 Withdrawal of Consent

Participating patients may withdraw or be withdrawn (by the LAR, treating physician, or investigator) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use data has also been withdrawn. Withdrawal of consent prior to receipt of study drug will constitute a screen-failure and will be recorded. Withdrawal of consent after randomization and administration of one or more doses of study drug will lead to discontinuation of study interventions but site staff will request access to medical records for data related to the trial.

10.6 Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will have impaired decision-making capacity due to critical illness and will not be able to provide informed consent. Accordingly, informed consent will be sought from the patient's LAR.

Regarding consent from the LAR, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally

authorized representative"; and defines at 45 CFR 46 102 (c) a LAR as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for participant participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the central IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential participant who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.[46] Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study

10.7 Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. One method that serves to protect patients is restrictions on the participation of patients in research that presents greater than minimal risk. Commentators and research ethics commissions have held the view that it is permissible to include incapable participants in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.[47] Several U.S. task forces have deemed it permissible to include incapable participants in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable participants only "if the net additional risks of participation are not substantially greater than the risks of standard treatment".[48] Finally, NBAC stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the participant, provided that "the potential subject's LAR gives permission…".[46]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable participant in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is similar to that available in the clinical setting.

10.8 Additional Safeguards for Vulnerable Participants

The present research will involve participants who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these participants. Such safeguards might include but are not limited to: a) assessment of the potential participant's capacity to provide informed consent, and b) the availability of the LAR to monitor the participant's subsequent participation and withdrawal from the study. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

10.9 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered directly into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated. Further, tools within the secure online database will be used so that only the coordinating center and investigators from the enrolling site will have access to data from participants enrolled at that site.

11. ADVERSE EVENTS

Assuring patient safety is an essential component of this protocol. Hydroxychloroquine has been approved by the Food and Drug Administration and used in clinical practice for decades with an established safety profile. Use of hydroxychloroquine for the treatment of acute respiratory infection due to COVID-19, however, raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events with receipt of hydroxychloroquine;
2. Proactive education of treating clinicians regarding medication interactions relevant to use of hydroxychloroquine in the inpatient setting;
3. On-study monitoring of co-interventions (e.g., medications) and patient characteristics (e.g., EKG) to intervene before adverse events occur;
4. Systematic collection of safety outcomes relevant to use of hydroxychloroquine in this setting;
5. Structured reporting of adverse events

11.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

Serious Adverse Event: A serious adverse event is any adverse event that results in one of the outcomes listed in section 11.3 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a

causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

11.2 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will determine daily if any adverse events occur during the period from enrollment through **study day 7** (48 hours after completion of the study drug) or hospital discharge, whichever occurs first and will determine if such adverse events are reportable. Thereafter, adverse events are not required to be reported unless the investigator feels the adverse event was related to study drug or study procedures.

The following adverse events will be considered reportable and thus collected in the adverse event case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship (Appendix C)
- Events leading to permanent discontinuation of study drug

Study-specific clinical outcomes (Primary, Secondary and Safety Outcomes and Assessments During the Study), including serious outcomes such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix C.

After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the CCC their assessment of the potential relatedness of each adverse event to the study drug or protocol procedure via electronic data entry. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on the criteria outlined in Appendix C. Investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the study protocol and the investigator brochure for Hydroxychloroquine. Investigators will also determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must also report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

11.3 Serious Adverse Events

Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event after consent, but prior to randomization or starting study procedures, the event will NOT be collected. Study site personnel must alert the CCC of any **serious and**

study procedure related adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix C for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs)

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Persistent or significant disability/incapacity

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected during the first **7 study days** or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation.

12. Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of participants in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and NHLBI with respect to:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

The NHLBI PETAL Network DSMB is appointed by the Director of the NHLBI and makes recommendations to the Director. The DSMB reviews all protocols for safety following review by an

independent NHLBI Protocol Review Committee. The DSMB will consist of members with expertise in acute lung injury, emergency medicine, biostatistics, ethics, and clinical trials. An NHLBI staff member not associated with PETAL will serve as Executive Secretary. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and the Medical Monitor of the CCC will be responsible for the preparation of all DSMB and adverse event reports and may review unblinded data. The DSMB will develop a charter and review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the CCC. When appropriate, conference calls may be held in place of face-to-face meetings. Recommendations to end, modify, or continue the trial will be prepared by the DSMB executive secretary for review by the NHLBI Director. Recommendations for major changes, such as stopping the trial, will be reviewed by the NHLBI Director and communicated immediately. Other recommendations will be reviewed by the NHLBI director and distributed in writing to the CCC, which will distribute to the PETAL steering committee with instructions for reporting to local IRBs when appropriate.

Details of the NHLBI policies regarding DSMBs can be found at the following URL:

https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-data-and-safety-monitoring-extramural-clinical-studies

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14. APPENDICES

Appendix A. Schedule of Events

Study Activity	Pre-Enrollment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 29	3 Months	6 Months	12 Months
Eligibility assessment	X											
EKG	X		X[a]									
Pregnancy test (if applicable)	X											
Informed consent	X											
Demographic and baseline variable collection		X										
Randomization		X										
Study drug delivery		X	X	X	X	X						
Assessment for study drug adherence		X	X[a]	X[a]	X[a]	X[a]	X[b]					
Safety monitoring for adverse events		X	X[a]	X[a]	X[a]	X[a]	X[b]	X[b]	X[b]			
Assessment of COVID ordinal outcome score	X		X[a]	X[a]	X[a]	X[a]	X[b]	X[b]	X[b]			
Mortality assessment								X[b]	X[b]			
28-day in-hospital outcomes (chart review)									X			
Long-term outcomes										X[c]	X[c]	X[c]

a. Assessed only if patient remains hospitalized.
b. Assessed by telephone follow-up if the patient has been discharged.
c. Assessed in selected patients in-person, or by telephone or videophone.

Appendix B. Potential medication interactions with hydroxychloroquine

A. Medications considered contraindicated, which if ordered on an inpatient during the 5-day study period will prompt study personnel to discuss with treating clinicians whether stopping the study drug is appropriate or if this medication cannot be stopped or substituted: amiodarone; chloroquine; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol.

B. Medications considered to present a potential interaction with hydroxychloroquine, which if ordered on an inpatient during the 5-day study period, will prompt study personnel to discuss with treating clinicians the risk-benefit assessment of this medication and potential need for additional monitoring: ampicillin, antacids, cyclosporine, digoxin, flecainide, mefloquine, methotrexate, mexilitine, rifampicin, rifapentine.

Appendix C: Adverse Event Reporting and Unanticipated Events

As noted in section 11, investigators will report all "serious adverse events," defined as adverse events that are serious and have a reasonable possibility that the event was due to a study drug or procedure (or of uncertain relatedness), to the CCC within 24 hours. The CCC will then notify the NHLBI and Central Institutional Review Board (cIRB).

The Medical Monitor at the CCC will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study drug or study procedure, as outlined in 21 CFR 312.32**(a)**(1), and below. The Medical Monitor will be unblinded and will also determine if the event is unexpected for hydroxychloroquine. An adverse is considered "unexpected" if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The CCC will report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB, NHLBI, and cIRB within 7 days after receipt of the report from a clinical site. A written report will be sent to the NHLBI, DSMB, FDA, and the cIRB within 15 calendar days. The DSMB will also review all reported adverse events and clinical outcomes during scheduled interim analyses. The CCC will distribute the written summary of the DSMB's periodic review of reported adverse events to the cIRB in accordance with NIH guidelines (http://grants.nih.gov/grants/guide/notice-files/not99-107.html). The Medical Monitor will provide to Sandoz Pharmacovigilance any significant safety findings (without disclosing protected health information) during the conduct of the trial.

