Rationale and Design of ORCHID: A Randomized Placebo-Controlled Trial of Hydroxychloroquine for Adults Hospitalized with COVID-19

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Abstract

The Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID) trial is a multicenter, blinded, randomized trial of hydroxychloroquine versus placebo for the treatment of adults hospitalized with COVID-19. This document provides the rationale and background for the trial and highlights key design features. We discuss five novel challenges to the design and conduct of a large, multi-center, randomized trial during a pandemic, including: 1) widespread, off-label use of the study drug before the availability of safety and efficacy data; 2) the need to adapt traditional procedures for documentation of informed consent during an infectious pandemic; 3) developing a flexible and robust Bayesian analysis incorporating significant uncertainty about the disease, outcomes, and treatment; 4) obtaining indistinguishable drug and placebo without delaying enrollment; and 5) rapidly obtaining administrative and regulatory approvals. Our goals in describing how the ORCHID trial progressed from study conception to enrollment of the first patient in 15 days are to inform the development of other high-quality, multi-center trials targeting COVID-19. We describe lessons learned to improve the efficiency of future clinical trials, particularly in the setting of pandemics. The ORCHID trial will provide high-quality, clinically relevant data on the safety and efficacy of hydroxychloroquine for the treatment of COVID-19 among hospitalized adults. This trial was registered with ClinicalTrials.gov (NCT04332991) prior to enrollment of the first patient on April 2, 2020.

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Coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) (1). While most adults with COVID-19 recover after a mild course (2, 3), a minority develop pneumonia and hypoxemic respiratory failure requiring hospitalization. Severe illness may progress to acute respiratory distress syndrome (ARDS) and death (1, 2, 4). Hydroxychloroquine has generated substantial interest as a potential treatment for COVID-19 due to its widespread availability, antiviral and immunomodulatory activity, and established safety profile from historical use for other indications (5, 6).

Hydroxychloroquine is approved by the United States (US) Food and Drug Administration (FDA) as an antiparasitic agent for malaria and an immunomodulatory agent for rheumatologic diseases (7–9). In vitro, hydroxychloroquine limits entry of SARS-CoV-2 into cells by inhibiting glycosylation of cell receptors targeted by coronaviruses, interfering with proteolytic processing, and increasing endosomal pH to limit endosome-mediated viral entry and late stage viral replication (5, 6, 10–14). Further, hydroxychloroquine reduces the production of several pro-inflammatory cytokines potentially involved in the development of ARDS among those infected with SARS-CoV-2 (8, 9, 15).

Based on these mechanisms of action and clinical experience early in the pandemic, hydroxychloroquine is being widely used off-label as a treatment for COVID-19 in routine clinical care (16). Hydroxychloroquine has been adopted into treatment guidelines for COVID-19 in China (17) and some US hospitals (18–20). Interim guidance from an International Task Force for the American Thoracic Society suggested administering hydroxychloroquine to hospitalized COVID-19 patients with pneumonia (21). On March 28, 2020, the FDA issued an emergency use authorization (EUA) to allow use of hydroxychloroquine from the Strategic

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National Stockpile to treat COVID-19 patients hospitalized in the US when enrollment in a clinical trial is not feasible (22).

Despite widespread use and rapid incorporation into treatment guidelines, data informing the efficacy and safety of hydroxychloroquine as a treatment of COVID-19 remain very limited. In a small case series, hydroxychloroquine may have been associated with more rapid viral clearance (23). In a 62-patient randomized trial, hydroxychloroquine may have shortened the duration of fever and cough (24). In other studies, however, hydroxychloroquine failed to improve viral clearance or clinical endpoints (25, 26). In an observational study of 1,446 patients hospitalized at New York–Presbyterian Hospital with COVID-19, use of hydroxychloroquine was not associated with improved outcomes (27). Results from an international registry including over 96,000 adults hospitalized with COVID-19 suggested that hydroxychloroquine may be associated with harm, but the ability to control for indication bias was extremely limited (28). Recently, concerns have been raised regarding QT prolongation and arrhythmias associated with hydroxychloroquine use, particularly among patients receiving high doses of chloroquine or hydroxychloroquine in combination with other QT-prolonging medications (29, 30).

On April 21, 2020, the US National Institutes of Health posted COVID-19 treatment guidelines stating there are insufficient clinical data to recommend either for or against the use of hydroxychloroquine (31). In COVID-19 treatment guidelines published April 11, 2020, the Infectious Disease Society of America recommended hydroxychloroquine be used within the context of a clinical trial and called for additional high-quality clinical trial data on the safety

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and efficacy of hydroxychloroquine as a treatment for COVID-19 among hospitalized patients (32).

Given the urgent need for effective therapies for COVID-19 and the public health imperative to evaluate an unproven treatment being broadly administered to patients, we designed the Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID) trial.

Methods

Trial methods are summarized in Tables 1-3 with the following sections providing additional context. The complete protocol, the SPIRIT checklist, and a schedule of enrollment, interventions, and assessments are provided in the Supplementary Appendix (33).

Trial Design

The ORCHID trial is a patient-level, parallel-group, blinded, randomized clinical trial evaluating the superiority of hydroxychloroquine compared to placebo. The trial aims to enroll patients early after hospital presentation, screening in emergency departments (EDs), inpatient floors, and intensive care units (ICUs) of participating hospitals. The trial protocol was approved by the single institutional review board (sIRB) at Vanderbilt University Medical Center and is being conducted with an exception from Investigational New Drug (IND) application requirements. An independent Data and Safety Monitoring Board (DSMB) is monitoring the trial.

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Study Sites

The ORCHID trial is being conducted by the National Heart, Lung and Blood Institute (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network. The PETAL Network consists of acute care and critical care researchers at more than 50 enrolling centers dedicated to conducting randomized trials to treat patients with or at risk for ARDS (additional details in Supplementary Appendix) (34, 35). Massachusetts General Hospital serves as the coordinating center for the PETAL Clinical Trials Network.

Population

The trial includes hospitalized adults with laboratory-confirmed SARS-CoV-2 and symptoms of acute respiratory infection. Given delays in SARS-CoV-2 testing early in the pandemic, the trial initially included hospitalized patients with suspected or confirmed SARS-CoV-2 infection, but as testing capabilities improved, the inclusion criteria were narrowed on April 21, 2020 to include only laboratory-confirmed cases. Key exclusion criteria are: QTc interval >500 milliseconds, history of long QT syndrome, seizure disorder, respiratory symptoms for more than 10 days, hospitalization for greater than 48 hours, and receipt of medications that may adversely interact with hydroxychloroquine. A complete list of exclusion criteria is presented in Table 1.

Justification for ORCHID Trial Population

Eligibility criteria focusing on hospitalization and duration of symptoms are intended to target a population that is at high risk of poor clinical outcomes while still being in the acute phases of illness where viral replication may still play a pathophysiologic role. Remaining exclusion criteria

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serve to protect vulnerable populations (e.g., prisoners) and exclude patients for whom receipt of hydroxychloroquine might increase the risk of serious adverse events (e.g., patients with a prolonged QTc or seizure disorder). Pregnant women are excluded from ORCHID because 1) hydroxychloroquine crosses the placental barrier, 2) while hydroxychloroquine is sometimes used in pregnancy for malaria and rheumatologic conditions, there is known clinical efficacy for those conditions but not for COVID-19, 3) the trial would not enroll a sufficiently large number of pregnant women to be able to draw meaningful conclusions, and 4) the drug is available outside of the clinical trial if there are particular pregnant patients for whom a clinician believes the potential benefits outweigh potential risks.

