Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine Trial (HERO-HCQ Trial)

Protocol Number:	COVID-19-2020-001
IND Number:	149266
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Lead Funding Agency:	Patient-Centered Outcomes Research Institute
Version:	3.0
Date:	7/07/2020

Statement of Compliance

This trial will be conducted in compliance with the International Council for Harmonisation (ICH) E6(R2) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (Human Subjects Protection); 21 CFR 312 (Investigational New Drug); 21 CFR 50 (Informed Consent), and 21 CFR 56 (Institutional Review Board [IRB]).

All individuals who are responsible for the conduct, management, or oversight of this study have completed Human Subjects Protection and ICH GCP Training.

Site Principal Investigator Statement

I have read the protocol, including all appendices, and the package insert/product label, and I agree that the protocol contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the Institutional Review Board (IRB), or equivalent oversite entity must approve this protocol in the clinical facility where it will be conducted.

I agree to obtain informed consent from participants, as required by the IRB of record and according to government regulations and ICH guidelines. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.64, ICH GCP 4.11. I further agree to ensure the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

_____

Site Principal Investigator Name (Print)

_____ _____

Site Principal Investigator Signature Date

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Abbreviations

ACE	Angiotensin-converting Enzyme
AE	Adverse Event
AGEP	Acute Generalized Exanthematous Pustulosis
ARB	Angiotensin II Receptor Blockers
ARDS	Acute Respiratory Distress Syndrome
ARNI	Angiotensin Receptor Neprilysin Inhibitor
CCC	Clinical Coordinating Center
CONSORT	Consolidated Standards of Reporting Trials
DCC	Data Coordinating Center
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety Monitoring Board
DUA	Data Use Agreement
EC50	Half Maximal Effective Concentration
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EE	Emotional Exhaustion
EOSI	Event of Special Interest
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
HCQ	Hydroxychloroquine
HCW	Healthcare Worker
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form

ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IRB	Institutional Review Board
MBI	Maslach Burnout Inventory
MOI	Multiplicity on Infection
MOP	Manual of Procedures
NIH	National Institute of Health
OHRP	Office for Human Research Protections
PHI	Personal Health Information
PHQ	Patient Health Questionnaire
PROMIS	Patient-reported Outcomes Measurement Information System
QoL	Quality of Life
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Suspected Adverse Reaction
UP	Unanticipated Problems

