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

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Abstract

The ORCHID (Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease) trial is a multicenter, blinded, randomized trial of hydroxychloroquine versus placebo for the treatment of adults hospitalized with coronavirus disease (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, multicenter, 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, multicenter 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.

Clinical trial registered with www.clinicaltrials.gov (NCT04332991).

Keywords: COVID-19; SARS-CoV-2; ARDS; hydroxychloroquine; ORCHID

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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). Though 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 because of 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 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). Furthermore, hydroxychloroquine reduces the production of several proinflammatory 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 U.S. 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 to allow use of hydroxychloroquine from the Strategic National Stockpile to treat COVID-19 patients hospitalized in the United States 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 for 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). 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 (28, 29).

On April 21, 2020, the U.S. 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 (30). 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 and efficacy of hydroxychloroquine as a treatment for COVID-19 among hospitalized patients (31).

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 ORCHID (Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease) trial.

Methods

Trial methods are summarized in Tables 1, 2, and 3 with the following sections providing additional context. The complete protocol, the Standard Protocol Items: Recommendations for Interventional Trials checklist, and a schedule of enrollment, interventions, and assessments are provided in the online supplement (32).

Trial Design
The ORCHID trial is a patient-level, parallel-group, blinded, randomized clinical trial evaluating the superiority of hydroxychloroquine compared with placebo. The trial aims to enroll patients early after hospital presentation, screening in emergency departments, inpatient floors, and intensive care units of participating hospitals. The trial protocol was approved by the single institutional review board (IRB) at Vanderbilt University Medical Center and is being conducted with an

Table 1. Eligibility criteria

Inclusion criteria	1. Age ≥18 yr
	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 $Sp_{O_2} < 92\%$ on room air or increased oxygen requirement for a patient on chronic oxygen to maintain $Sp_{O_2} \geq 92\%$; tachypnea with respiratory rate ≥22/min).
	  d. Sore throat
	4. Laboratory-confirmed SARS-CoV-2 infection within the past 10 d before randomization

Exclusion criteria	1. Prisoner 2. Pregnancy 3. Breast feeding 4. Unable to randomize within 10 d after onset of acute respiratory infection symptoms 5. Unable to randomize within 48 h after hospital arrival 6. Seizure disorder 7. Porphyria cutanea tarda 8. QTc > 500 ms on electrocardiogram within 72 h before enrollment 9. Diagnosis of long QT syndrome 10. Known allergy to hydroxychloroquine, chloroquine, or amodiaquine 11. Receipt in the 12 h before enrollment or planned administration during the 5-d 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 d before enrollment 13. Inability to receive enteral medications 14. Refusal or inability to be contacted on Day 15 for clinical outcome assessment if discharged before 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

Definition of abbreviations: QTc = corrected QT; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

exception from Investigational New Drug application requirements. An independent Data and Safety Monitoring Board (DSMB) is monitoring the trial.

Study Sites

The ORCHID trial is being conducted by the National Heart, Lung and Blood Institute 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 online supplement) (33, 34).

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 corrected QT

(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 for poor clinical outcomes while still being in the acute phases of illness in which viral replication may still play a pathophysiologic role. Remaining exclusion criteria serve to protect vulnerable populations (e.g., prisoners) and exclude patients for whom receipt of hydroxychloroquine might increase the risk for 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*) although 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. Furthermore, face-to-face interaction between patients and research personnel would expend valuable personal protective equipment, which has limited availability in many areas of the United States. Finally, legally authorized representatives (LARs) are often prohibited from in-person visits. Following guidance from the FDA and Office for Human Research Protections, the ORCHID trial therefore documents the completion of written informed consent from the patient or LAR using "no-touch" procedures (35).

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 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 online supplement).

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.

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 in which 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 versus placebo was chosen because it is the approach to allocation that most efficiently produces robust data on efficacy 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 5 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 placebo 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 online supplement). 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 (36). The dosing regimen in 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 considere, but was not selected because of the overall risk-to-benefit balance, with higher doses potentially leading to increased risk for ventricular dysrhythmias (30).

Approach to cointerventions. 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. Coenrollment 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 preenrollment 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 milliseconds 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 milliseconds (details in online supplement).

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) (37). To distinguish between categories 6 (not hospitalized but unable to perform normal activities) and 7 (not hospitalized and 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 (38, 39). 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 Research and Development Blueprint for COVID-19 (37). 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 (40). There is a mandate for trial efficiency during a pandemic, and by capturing the broad spectrum of clinical outcomes experienced by patients with COVID-19, the COVID Ordinal Outcome Scale has the advantage of increasing statistical efficiency compared with dichotomous outcomes.

We selected 14 days after randomization (on Study Day 15) as the time point at which we would assess the

Table 2. Trial outcomes

Primary outcome	COVID Ordinal Outcomes Scale assessed 14 d 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-d mortality (assessed on Study Day 15) All-location, all-cause 28-d mortality (assessed on Study Day 29) COVID ordinal outcomes scale measured 2 d after randomization (assessed on Study Day 3) COVID ordinal outcomes scale measured 7 d after randomization (assessed on Study Day 8) COVID ordinal outcomes scale measured 28 d 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

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID = coronavirus disease; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit.

patient's clinical status for the primary analysis of the primary outcome. This time point 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 insensitive to treatment differences that occur after this time point. However, the median length of stay among patients hospitalized with COVID-19 is approximately 4 days (41), 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 (42).