C.1. Unanticipated Problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

C.2. Determining Relationship of Adverse Events to Study Drug or Study Procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study drug or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

C.3. Clinical Outcomes that may be Exempt from Adverse Event Reporting

Study-specific outcomes of acute respiratory infection, COVID-19, and critical illness will be systematically collected for all patients in both study group and are exempt from adverse event reporting unless the investigator considers the event to be Definitely or Possibly Related (or of an Uncertain Relationship) to the study drug or study procedures. Examples of study-specific clinical outcomes include:

- Death not related to the study procedures
- Neurological events
    - Seizure
- Cardiovascular events
    - Receipt of vasopressors
    - Atrial or ventricular arrhythmia
    - Cardiac arrest
- Respiratory events
    - Hypoxemia requiring supplemental oxygen
    - Acute respiratory distress syndrome
    - Receipt of mechanical ventilation
    - Receipt of extra-corporeal membrane oxygenation
- Gastrointestinal events
    - Elevation of aspartate aminotransferase or alanine aminotransferase
    - Acute pancreatitis
- Renal events
    - Acute kidney injury
    - Receipt of renal replacement therapy
- Endocrine events
    - Symptomatic hypoglycemia
- Hematologic or coagulation events
    - Neutropenia, lymphopenia, anemia, or thrombocytopenia
- Dermatologic events
    - Severe dermatologic reaction (e.g., Steven's Johnson Syndrome)

Note: A study-specific clinical outcome may also qualify as a reportable adverse event. For example, a ventricular arrhythmia that the investigator considers Definitely or Possibly Related to the study drug would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely or Possibly Related Adverse Event.

C.4. Decision tree for determining if an adverse event is reportable

Figure 1. Decision tree for determining if an adverse event is reportable

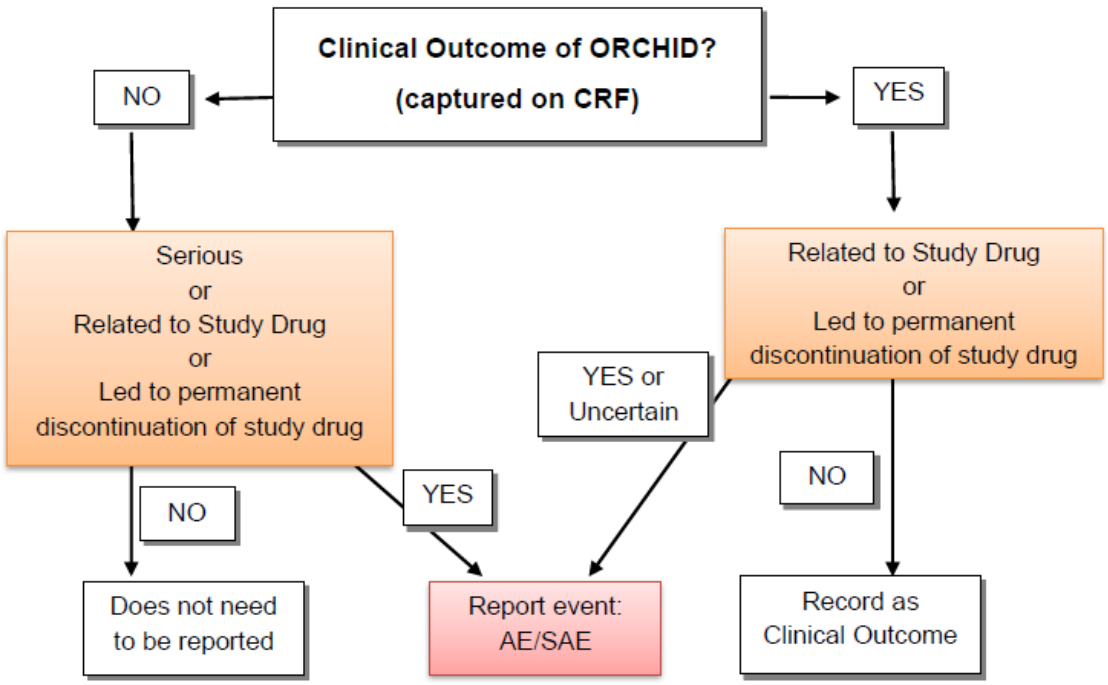

Figure adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. PMID: 22616830.