Process of Informed Consent during a Pandemic

Conducting clinical research in the setting of a pandemic infection presents unique challenges. Bringing a paper consent form and pen to the bedside of a patient with COVID-19 and then taking these out of the room would violate infection prevention principles and policies. Further, face-to-face interaction between patients and research personnel would expend valuable personal protective equipment (PPE), which has limited availability in many areas of the US. Finally, legally authorized representatives (LARs) are often prohibited from in-person visits. Following guidance from FDA and OHRP, the ORCHID trial therefore documents the completion of written informed consent from the patient or LAR using “no-touch” procedures (36). These include (1) electronic consent using a study device approved to store protected health information or the patient’s or LAR’s own smart phone with signatures uploaded directly to an electronic database, (2) paper-based consent with photographic documentation of signature

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pages, and (3) when the prior two are not feasible, signed attestation by study staff and an impartial witness that the patient reviewed and signed the paper informed consent document (details in Supplementary Appendix).

Randomization and Blinding

Patients are randomized 1:1 to hydroxychloroquine or placebo via central web-based randomization in permuted blocks of varying size, stratified by treatment site. The randomized sequence is stored on a secure, electronic server not available to site study personnel.

The patients, treating clinicians, study personnel, and outcome assessors are blinded to group assignment. The randomized sequence is stored on a secure server and not available to site study personnel.

During trial planning, it was noted that many participating institutions already included hydroxychloroquine as part of treatment algorithms for COVID-19. Concerns were raised regarding the feasibility of conducting a trial where participants might be randomized to a group that would not receive hydroxychloroquine. There was broad agreement that hydroxychloroquine administration as part of a clinical study was preferable to off-label clinical use because it would increase the quality of informed consent, improve safety monitoring, and contribute to understanding of possible efficacy. There were, however, discussions regarding alternative allocation strategies that would decrease the number of patients randomized to placebo. Ultimately, however, a 1:1 ratio to hydroxychloroquine vs placebo was chosen because it is the approach to allocation that most efficiently produces robust data on efficacy

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and safety while exposing the fewest patients to the study drug should it prove to be ineffective or harmful.

Study Interventions

Hydroxychloroquine group. Patients assigned to the hydroxychloroquine arm receive hydroxychloroquine sulfate enterally for a total of five days: 400 mg twice daily for the first two doses and then 200 mg twice daily for the subsequent eight doses.

Placebo Group. Patients randomized to the placebo group receive placebo twice daily in a dosing regimen matching that described above for hydroxychloroquine.

The process of manufacturing placebo tablets that are identical to study drug may be time consuming. In the face of a rapidly evolving pandemic, investigators faced the options of either delaying enrollment to await manufacture of placebos tablets or conducting an open-label trial without blinding. Instead, the ORCHID trial developed a process to create identical hydroxychloroquine and placebos through encapsulation of commercially available hydroxychloroquine (details in Supplementary Appendix). Because the manual encapsulation process was laborious and not available at all sites, it was replaced by centrally distributed, identical hydroxychloroquine and placebo tablets as soon as these were available (shipped to sites on April 23, 2020), but it allowed the rapid launch of the ORCHID trial while maintaining a high-quality double-blinded design.

Justification of drug and dosing regimen. Hydroxychloroquine was favored over chloroquine by the ORCHID investigators given in vitro data demonstrating more potent antiviral activity against SARS-CoV-2 (6) as well as lower toxicity (37). The dosing regimen in

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ORCHID was chosen for several reasons. This dosing regimen has demonstrated safety when used for other conditions. In vitro studies suggest that this dosing regimen is sufficient to achieve SARS-CoV-2 inhibition. This dosing regimen results in therapeutic drug concentrations in lung tissue for up to 10 days (6). A higher dose (400 mg twice daily) for 5 days was considered, but was not selected because of the overall risk:benefit balance with higher doses potentially leading to increased risk of ventricular dysrhythmias (30).

Approach to co-interventions. The ORCHID trial restricts the use of open-label hydroxychloroquine or chloroquine during the 5-day intervention period. All other clinical treatment decisions are made by treating clinicians. Administration of other open-label antiviral and immune modulating medications is allowed at the discretion of treating clinicians and is recorded. Co-enrollment in other interventional trials is allowed on a case-by-case basis after consideration of potential interactions between agents under investigation, safety assessment and adverse event reporting, and the interpretability of trial results.

Study monitoring and adherence. In addition to routine clinical monitoring (including a pre-enrollment electrocardiogram (EKG)), research staff monitor daily for adherence to study drug dosing and potential drug interactions. To assess for QTc prolongation, study personnel review all clinically obtained EKGs, and the protocol requires measuring the QTc by EKG or a telemetry tracing 24-48 hours after administration of the first dose of study drug (29). If the QTc is >500 ms on any assessment during the course of the study drug, study drug is held for a minimum of 24 hours and is not restarted until a subsequent EKG demonstrates a QTc ≤500 ms (details in Supplementary Appendix).

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Outcomes

Primary outcome. The primary outcome is patients' clinical status 14 days after randomization (measured on Study Day 15) as assessed with the seven-category COVID Ordinal Outcome Scale (Table 2) (38). To distinguish between categories 6 (not hospitalized, but unable to perform normal activities) and 7 (not hospitalized, able to perform normal activities), study personnel blinded to group assignment call patients or caretakers and assess the patient's performance of "usual activities" with questions consistent with validated health status measures (39, 40). An answer of "no problems doing my usual activities" results in assignment to category 7.

The COVID Ordinal Outcomes Scale serves as the primary outcome in multiple ongoing COVID-19 trials and is recommended by the World Health Organization (WHO) Research and Development Blueprint for COVID-19 (38). Although this novel outcome has not yet been validated in prospective studies, use of this standardized outcome facilitates comparison and combination of results across trials (41). There is a mandate for trial efficiency during a pandemic, and by capturing the broad spectrum of clinical outcomes experienced by COVID-19 patients the COVID Ordinal Outcome Scale has the advantage of increasing statistical efficiency compared to dichotomous outcomes.

We selected 14 days after randomization (on Study Day 15) as the timepoint at which we would assess the patient's clinical status for the primary analysis of the primary outcome. This timepoint was selected by many ongoing clinical trials for COVID-19 because it captured the majority of early deaths and hospital discharges and was felt to be sufficient to capture the patient's clinical trajectory while also being available rapidly enough for use with frequent interim analyses. Measurement of the primary outcome 14 days after randomization could be

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insensitive to treatment differences that occur after this timepoint. However, the median length of stay among patients hospitalized with COVID-19 is approximately 4 days (42), and results from a comparison of the COVID Ordinal Outcomes Scale at 14 days after randomization were concordant with results of other 28-day outcomes in the largest trial of COVID-19 to date (43).