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1. Protocol Summary

1.1. Synopsis

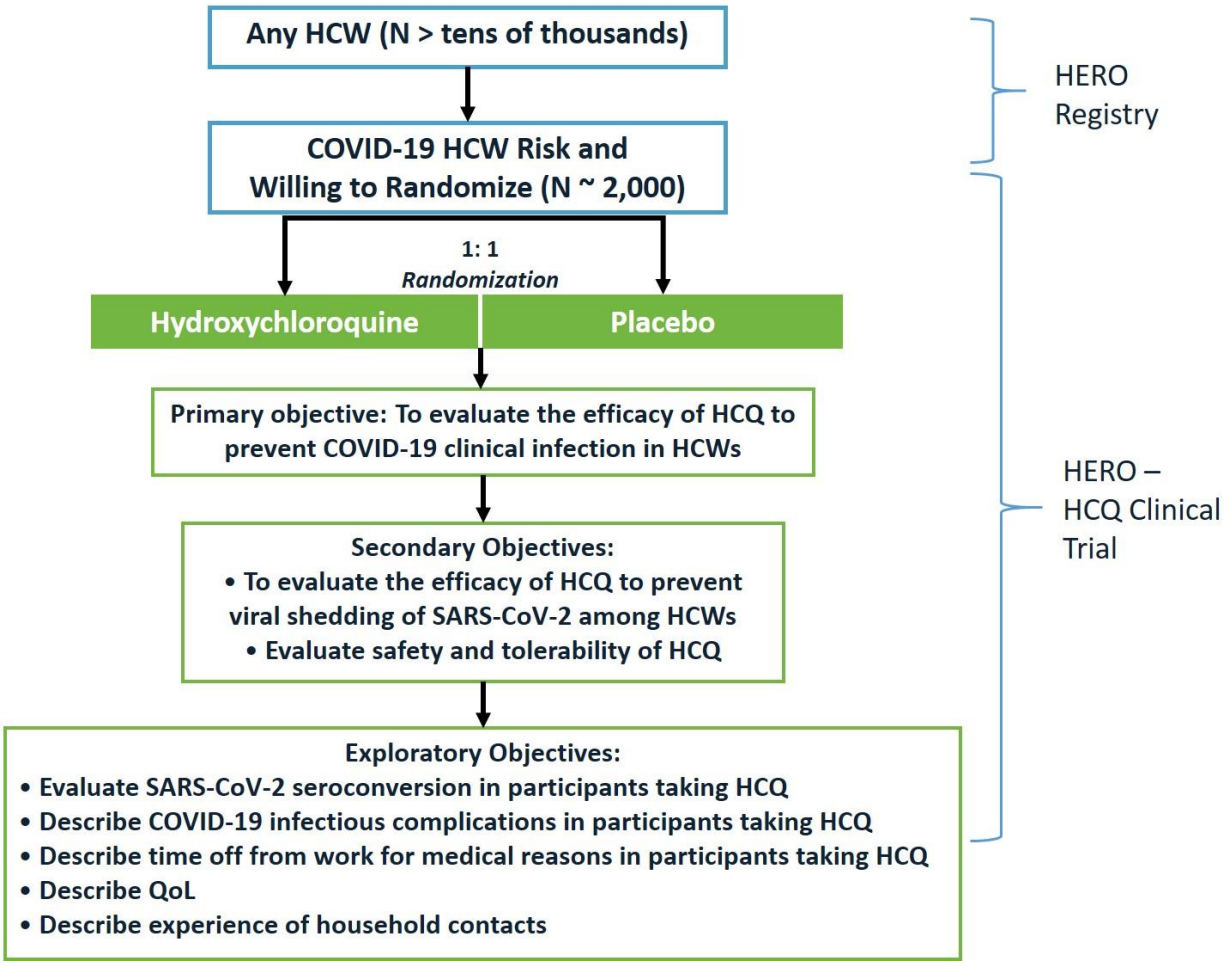
Title	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine Trial (HERO-HCQ Trial)
Clinical study phase	III
Rationale	Severe acute respiratory syndrome coronavirus 2 associated disease or COVID-19 is caused by a novel betacoronavirus, SARS-CoV-2, that was first isolated in January 2020 and has since caused a global pandemic unseen in decades in cases and mortality. [1, 2] At the time of initial protocol submission in April 2020, human vaccine clinical trials had just begun and experts predicted that a vaccine would not be available until April 2021 at the earliest, therefore new measures remain desperately needed to prevent the spread of disease.[3] *In vitro* studies suggest a potential moderate antiviral effect of hydroxychloroquine (HCQ) and its well known safety profile and oral formulation make it an ideal drug candidate for prevention.
Primary Objective	• To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in healthcare workers (HCWs)
Secondary Objectives	• To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs • Evaluate safety and tolerability of HCQ
Exploratory Objectives	• Evaluate SARS-CoV-2 seroconversion in participants taking HCQ • Describe COVID-19 infectious complications in participants taking HCQ • Describe time off from work for medical reasons in participants taking HCQ • Describe Quality of Life (QoL) • Describe experience of household contacts
Intervention	Treatment Group: Hydroxychloroquine 600 mg BID (two times a day) loading dose for 1 day, followed by 400 mg QD (once a day) for 29 days Control Group: placebo
Study Design	Eligible participants will be randomized (1:1), stratified by site, in a blinded fashion to either the treatment group (HCQ) or placebo. Participants will receive a 30-day supply of study drug or placebo, depending on randomization arm. There will be two on-site visits and four remote visits over an approximately 60 day period during which participants will complete various QoL questionnaires, provide serum samples, and undergo COVID-19 testing.
Population	Approximately 2,000 adult HCWs

Study Duration	12 months
Study Location	Approximately 40 US PCORnet sites
Key Inclusion Criteria	• Healthcare worker age ≥18 years old • Currently working in any environment in which there is a risk of exposure to patients with COVID-19 infections ("healthcare worker")