Appendix D. Public Readiness and Emergency Preparedness Act

This study is being conducted to determine whether hydroxychloroquine can safely and effectively be used to mitigate, treat, or cure COVID-19 or limit the harm of the COVID-19 pandemic in accordance with the Secretary of the Department of Health and Human Services' (HHS's) Declaration under the Public Readiness and Emergency Preparedness Act for medical countermeasures against COVID-19 (COVID-19 Declaration) effective February 4, 2020. The purpose of this study is to test if hydroxychloroquine results in clinical benefit in patients hospitalized with COVID- 19.

Hydroxychloroquine has been approved by the FDA for other uses and its investigational use for COVID-19 in this study has been exempted by the FDA from investigational new drug application requirements pursuant to 21 CFR 312.2(b)(1). This study is conducted under a Research Project Cooperative Agreement with the National Heart, Lung, and Blood Institute.

Appendix E: ORCHID-BUD Ancillary Study Protocol

1. Title: **O**utcomes **R**elated to **C**OV**ID**-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease – **B**rain **O**utcomes and Psychological **D**istress (**ORCHID-BUD**)
2. Objective:
   - Aim 1: To determine (a) the epidemiology (i.e., prevalence) of cognitive impairment (i.e., acquired-Alzheimer's Disease and Related Dementia [ADRD]) characterized by impairments in memory, attention, language, reasoning, and executive function at 12-months in adults hospitalized with COVID-19 infection, and (b) if hydroxychloroquine administration is associated with improvement in these same outcomes.
   - Aim 2: To determine (a) the epidemiology of post-traumatic stress disorder (PTSD) and depression at 12-months in adults who are hospitalized with COVID-19 infection, and (b) if hydroxychloroquine administration is associated with improvement in these same outcomes.
   - Aim 3: To identify modifiable risk factors (e.g., sedatives, isolation, intravenous fluids, antibiotics, pressor, angiotensin-converting enzyme [ACE]-inhibitor or angiotensin II receptor blocker [ARB] use, etc.) associated with worse long-term cognitive impairment, PTSD, and depression at 12 months in adults hospitalized with COVID-19 infection.
3. Hypothesis: The primary hypothesis of this proposal is that (a) COVID-19 survivors will have a high burden of ADRD, PTSD, and depression. The secondary hypothesis is that hydroxychloroquine will lower the burden of these three outcomes as compared to placebo.
4. Study Design: ORCHID-BUD will assess 12-month cognition, PTSD, and depression using a comprehensive phone battery in all patients enrolled in ORCHID since the beginning of the study (March 2020). ORCHID-BUD essentially expands and better defines the ORCHID's follow-up study procedures that are already described its study protocol (ORCHID protocol Version 1.1, Section 6.3.2, and page 22):"We will follow-up selected patients at 3, 6, and 12 months to assess vital status, cognition, basic and instrumental activities of daily living, quality of life, employment status, physical disability, and psychological distress (i.e., depression, post-traumatic stress disorder, etc.), place of residence, and rehospitalizations. These assessments may occur by phone, in-person, or videoconferencing." In anticipation of ORCHID-BUD, the ORCHID parent study has already added language to the informed consent document to conduct the proposed study procedures, including the baseline phone interview with the patient and family member:

Study Procedure 6: Follow-up Phone Calls	
Timing	Around Day 7, Day 15, and Day 28 if you have been discharged from the hospital before those times. **Long-term Follow-up** 3, 6, and 12 months
Explanation	A study team member will call you and/or a family member for follow-up information about how you are doing and if you have had any problems that might be due to the study medication. We may also contact you at 3, 6, and 12 months to see how you are doing. We may ask you do some tasks to see how your brain is working. For example, we may ask you to repeat a list of numbers or name many words that start with the letter "P". We may also ask you questions about your health, ability to do common daily activities, employment status, quality of life, and how you are feeling. These assessments may be done over the phone, in-person, or videoconferencing. **We will confidentially and securely** collect your medical record number and personal information, so we can stay in contact with you.
Risks or Discomforts	You may find the phone calls and questions inconvenient.