***Secondary and safety outcomes*.** Secondary and safety outcomes are shown in Table 2. Key secondary outcomes include: all-cause all-location mortality at 14 and 28 days after randomization (assessed on study days 15 and 29, respectively); COVID Ordinal Outcomes Scale at 2, 7, and 28 days after randomization (assessed on study days 3, 8, and 29 respectively); a composite of death or receipt of extracorporeal membrane oxygenation through study day 28 (assessed on study day 29), and days alive and free of each individual organ support (e.g., ventilator-free days) (additional details in Supplemental Methods). To allow comparison with the Adaptive COVID-19 Treatment Trial trial (NCT04280705), "time to recovery" was added as a secondary outcome before the first interim analysis.

Safety outcomes focus on potential adverse effects of hydroxychloroquine including atrial and ventricular dysrhythmias, cardiac arrest, seizure, acute hepatitis, acute pancreatitis, symptomatic hypoglycemia, bone marrow suppression, and severe dermatologic reactions.

Data Collection

Figure S1 in the Supplementary Appendix depicts the timeline of study procedures. The ORCHID trial was designed to minimize research activities that require person-to-person contact between study personnel and patients. This aimed to conserve PPE, reduce the risk of infection

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among study personnel, reduce the risk of spreading the virus, and enable conduct of the trial despite prohibitions against research staff entering clinical areas at many institutions. The trial, therefore, primarily uses data that can be collected from the electronic health record and assessments that can be completed by telephone. No biological specimens are required as part of the trial. At participating sites with the resources and expertise to collect and process potentially infectious material, a subset of ORCHID patients will be co-enrolled in an observational study to collect biological specimens and additional physiologic and laboratory data. We adopted this modular approach of augmented data collection to increase flexibility without losing rigor during a pandemic.

The effects of acute illness from COVID-19 on long-term patient-important outcomes such as cognitive and physical function are uncertain. Although follow up in the ORCHID trial ends 28 days after enrollment (and initial results from the ORCHID trial will be limited to outcomes in the first 28 days), an ancillary study will follow selected patients at 6 months to assess long-term patient-important outcomes, including survival, cognitive, physical, and psychological function.

Data quality monitoring. Structured data collection training is provided to centers before study initiation. The PETAL Clinical Coordinating Center ensures ongoing data quality by front-end range and logic checks at the time of data entry into the secure online database and back-end monitoring with monthly query reports and virtual site visits.

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Statistical Methods

Approach to analysis of the primary outcome. The primary analysis will be an intention-to-treat comparison of the COVID Ordinal Outcome score at 14 days after randomization (assessed on study day 15) between all patients randomized to hydroxychloroquine versus placebo (Table 3). This analysis will be conducted with a proportional odds model using the COVID Ordinal Outcome score as the dependent variable, randomized group assignment as the primary independent variable, and the following covariates: 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. The small number of patients enrolled with suspected rather than confirmed COVID-19 during the first 19 days of the trial (prior to limiting eligibility to laboratory-confirmed cases), will be included in the primary analysis. Sensitivity analyses will include an intention-to-treat comparison between groups, limited to patients with laboratory-confirmed SARS-CoV-2 infection.

The trial will be analyzed using a Bayesian framework. In addition to flexibility in the number and timing of interim analyses, a Bayesian framework allows consideration of new external data on the efficacy of hydroxychloroquine, which may become available during the trial. For the purpose of declaring success, we will use a skeptical prior, which assumes an equal chance of harm or benefit (normal distribution with mean log OR of 0.0) and assumes that the chance of a large benefit is small (standard deviation of log OR is 0.352).

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Approach to sample size calculation. Accurate sample size calculations using a frequentist approach require knowledge about the frequency and distribution of the trial outcome and estimates of the effect of the trial intervention on the outcome (41). At the time of trial planning, none of these data were available for the use of hydroxychloroquine among hospitalized patients with COVID-19. Given these uncertainties, we selected a Bayesian statistical framework because it permits flexibility in the number and timing of interim analyses, provides the best opportunity for the trial to be stopped early for efficacy or futility, and allows the trial to be continued if the clinical effect of hydroxychloroquine remains unclear after accrual of the initially planned sample size. Given the relative complexity of estimating sample sizes using a Bayesian approach and the need to rapidly finalize a protocol and start enrollment, the initial trial protocol included a frequentist sample size calculation with a pre-specified plan to transition to a Bayesian approach. This calculation used data from a prior trial of patients at risk of ARDS, the *Vitamin D to Improve Outcomes by Leveraging Early Treatment* (VIOLET) trial, to estimate the expected outcomes for the placebo group on the COVID Ordinal Outcome scale at 14 days after randomization (assessed on study day 15) (Supplementary Appendix, Table S1) (44). In brief, the initial sample size calculation estimated that enrollment of 510 patients would provide 90% power to detect an odds ratio of 1.82 with a two-sided significance level of $p<0.05$ (details in Supplementary Appendix).

The full Bayesian analysis plan was developed during the first three weeks of enrollment and before review of any trial data. It includes an interim analysis every 102 patients with the opportunity to increase the frequency of interim analyses as the trial approaches a stopping criterion. The DSMB will review the totality of accrued data at each interim analysis to inform

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their recommendation that enrollment continue or stop. The DSMB may consider stopping the trial if either of the following criteria is met:

- >95% probability of the odds ratio being >1.0 (suggesting high likelihood of at least some efficacy).
- >90% probability that the odds ratio is <1.1 (suggesting futility or harm).

For the purpose of stopping the trial for efficacy, we will use a skeptical prior, as described above. A threshold of 1.1 was chosen for the stopping criterion for futility as this was felt to be the minimal clinically significant difference for the primary outcome. This criterion can also be used to stop the trial if accrued data suggest harm (odds ratio <1.0). For the purpose of stopping the trial for futility or harm, we will use a non-informative prior which assumes an equal probability of benefit or harm but allows for the possibility of arbitrarily large treatment effects. The final sample size will be determined by when the stopping criteria are met. An illustration of the probability that the trial will meet the proposed efficacy or futility criteria at each interim analysis is provided in the supplementary appendix using hypothetical effect sizes (Supplementary Appendix, Table S2). In trials designed using frequentist approaches, stopping a trial early for efficacy has been shown to systematically overestimate treatment effects as large, random fluctuations of the estimated treatment effect are common early in a trial's progress (45, 46). The ORCHID trial protects against this type of effect overestimation by using a skeptical prior for efficacy. If the trial is stopped early for efficacy, the estimate of the treatment effect will be "pulled back" by the prior. The prior distribution's influence fades as the sample size grows with later interim analyses.

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Trial status. Figure 1 shows the 15-day timeline of study development from concept to enrollment of the first patient. The trial was registered (NCT04332991) prior to enrollment of the first patient on April 2, 2020. While trial duration will depend on both the epidemiology of the COVID-19 pandemic and the efficacy of hydroxychloroquine, the anticipated timeline for completion of the trial is three months.

Discussion

Since the first documented case in December 2019, COVID-19 has spread exponentially with over 4 million confirmed cases and over 275,000 deaths as of May 11, 2020. The pandemic has brought unprecedented challenges to clinical research. Designing the ORCHID trial required solutions to several significant barriers including widespread off-label use of hydroxychloroquine, the impracticability of traditional paper-based documentation of informed consent, the complexity of developing a flexible and robust Bayesian analysis plan under time constraints, avoiding delays typically required to obtain visually identical placebo pills; and the need to rapidly obtain administrative and regulatory approvals.