Key Exclusion Criteria	• Prior diagnosis of COVID-19 infection
	• Respiratory illness with new-onset fever (Temperature > 100°F) or ongoing cough or dyspnea within 14 days
	• Congenital prolonged QT syndrome
	• Current or planned use of QT prolonging drugs (see Section 5.2) and other contraindicated medications
	• End stage renal disease
	• Current or planned use of the following for treatment or prevention of COVID-19 infection:
	  ○ Hydroxychloroquine (study drug) or chloroquine
	  ○ Azithromycin
	• Ventricular arrhythmias requiring medical treatment
	• Severe coronary artery disease or heart failure/cardiomyopathy with ongoing symptoms

Sample Size Considerations	A sample size of approximately 2,000 randomized participants is expected to provide 80% power to detect a relative 50% reduction in the risk of clinical infection with COVID-19 assuming a control group risk of 5%.
Statistical Analysis Plan for Primary Objective	The primary objective will be assessed by the risk of clinical infection with COVID-19 at the end of the treatment period. For the clinical infection with COVID-19 endpoint, a comparison of treatment and control groups will be conducted using a Fisher's exact test. The primary measure of treatment effect will be based on a difference in proportions with the associated 95% confidence interval. A secondary analysis will be performed using a logistic regression model.
Data Safety Monitoring Board (DSMB)	Frequent DSMB reviews will be conducted to ensure the safety of study participants and evaluate the accumulating endpoint data by treatment group. Regular DSMB meetings will monitor the following parameters at a minimum: • Recruitment progress • Enrollment overall and by subgroups • Adherence, retention, and status of data collection • Serious adverse events
Interim Analysis	Given the rapid spread of COVID-19, it is expected that reviews of the study data will occur approximately weekly following the enrollment of the first participants. Formal interim reviews for efficacy will be based on the accrual of primary endpoint data.

1.2. Schema


Any HCW (N > tens of thousands)
COVID-19 HCW Risk and Willing to Randomize (N ~ 2,000)
1: 1
Randomization
Hydroxychloroquine
Placebo
Primary objective: To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in HCWs
Secondary Objectives:
• To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
• Evaluate safety and tolerability of HCQ
Exploratory Objectives:
• Evaluate SARS-CoV-2 seroconversion in participants taking HCQ
• Describe COVID-19 infectious complications in participants taking HCQ
• Describe time off from work for medical reasons in participants taking HCQ
• Describe QoL
• Describe experience of household contacts
HERO Registry
HERO – HCQ Clinical Trial

2. Introduction

2.1. Study Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus first isolated in January 2020 and has since caused a global pandemic unseen in decades with respect to the number of cases and overall mortality. [1, 2] The clinical disease related to SARS-CoV-2 is referred to as COVID-19. Human vaccine clinical trials have just begun, but experts predict that a vaccine will not be available for 12-18 months, and new measures are desperately needed to prevent the spread of disease. [3] *In vitro* studies suggest a potential moderate antiviral effect of hydroxychloroquine (HCQ) and its well known safety profile and oral formulation make it an ideal drug candidate for prevention.

2.2. Background

In December 2019, numerous patients in Wuhan, China were diagnosed with pneumonia caused by an unknown virus. By January 7, 2020, Chinese scientists had isolated SARS-CoV-2. This is a novel betacoronavirus closely related to severe acute respiratory syndrome coronavirus (SARS-CoV-1). [2] In the subsequent months the spread of the virus led to a global pandemic. As of March 31, 2020, there were approximately 803,313 confirmed COVID-19 cases resulting in 39,014 deaths worldwide. [1]

Healthcare workers have been disproportionately affected by the current pandemic. Over 3,300 Chinese healthcare workers have been infected. In Spain 5,400 healthcare workers have become infected, accounting for 14% of the country's total infections. In Brescia, the center of Italy's outbreak, 10-15% of doctors and nurses have been infected and are unable to work. [4] In addition to potential exposure to infected patients, a critical shortage of personal protective equipment and respirators put healthcare professionals at even greater risk. [5]

The virus continues to spread despite social distancing measures and travel restrictions. Human vaccine clinical trials have just begun, but experts predict that a vaccine will not be available for 12-18 months, and new measures are desperately needed to prevent the spread of disease. [3]

As of July 2020, multiple clinical trials have completed providing early guidance to clinical providers on management of COVID-19, particularly in the hospital setting. Two therapies, one investigational (remdesivir) and one that has been FDA approved for years (dexamethasone), have been reported to improve clinical disease and in the case of dexamethasone, mortality. [6, 7] Numerous medications are currently under investigation including additional studies of remdesivir, lopinavir/ritonavir, chloroquine, HCQ, and numerous immunomodulatory agents. No therapies have been approved for pre- or post-exposure prophylaxis and clinical trials are currently underway. [8, 9] While the large RECOVERY trial has reported results from the HCQ arm and report no benefit from HCQ for therapy in the hospital setting, it remains unclear if there is a benefit from HCQ in the setting of pre- or post-exposure prophylaxis.