Therefore, the ORCHID-BUD study activities will be considered part of the ORCHID parent study activities, and separate informed consent will not be performed.

5. Study procedures:

5.1 Baseline data collection study procedures

For ORCHID-BUD, we will contact the surrogate approximately 3-months (+/- 2 months) after hospital discharge in order to establish baseline cognition, PTSD, and depression. We will contact the surrogate listed on ORCHID by their preferred method of contact (phone, text message, or e-mail).

For the family member, we will administer the short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) establish the subject's baseline cognition; this 16-item questionnaire takes less than 5 minutes to complete. We will also ask the surrogate if they thought the patient was more confused than usual during hospitalization. We will also conduct the FAM-CAM and SQiD, which are informant-based delirium assessments, to further characterize delirium during hospitalization. We will ask them to estimate the number of days they felt the patient was confused. We will also ask if they (or any family members) were able to visit the patient in person, by phone, or by mobile device. We will also ask them to estimate the number of days the subject was hospitalized for and if applicable, duration of ICU length of stay and mechanical ventilation. We will also ask if the surrogate whether or not the subject has baseline dementia, PTSD, or depression. We will also ask about the subject's race, ethnicity, age, level of education, highest occupation, and region of residence. These data will be obtained over the phone, but the family member will have the option to complete the surveys via an online REDCap survey if preferred.

If no surrogate is listed for ORCHID, we will contact the patient by their preferred method of contact (phone, text message, or e-mail). If the surrogate is available, we obtain the surrogate's contact information. For the patient, we will administer the IQCODE and ask if they have baseline dementia, PTSD, or depression. We will also ask if they were on cholinesterase inhibitors before they were hospitalized for COVID-19. We will also ask their race, ethnicity, age, level of education, highest occupation, and region of residence. We will ask patients some questions about their hospitalization. We will also ask how long they were hospitalized, how long were they in the ICU, and how long they were mechanically ventilated. These questions may be answered by their family member or caregiver if requested. We will also ask patients if they felt confused, disoriented, or had hallucinations during hospitalization. We will ask them to estimate the number of days during the hospitalization they felt they had these symptoms. We will also ask how much contact family and friends had with the patient during hospitalization and if the contact was in person, by video conferencing, or by phone. We will also ask about the subject's race, ethnicity, age, level of education, highest occupation, and region of residence. These data will be obtained over the phone, but the subject will have the option to complete the surveys via an online REDCap survey if preferred.

After the conversation has concluded, we will let them know that we will contact them approximately 12-months (+/- 3 months) after randomization to assess their cognition and psychological well-being using a phone battery. We will also let them know that we will give them a gift card after they complete the 12-month phone call.

5.2 Twelve-month study procedures

The CIBS Center will then contact enroll subjects at approximately 12-months (+/- 3 months). We will perform the phone battery as described in the **Primary Endpoints (Section 10) and Secondary Endpoints (Section 11)** section. Any data not obtained during the baseline phone call will be obtained during the 12-month phone call to minimize missing data. After the 12-month follow-up is completed, patients will be given a gift card.

It is possible that ORCHID-BUD patients will be co-enrolled with other PETAL network COVID-19 trials (e.g., BLUE CORAL) who are conducting long-term follow-ups. We may coordinate with the University of Washington and University of Michigan study teams to streamline data collection and minimize overburdening the patient.

5.3 Medical Record Review

We will use electronic medical records, in whatever institutions make this this available, to obtain detailed data regarding these potentially modifiable risk factors. Specifically, we will evaluate how modifiable risk factors such as the use of sedative medications and oxygen therapy, mechanical ventilation settings, social isolation, ventilator weaning protocols, intravenous fluid administration, antibiotics, medications such as ACE-inhibitors, ARBs, antacids, and pressors affect the 12-month outcomes.