In the early stages of the COVID-19 pandemic, anecdotes and small case series about potential treatments for COVID-19 circulated in social medica, pre-print servers, and the lay press. Some of these treatments were rapidly adopted into clinical care (47–51). Despite a lack of data from clinical trials informing efficacy and safety in the treatment of COVID-19, hydroxychloroquine was adopted as first-line treatment for adults hospitalized with COVID-19 in treatment guidelines at many US medical centers (18–20). Administration of

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hydroxychloroquine to inpatients with COVID-19 became so common that questions were raised regarding the feasibility of conducting a randomized trial in which half the patients did not receive hydroxychloroquine (52). The investigators assessment that the benefits and risks to individual patients and to society favor preferentially administering hydroxychloroquine in a clinical trial rather than in clinical care has been confirmed by guidance from the Infectious Disease Society of America, the National Institutes of Health, and the Society of Critical Care Medicine (31, 32, 53).

An additional challenge has been documenting informed consent to participate in the trial. Traditional methods of written informed consent, in which a patient or legally authorized representative (LAR) physically signs a paper document that is retained by study staff, are infeasible during an infectious pandemic. Fortunately, guidance released by FDA in 2016 provided information on obtaining written informed consent from patients or their LAR using electronic methods (54), which can be utilized in pandemic circumstances. However, developing consent procedures for an infectious pandemic, during which the patient, LAR, research staff, and witness may be in four physically distinct locations at the time of consent has required the development of new operating procedures and adaptations of available technology.

Given the uncertainties regarding the epidemiology of COVID-19 and the efficacy of hydroxychloroquine, a Bayesian analytic framework was developed for ORCHID. High-quality data demonstrating efficacy, inefficacy, or harm associated with use of hydroxychloroquine for COVID-19 would immediately impact clinical care. Therefore, the design of ORCHID required frequent and flexible interim analyses to ensure that as soon as definitive results were known,

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the trial could be terminated and the results disseminated. Developing a robust Bayesian analysis requires time-consuming statistical simulations. Because the analysis plan would not affect any trial decisions prior to the first interim analyses, we chose to launch the trial with a preliminary frequentist analysis plan with the expectation of shifting to a Bayesian approach prior to the first interim analysis. This approach provided sufficient time to develop a robust analysis plan without delaying enrollment.

Because the manufacture and distribution of visually identical placebos is a potentially rate-limiting step in the launch of a randomized trial, many ongoing trials of COVID-19 interventions have chosen to forego blinding. By using encapsulation of a commercially available medication, the ORCHID trial demonstrates a method to maintain blinding without delaying enrollment.

The rapid launch of the ORCHID trial would not have been possible without a large, pre-existing clinical trials network. The traditional process of designing a clinical trial within a trials network, however, can be time-consuming. Trials networks function as large collaborations with existing agreements that govern trial selection, protocol development and review, and creation of study documents. These processes are accompanied by external reviews by institutional review boards (IRBs), funding organizations, regulatory bodies such as the FDA, scientific review committees, and DSMBs. These tasks are designed to occur serially, with each step frequently occurring over weeks to months. Within the PETAL Network, the time from the selection of an idea for a new trial to the initiation of enrollment has been 12-18 months. Legitimate concerns have been raised regarding the feasibility of designing and conducting novel clinical trials within a discrete pandemic (50, 55). Some have suggested that pre-existing

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platform or adaptive trials might be the only practicable options (56). However, the successful development of, regulatory approval of, and initiation of enrollment in the ORCHID trial in 15 days demonstrates that, within an established multicenter clinical trials network, large, novel trials can be conceived and launched within a timeframe relevant for pandemics. This rapid launch required flexibility and timely reviews, completed in parallel by multiple oversight bodies, including the funder (National Heart, Lung, and Blood Institute), the FDA, a single IRB, and the PETAL steering committee, coordinating center, Protocol Review Committee (the peer review group for PETAL trials), and DSMB.

Conclusion

We describe the rationale and design of the ORCHID trial, which is a multi-center, blinded, randomized trial comparing hydroxychloroquine versus placebo among hospitalized adults with COVID-19. This pre-specified framework will enhance the rigor and reproducibility of the final report and will allow readers to better judge the impact of our findings. We also hope that publishing our full trial protocol and explaining how we overcame the unique challenges to conducting clinical research during the COVID-19 pandemic will assist other investigators working to address this public health crisis.

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Table 1. Eligibility Criteria

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/surrogate; hypoxemia, defined as SpO2 <92% on room air or increased oxygen requirement for a patient on chronic oxygen to maintain SpO2 ≥92%; tachypnea with respiratory rate ≥22 /minute). 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

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	16. The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient

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Table 2. Trial Outcomes

Primary outcome	**COVID Ordinal Outcomes Scale assessed 14 days after randomization (on Study Day 15):** 1. Death 2. Hospitalized on invasive mechanical ventilation or ECMO 3. Hospitalized on non-invasive ventilation or HFNC 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 measured 2 days after randomization (assessed on Study Day 3) COVID Ordinal Outcomes Scale measured 7 days after randomization (assessed on Study Day 8) COVID Ordinal Outcomes Scale measured 28 days after randomization (assessed 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 AST or ALT to twice upper limit of normal Acute pancreatitis Acute kidney injury Receipt of renal replacement therapy Symptomatic hypoglycemia Neutropenia, lymphopenia, anemia, or thrombocytopenia Severe dermatologic reaction

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; HFNC: high flow nasal cannula; ECMO: extracorporeal membrane oxygenation.

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Table 3. Allocation, blinding, and statistical methods

SPIRIT	ORCHID
Allocation	
Sequence generation	Patient-level randomization 1:1 ratio of hydroxychloroquine to placebo Randomized in permuted blocks of varying size, stratified by treatment site
Allocation concealment	The randomized sequence is stored on a secure server and not available to site study personnel
Enrollment and Randomization	Patients are enrolled via central web-based randomization, accessible 24 hours/day.
Blinding	Blinded, placebo-controlled
Statistical methods	Intention-to-treat comparison between groups using a proportional odds model with the COVID Ordinal Outcome score 14 days after randomization (assessed on study day 15) as the dependent variable, randomized group assignment as the primary independent variable, and the following covariates: age, sex, baseline COVID Ordinal Outcome score, baseline SOFA score, and duration of acute respiratory infection symptoms prior to randomization.
Interim analyses	Bayesian sequential design with interim analyses at least every 102 patients and suggested stopping rules for efficacy and futility Statistician will present unblinded outcomes with Bayesian posterior probabilities to data and safety monitoring board at each interim analysis

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Figure Legends:

Figure 1. Timeline from Study Conception to Enrollment of the First Patient. On February 28, 2020 the first death from COVID-19 in the United States was reported. On March 16, 2020 an initial PETAL network conference call was held to discuss proposed interventions to treat COVID-19. On March 19, 2020, a brief trial concept and 2-page summary was developed for a trial of hydroxychloroquine among hospitalized patients with COVID-19 and presented to the network along with other trial proposals. Following a PETAL Steering Committee vote on March 20, 2020, a trial of hydroxychloroquine was chosen as the first interventional trial for COVID-19 in the PETAL network. On the same day, the NHLBI reviewed the 2-page summary and endorsed protocol development. A first draft of the trial protocol was completed in 72 hours and distributed to the PETAL Steering Committee. The trial protocol was finalized and submitted to the single IRB on March 25, 2020. The trial was reviewed simultaneously by the single IRB and PETAL Protocol Review Committee with both providing approval on March 28, 2020. Following an investigational new drug (IND) application submission to the FDA on March 27, 2020, a notification of IND exemption was received on March 30, 2020. The trial was submitted to clinicaltrials.gov on March 31, 2020. The trial was presented to the PETAL DSMB on April 1, 2020, with approval granted on the same day. The first patient was randomized on April 2, 2020, with blinding maintained by encapsulation of hydroxychloroquine and placebo by local pharmacies.