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 online supplement). 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 E1 in the online supplement 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 personal protective equipment, reduce the risk of infection 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.

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 12 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 query reports and virtual site visits.

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 Sequential Organ Failure Assessment score, and duration of acute respiratory infection symptoms prior to randomization. An odds ratio (OR) >1.0 indicates more favorable outcomes with hydroxychloroquine on the COVID Ordinal Outcome scale, whereas an OR <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).

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 (40). 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 prespecified plan to transition to a Bayesian approach. This calculation used data from a prior trial of patients at risk for ARDS, the VIOLET (Vitamin D to Improve Outcomes by Leveraging Early Treatment) 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) (Table E1) (43). In brief, the initial sample size calculation estimated that enrollment of 510 patients would provide 90% power to detect an OR of 1.82 with a two-sided significance level of $P < 0.05$ (details in online supplement).

The full Bayesian analysis plan was developed during the first 3 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 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 OR being >1.0 (suggesting high likelihood of at least some efficacy) or
- >90% probability that the OR 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 (OR <1.0). For the purpose of stopping the trial for futility or harm, we will use a noninformative 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

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 enrollment and randomization	The randomized sequence is stored on a secure server and not available to site study personnel; patients are enrolled via central web-based randomization, accessible 24 h/d.
Blinding	Blinded, placebo-controlled
Statistical methods	Intention-to-treat comparison between groups using a proportional odds model with the COVID ordinal outcome score 14 d 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 before 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.

Definition of abbreviations: COVID = coronavirus disease; ORCHID = Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease; SOFA = Sequential Organ Failure Assessment; SPIRIT = Standardized Protocol Items: Recommendations for Interventional Trials.

or futility criteria at each interim analysis is provided in the online supplement using hypothetical effect sizes (Table E2). 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 (44, 45). 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.

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. Though 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 3 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 on social medica, preprint servers, and the lay press. Some of these treatments were rapidly adopted into clinical care (46–50). 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 U.S. medical centers (18–20). Administration of 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 (51). 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 (30, 31, 52).

An additional challenge has been documenting informed consent to participate in the trial. Traditional methods of written informed consent, in which a patient or 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
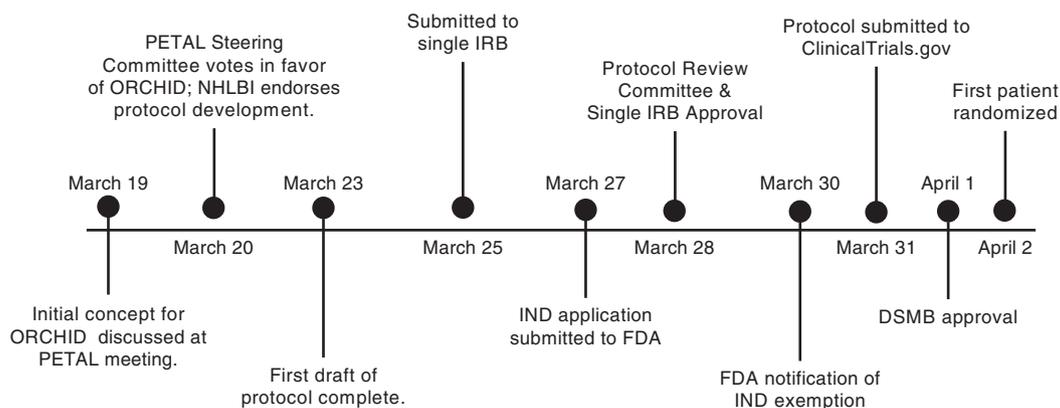

Figure 1. Timeline from study conception to enrollment of the first patient. On February 28, 2020, the first death from coronavirus disease (COVID-19) in the United States was reported. On March 16, 2020, an initial Prevention and Early Treatment of Acute Lung Injury (PETAL) network conference call was held to discuss proposed interventions to treat COVID-19. On March 19, 2020, a brief trial concept and two-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 National Heart, Lung and Blood Institute reviewed the two-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 institutional review board (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 Food and Drug Administration 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 Data and Safety Monitoring Board 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. DSMB = Data and Safety Monitoring Board; FDA = Food and Drug Administration; NHLBI = National Heart, Lung, and Blood Institute; ORCHID = Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease.

written informed consent from patients or their LAR using electronic methods (53), 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, 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, preexisting clinical trials network. The traditional process of designing a clinical trial within a trials network, however, can be time consuming. Trial 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 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 (49, 54). Some have suggested that preexisting platform or adaptive trials might be the only practicable options (55). However, the successful

development, regulatory approval, 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.

Conclusions

We describe the rationale and design of the ORCHID trial, which is a multicenter, blinded, randomized trial comparing hydroxychloroquine versus placebo among hospitalized adults with COVID-19. This prespecified 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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