6. Risks: Because ORCHID-BUD is only adding a comprehensive phone battery at 12-months, its risks are minimal:

6.1 Fatigue or distress: For ORCHID-BUD specifically, subjects will undergo a comprehensive phone battery at 12-months that can take up to 45 to 60 minutes to perform. There is a small risk that the patient may become fatigued or distressed during the study's cognitive assessments.

6.2 Confidentiality: Because patient identifiers are accessed throughout all phases of the study, there is a small risk of loss of patient confidentiality.

7. Inclusion Criteria: : All patients enrolled in ORCHID will be included.

8. Exclusion Criteria: ORCHID-BUD will exclude patients who are:

(1) non-English or non-Spanish speaking,
(2) deaf, or
(3) non-verbal or unable to follow simple commands prior to the COVID-19 illness.

We will exclude non-English and Non-Spanish speaking patients because our neuropsychological raters can only provide their assessments in these languages. We will also exclude patients who are non-verbal or unable to follow simple commands prior to the COVID-19 illness to exclude patients with end-stage dementia.

9. Randomization and Study Initiation Time Window: The ORCHID-BUD ancillary study will enroll patients from ORCHID parent study. ORCHID-BUD study activities will the subject and/or surrogates approximately one to three months after ORCHID randomization. At approximately 12-months (+/- 3 months) after randomization, we will call the patients and conduct the phone battery to assess cognition, PTSD, and depression.

10. Primary Endpoint

	Assessment	Domain	Description
Cognition	Telephone Montreal Cognitive Assessment	Global Cognition	Measure of global cognition and assesses attention concentration, memory, language, conceptual thinking, calculations, and orientation.
	WAIS-IV Digit Span[3]	Attention	Subject repeats a string of numbers forwards, backwards, and ascending order
	Hayling test[4]	Executive Function	It consists of two sets of 15 sentences; the examiner reads the questions aloud and subject completes the sentences
	DKEFS Verbal Fluency[5]	Language	Subject is asked to name as many animals they can think of 60 seconds and as many words that begin with the letter "F", "A", and "S" over 60 seconds
	Paragraph Recall - Immediate[6]	Immediate Memory	Subject is read a paragraph and then recalls the paragraph immediately
	Paragraph Recall - Delayed[6]	Delayed Memory	Subject recalls the paragraph memorized from the immediate memory task 15 to 20 minutes later
	WAIS-IV Similarities[3]	Reasoning/Verbal Abstraction	Subject is given two words and then is asked how they are alike
	DKEFS Proverbs[5]	Reasoning/Verbal Abstraction	Subject is asked to interpret 5 proverbs
Psychological	Hospital Anxiety and Depression Scale [7]	Depression	Multiple-choice inventory that is used for measuring the severity of depression
	PTSD Checklist for the DSM-V (PCL-5)[8]	PTSD	Multiple-choice questions reflecting DSM-IV symptoms of PTSD. Subjects with a score of > 35 will receive a formal assessment performed over the phone by a clinical psychologist using the CAPS-5

Table 1. Telephone Battery to assess cognitive, psychological, and functional outcomes. WAIS-IV, Wechsler Adult Intelligence Scale-IV; DKEFS, Delis–Kaplan Executive Function System; PTSD, Post-Traumatic Stress Disorder; Clinician Administered PTSD Scale for the DSM-5 (CAPS-5).

11. Secondary Endpoint: We will also record 12-month mortality and place of residence. We will also ask the number of times the patient was re-hospitalized since the index hospitalization.

12. Sample Size / Interim Monitoring

All patients enrolled in the ORCHID parent study will be screened for ORCHID-BUD. ORCHID will enroll 460 patients who are hospitalized with COVID-19. We estimate that 70% will survive and of these, 93% will meet ORCHID-BUD's eligibility criteria. We estimate that we will

successfully complete the phone battery in 90% of eligible patients providing 270 patients for ORCHID-BUD's analysis.

Appendix E: References

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