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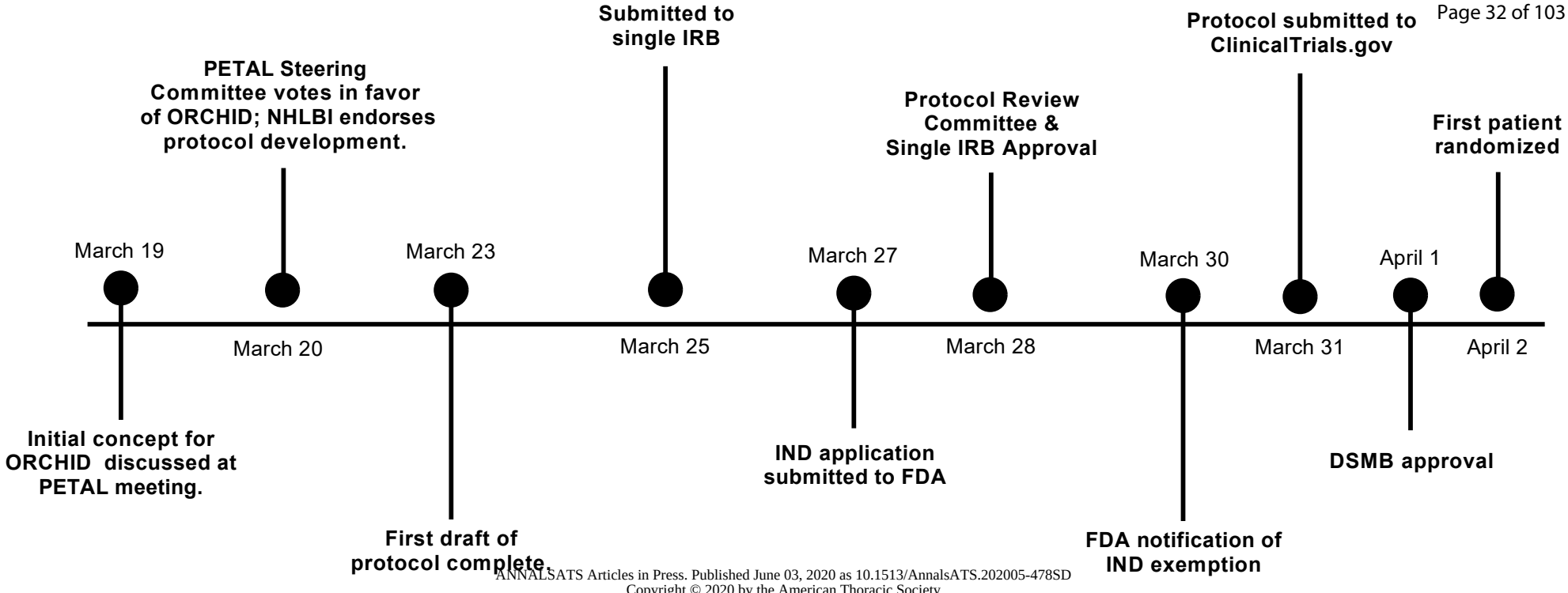

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Rationale and Design of ORCHID: A Randomized Placebo-Controlled Trial of Hydroxychloroquine for Adults Hospitalized with COVID-19

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Supplementary Appendix

CONTENTS

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SUPPLEMENTAL METHODS

A. Description of the PETAL Network

The National Heart, Lung, and Blood Institute (NHLBI) Prevention and Early Treatment of Acute Lung injury (PETAL) Network is a clinical trials network based in the United States and composed of 12 clinical centers and one Clinical Coordinating Center (CCC) (1). The primary mission of PETAL is to develop and conduct randomized controlled clinical trials to prevent and treat Acute Respiratory Distress Syndrome (ARDS). The PETAL Network steering committee is composed of a chairperson, an NHLBI representative, members of the CCC, and two investigators from each clinical center, including one critical care investigator and a second investigator from a different acute care specialty (e.g., emergency medicine, surgery, anesthesiology). Each clinical center consists of a lead academic medical center, with one or more affiliated satellite recruiting institutions, for a total of approximately 50 hospitals. In March 2020, the PETAL steering committee committed to redirecting PETAL Network efforts to rapidly focus on studies relevant to the COVID-19 pandemic.

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B. Documentation of Informed Consent

Because traditional methods of documenting written informed consent, in which a patient or legally authorized representative (LAR) physically signs a paper document that is retained by study staff, are infeasible during an infectious pandemic, the ORCHID trial with guidance from the FDA and single IRB, rapidly developed several options for the informed consent procedure. The coordinating center developed a mechanism for the documentation of consent using the REDCap study database platform, but sites are also allowed to use other locally-approved methods of electronic consent. All approaches are accompanied by a detailed conversation, often by telephone or virtual meeting platform, with the patient or LAR covering all elements of the informed consent procedure. The methods developed by the coordinating center include:

1. **Electronic consent (E-consent):** The informed consent discussion occurs (in-person, by phone, or by video chat). Once the informed consent has been reviewed and all questions have been answered, the patient or LAR signs an electronic version of the consent on a personal device (using an email or text to link to a secure web-based study database) or a secure research or hospital device approved to store protected health information. When using a study or hospital device, it is decontaminated following hospital protocol.
2. **Electronic consent using Short Forms:** When English is not the patient or LAR's preferred language, a short-form consent and qualified interpreter are employed. To facilitate the enrollment on non-English speaking participants, electronic versions of the non-English short-form consents were created using the same processes as described in #1.
3. **Paper-based consent with photographic documentation of signature pages:** The informed consent discussion occurs (in-person, by phone, or by video chat). The patient

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or LAR is delivered a paper copy of the informed consent document (in-person or emailed, faxed, or otherwise electronically transferred to the LAR). If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document and retains the original copy. A photograph is taken of the signature page of the informed consent document and uploaded into the electronic database. If using the patient's device (such as a patient's personal cellular phone), a survey link is sent to their device to allow direct upload of the image into the electronic database. If using a staff device approved to store PHI by the local institution, 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. This process can be conducted using an English paper consent or a non-English Short Form, which are available in a variety of other languages.

4. **Witnessed paper consent:** In addition to affirming the validity of the electronic methods described above, the FDA provided guidance in an April 2, 2020 update of their COVID-19 research guideline, for a witnessed consent in circumstances where communication with a patient is not safe and electronic documentation of consent is not feasible. Using this method, an unsigned paper consent form is provided to the patient. A three-way telephone call is initiated with the patient, study personnel, and an impartial witness. The informed consent is reviewed, and the patient's questions are answered. If the patient agrees to participate in the trial, he/she signs the informed consent document while the impartial witness is listening on the phone and provides verbal confirmation. The witness

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and study personnel then sign attestations stating that the patient agreed to participate in the trial and signed the consent document.

After documentation of the patient's written informed consent using one of the processes above, research staff and witness (if applicable) provide electronic signatures within the electronic database (e.g. REDCap) confirming their participation in the informed consent process. Use of an interpreter and the interpreter's identity are documented on the electronic consent.

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C. Process of Locally Compounding Study Drug

The process of manufacturing placebo tablets that are identical to study drug may be time consuming. Investigators, therefore, are faced with the options of either delaying enrollment to await placebos or conducting an open-label trial without blinding. To maintain blinding without delaying enrollment, ORCHID research staff developed a process by which local pharmacies could encapsulate commercially available hydroxychloroquine and create matching placebos. The process involved the inserting hydroxychloroquine 200 mg tablets into microcrystalline cellulose capsules and was used to initiate enrollment while awaiting the manufacture of visually indistinguishable study drug and placebo tablets that were. Stepwise instructions are as follows:

Hydroxychloroquine 200 mg blinded capsules

Ingredients:

Hydroxychloroquine 200 mg tablets

Microcrystalline cellulose to cover tablets (PCCA #30-1130)

Starting Materials:

Capsule machine

Capsule cleaning towel

Size “00” purple opaque locking capsules (Letco Item # 693497)

Compounding:

1. Don appropriate attire for compounding.

2. Place the number of empty capsules you wish to make into the capsule machine. Remove tops.

3. Place one Hydroxychloroquine 200 mg tablet into each of the empty capsules.

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4. Cover with microcrystalline, shaking the capsule machine to distribute the powder around the capsules. Replace tops and clean capsules.

5. Place into prescription bottle and label appropriately.

Placebo for Hydroxychloroquine 200 mg blinded capsules

Ingredients:

Microcrystalline cellulose to cover capsules (PCCA #30-1130)

Starting Materials:

Capsule machine

Capsule cleaning towel

Size “00” purple opaque locking capsules (Letco Item # 693497)

Compounding:

1. Don appropriate attire for compounding.

2. Place the number of empty capsules you wish to make into the capsule machine. Remove tops.

3. Fill capsules with microcrystalline, shaking the capsule machine to distribute the powder around the capsules.

4. Replace tops and clean capsules.

5. Place into prescription bottle and label appropriately.

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D. QTc Criteria for Stopping Study Drug

In addition to routine excluding patients with a history of prolonged QT syndrome and patients with a prolonged QT at baseline, patients are monitored for new QT prolongation after randomization in the ORCHID study. In addition to routine clinical monitoring, study staff assess all clinically obtained EKGs daily. In addition, the protocol requires measuring the QTc by EKG or a telemetry tracing 24-48 hours after administration of the first dose of 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 study procedure.

If the QTc assessed after enrollment is greater than or equal to 500 milliseconds (ms) on any clinically obtained or research study, the study drug will be discontinued for a minimum of 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 enrollment, or until 5 days after enrollment 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 daily on study days 1-5 when the patient is receiving study drug. If the QTc in hospitalized patients cannot be assessed at 24-48 hours, study drug will be discontinued until the QTc can be assessed.

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E. Outcome Definitions

For all outcomes related to days alive and free from a supportive therapy, "-free days" are calculated as the number of whole calendar days from 00:00 on the day of randomization (Study Day 1) to 23:59 on Study Day 28. The day of randomization contributes to the count of "-free days". Days between randomization and the first receipt of the supportive therapy and days following the last day of the support therapy both count towards the total number of "-free days". Days alive and free of the supportive therapy that occur between periods receiving support do not count towards "-free days".

Oxygen-free days through Day 28

For oxygen-free days, supplemental oxygen is defined as oxygen administered by nasal cannula, face mask, high-flow nasal cannula, non-invasive ventilation, or invasive ventilation. Positive airway pressure (CPAP, BiPAP) provided solely at night as treatment for sleep-disordered breathing (e.g. obstructive sleep apnea) is not considered supplemental oxygen. Oxygen-free days will be counted as the number of whole calendar days alive and not receiving supplemental oxygen between randomization and study day 28. Patients who die before day 28 receive a value of 0. If a patient survives through study day 28 and never receives supplemental oxygen, the number of oxygen-free days is 28. If a patient receives supplemental oxygen and survives through study day 28, the number of oxygen free-days is computed as 28 minus the number of calendar days from the first day on which the patient received supplemental oxygen until the last day on which the patient received supplemental oxygen. Days on which the patient did not receive supplemental oxygen that occur between days on which the patient received supplemental oxygen do not count towards the number of oxygen free days. Data on receipt of supplemental oxygen following discharge will be obtained from follow-up phone calls. For participants alive but with missing information about receipt of supplemental oxygen through study day 28 (e.g., participants who are discharged or transferred to another facility and in whom follow up regarding receipt of supplemental oxygen is unsuccessful), the last observed status will be carried forward. That is, if the participant was last known to be receiving supplemental oxygen, the analysis will assume they continued to receive supplemental oxygen through study day 28. If the participant was not receiving supplemental oxygen at the last assessment for

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which data are available, the analysis assumes the patient continued not to receive supplemental oxygen through study day 28.

Ventilator-free days (VFDs) through Day 28

The number of whole calendar days alive and breathing without invasive mechanical ventilation from 00:00 on the day of randomization through study day 28. Patients who die before the first of discharge or study day 28 receive a value of 0. If a patient survives to the first of discharge or study day 28 and never receives invasive mechanical ventilation, the number of VFDs is 28. If a patient receives invasive mechanical ventilation and survives to the first of discharge or study day 28, the number of VFDs is computed as 28 minus the number of calendar days from the first day on which the patient received invasive mechanical ventilation until the last day on which the patient received invasive mechanical ventilation. Days on which the patient did not receive invasive mechanical ventilation that occur between periods days on which the patient received mechanical ventilation do not count towards the number of VFDs. Data is censored at hospital discharge and the last observed status will be carried forward. That is, if the participant was receiving invasive mechanical ventilation at hospital discharge, the analysis will assume they continued to receive invasive mechanical ventilation through study day 28. If the participant not receiving invasive mechanical ventilation at hospital discharge, the analysis assumes the patient continued not to receive invasive mechanical ventilation through study day 28.

Vasopressor-free days through Day 28

For vasopressor-free days, the receipt of any of the following medications via intravenous drip or push at any dose will be considered a day receiving vasopressors: norepinephrine, epinephrine, vasopressin, phenylephrine, angiotensin II, dobutamine, dopamine, or milrinone. Vasopressor-free days will be counted as the number of whole calendar days alive and not receiving intravenous vasopressors or inotropes from 00:00 on the day of randomization through study day 28. Patients who die before the first of discharge or study day 28 receive a value of 0. If a patient survives to the first of discharge or study day 28 and never receives intravenous vasopressors or inotropes, the number of vasopressor-free days is 28. If a patient receives intravenous vasopressors or inotropes and survives to the first of discharge or study day 28, the

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number of vasopressor-free days is computed as 28 minus the number of calendar days from the first day on which the patient received vasopressors or inotropes until the last day on which the patient received vasopressors or inotropes. Days on which the patient did not receive vasopressors or inotropes that occur between days on which the patient received vasopressors or inotropes do not count towards the number of vasopressor-free days. Data is censored at hospital discharge and the last observed status will be carried forward. That is, if the participant was known to be receiving vasopressors or inotropes at hospital discharge, the analysis will assume they continued to receive vasopressors or inotropes through study day 28. If the participant not receiving vasopressors or inotropes at hospital discharge, the analysis assumes the patient continued not to receive vasopressors or inotropes through study day 28.

ICU-free days through Day 28

The number of whole calendar days alive and not admitted to an intensive care unit from 00:00 on the day of randomization through study day 28. Patients who die before the first of discharge or study day 28 receive a value of 0. If a patient survives to the first of discharge or study day 28 and is never admitted to an ICU, the number of ICU-free days is 28. If a patient is admitted to an ICU and survives to the first of discharge or study day 28, the number of ICU-free days is computed as 28 minus the number of calendar days from the first ICU admission to final ICU discharge. Days on which the patient was not admitted to an ICU that occur between days on which the patient was admitted to an ICU do not count towards the number of ICU-free days. Data is censored at hospital discharge and the last observed status will be carried forward such that the analysis will assume that the patient was not admitted to an ICU from ICU discharge through study day 28.

Hospital-free days through Day 28

The number of whole calendar days alive and not in the hospital during the index hospitalization from 00:00 on the day of randomization through study day 28. Patients who die before discharge from the index hospitalization receive a value of 0. If a patient remains in the hospital during the index hospitalization through study day 28, the number of hospital-free days is 0. For patients discharged from the index hospitalization prior to study day 28, the number of hospital-free days is calculated as 28 minus the number duration of the index hospitalization in

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calendar days. Data collection is censored at hospital discharge; readmissions are not considered in the calculation of the hospital-free days outcomes.

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F. Initial Sample Size Calculation

As described in the protocol manuscript, the initial sample size calculation was based on a frequentist approach which facilitated rapidly launching the trial with a plan to develop a Bayesian statistical analysis plan prior to the first interim analysis. Below, is the initial, frequentist, sample size calculation.

The trial was powered based on the number of patients with laboratory confirmed COVID-19 (the primary population for analysis). We anticipate that 90% of enrolled patients will have laboratory-confirmed COVID-19. We plan to enroll up to 510 patients and anticipate approximately 460 of these patients will be in the primary population of laboratory-confirmed COVID-19 patients.

We calculated the power of the study based on data from our prior PETAL trial, *Vitamin D to Improve Outcomes by Leveraging Early Treatment* (VIOLET) (2). In that study at 15 days, 11.5% of the patients had died, 5.8% were on invasive mechanical ventilation, 22% remained hospitalized, and the remaining had been discharged from the hospital. We used these outcomes in VIOLET to approximate Day 15 outcomes on the COVID Ordinal Outcome scale that we are likely to observe in this trial. Based on these assumptions, enrollment of 510 patients (460 patients with laboratory confirmed COVID) will result in 90% power to detect an odds ratio of 1.82 at a p=0.05 with two-sided significance level using Haybittle-Peto Stopping Boundaries. An example of effect sizes that correspond to an odds ratio 1.82 include: death in 6.7% of the hydroxychloroquine group versus 11.5% of the control group; composite of death or invasive mechanical ventilation in 10.3% of the hydroxychloroquine group versus 17.3% in the control group; and composite of death, invasive mechanical ventilation or hospitalization in 26.3% of the hydroxychloroquine group versus 39.3% of the control group. The variance of the odds ratio was calculated using the approach described by Whitehead.(3)

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G. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication, will patient identities be revealed in any manner. All subjects are assigned a unique study ID number for tracking. Data collected from the medical record are entered into the secure online database, REDCap. Private health information (PHI) required to accurately collect data are available only to investigators at the site at which the subject was enrolled. All data available to the coordinating center and investigators at other sites are de-identified. The de-identified dataset housed in REDCap will be accessed by the Clinical Coordinating Center for analyzing and reporting the results of this trial. Data will be maintained in the secure online database REDCap. Potential future use of de-identified data generated in the course of this study will be governed by mutual data use agreements.

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SUPPLEMENTAL FIGURES

Figure S1. Schedule of Study 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.

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SUPPLEMENTAL TABLES

Table S1. Patient status 14 days ("Day 15") after randomization in the VIOLET trial.

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%

Shown above are the day 15 outcomes from the Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial, which were used to approximate the expected day 15 outcomes of patients with COVID-19 enrolled in the ORCHID study. These estimated outcomes were used in sample size calculations and simulations to estimate the likelihood of stopping for efficacy or futility at each planned interim analysis.

Table S2. Probabilities of Continuing or Stopping at each Interim Analysis

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

Shown above are the probability the trial will be either continued, stopped for efficacy, or stopped for futility at each interim analysis (conducted every 102 patients), assuming that hydroxychloroquine has no effect on the primary outcome (true odds ratio of 1.0; shown on left) or assuming that hydroxychloroquine has a clinically significant treatment benefit with regard to the primary outcome (true odds ratio of 1.8; shown on right)

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SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4,14
	2b	All items from the World Health Organization Trial Registration Data Set	1-18
Protocol version	3	Date and version identifier	Supplement
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3

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	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-3, Supplement
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7, 10-11
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, Supplement
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11,12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12, 13 Supplement
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,13 Supplement

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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13,14, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure S1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17,18, Supplement
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	17,18

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, Fig. S1
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14, 15, Figure S1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-15, Figure S1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplement
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-18

Methods: Monitoring

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_7, Supplement_
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_16-18_
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12, Supplement
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Figure S1, Supplement

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__7__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplement
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	9,10 Supplement
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__N/A__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplement
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__3__

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Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplement
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2,3
	31b	Authorship eligibility guidelines and any intended use of professional writers	2,3
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2,3
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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)
Network:	The Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network
Protocol:	Version 3.0
Date:	May 4, 2020

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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

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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).

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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

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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

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	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

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	• 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 >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. The trial is designed with a Bayesian monitoring plan and has an anticipated sample size around 510 patients. The trial will stop for efficacy if the probability is over 95% that the odds ratio is >1.0 with a skeptical prior distribution. 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.

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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

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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.

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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.

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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.

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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*.

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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

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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

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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.

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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

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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

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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

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- 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)

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- 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)

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- 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.

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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. On the other hand, if we determine there is >90% probability that the odds ratio is <1.1, the DSMB should consider stopping the trial for futility. 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

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for tests of futility. 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.

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)

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FIGURE 1

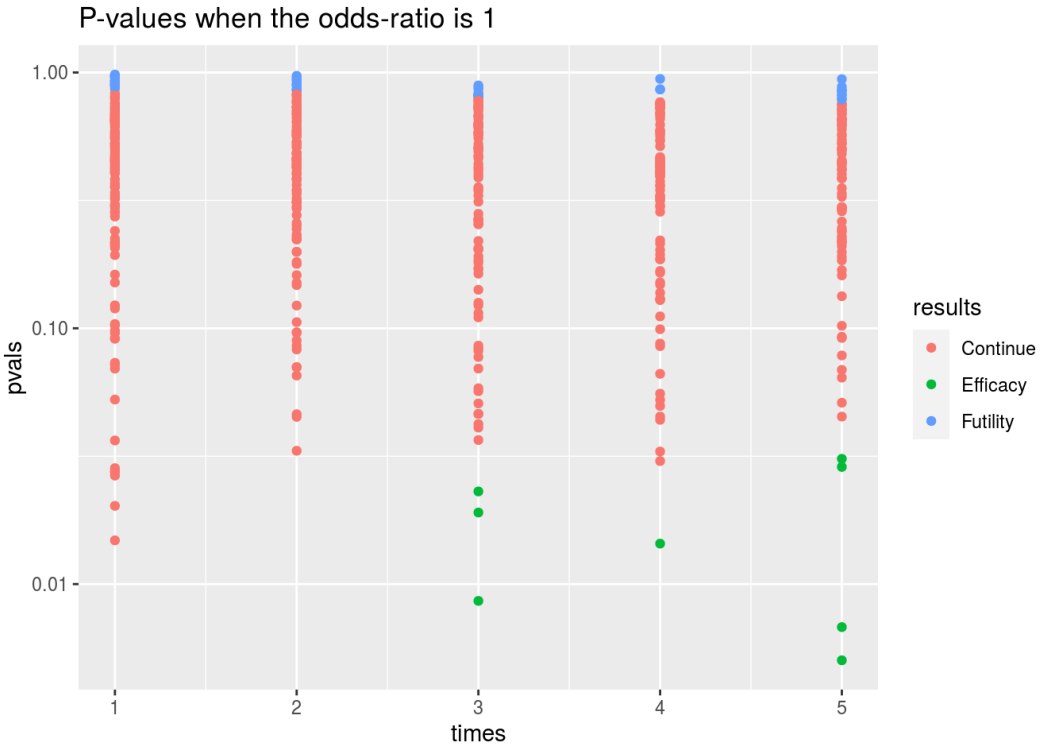
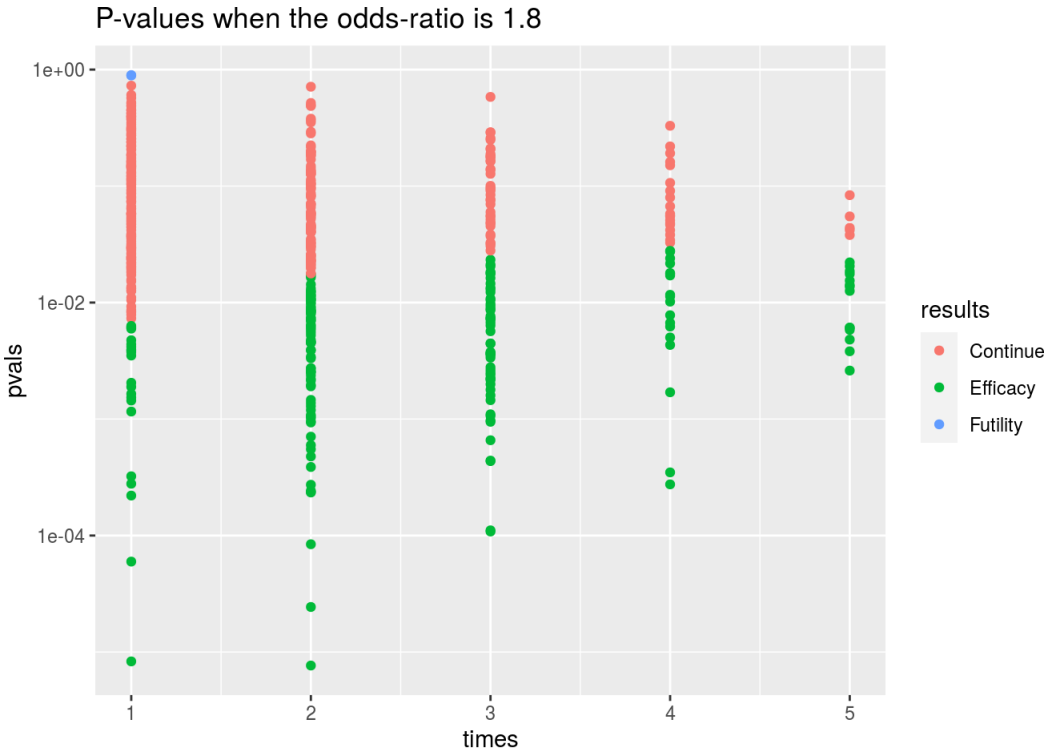


FIGURE 2



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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]

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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

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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

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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.

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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

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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.

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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

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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**

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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

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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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13. 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.

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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.

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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:

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- 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)

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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

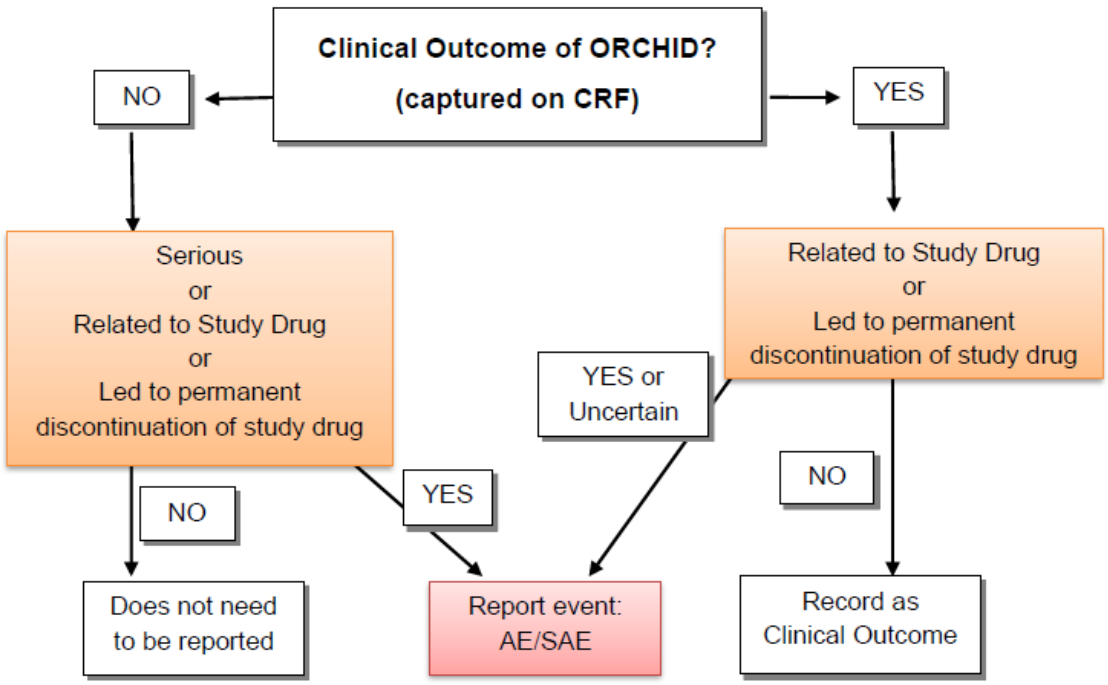

Figure adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. PMID: 22616830.

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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.

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