In February 2020, Wang and his colleagues demonstrated potent *in vitro* activity of chloroquine against SARS-CoV-2 at low micromolar concentrations. This was consistent with prior data illustrating chloroquine's activity against SARS-CoV-1 and MERS-CoV. [10] Liu et al and Yao et al have similarly reported micromolar concentration EC50 for hydroxychloroquine on SARS-CoV-2. [11, 12]

Both Chloroquine and HCQ are alkalinizing lysosomatrophic drugs that accumulate in lysosomes and block viral infection by increasing lysosomal pH, which is required for the virus/cell fusion. Coronavirus infectivity is extremely sensitive to pH, and increasing the pH inhibits virus/cell fusion. [13] They also interfere with the glycosylation of the cellular receptors of coronaviruses, including SARS-CoV-2. One of the benefit of chloroquine and HCQ function at both entry and post-entry stages of the infection. [10]

In addition to the potential antiviral effect, hydroxychloroquine is a well-recognized immunomodulatory agent, currently used as a disease-modifying agent in autoimmune diseases including systemic lupus erythematosus. Use may prevent the severity of COVID-19 or attenuate the development of immune-mediated complications such as acute respiratory distress syndrome (ARDS). [14] ARDS is a potentially severe complication of COVID-19 infection. In the study of 138 patients in Wuhan, ARDS developed in 20 percent after a median of eight days, and mechanical ventilation was implemented in 12.3 percent. [15] In another study of 201 hospitalized patients with COVID-19 in Wuhan, 41 percent developed ARDS. Of note, age greater than 65 years, diabetes mellitus, and hypertension were all associated with development of ARDS. [16]

Hydroxychloroquine has similar activity to chloroquine in prior studies examining its efficacy in treatment of MERS and SARS. It has a better safety and tolerability profile than chloroquine. [8] It has already been FDA approved for malaria prophylaxis and treatment of various autoimmune conditions including rheumatoid arthritis and lupus. It can be dosed orally in a once daily formulation, which would be ideal for prophylaxis. It has a long serum half-life and, if effective, protection should last beyond cessation of prophylaxis.

2.3. Benefit/Risk Assessment

The risks for participation in this study include taking study drug, phlebotomy blood draws, and nasopharyngeal swabs. The safety of HCQ is well known and the risk of taking the drug is particularly low given the short course of therapy. There may be some benefit to the participant if the prophylactic therapy is effective and prevents transmission of infection and/or clinical disease.

2.3.1. Risk Assessment

Blood draw risks: Risks associated with drawing blood include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Nasopharyngeal swab risks: Risks include mild irritation, insignificant local pain, and minor bleeding.

Hydroxychloroquine risks: Hydroxychloroquine has been used clinically for years as a prophylactic and treatment for malaria, and in the United States more broadly for autoimmune conditions. The primary toxicity concerns include retinopathy, QTc prolongation, nausea, rash and bone marrow suppression. While toxicity is more common with long-term use as done for autoimmune conditions, it's prudent to consider these risks. Risks of HCQ include:

- Retinopathy: The recommended maximum dose to limit toxicity is 5 mg/kg actual body weight per day. The retinopathy risks increases once the total exposure is >1000 g. The

proposed dose of 600 mg BID on day 1 followed by 400 mg QD for 29 days does not exceed 20 g. Due to the finite therapy and the low total exposure, the risk for retinopathy is low and thus does not warrant a baseline eye exam.

- QTc prolongation: QTc prolongation is a risk for chloroquine and thus may be a risk for HCQ, although the risk is believed to be lower. The risk of QTc prolongation is more likely an issue for HCQ when dosed with other concomitant medications that prolong QTc. For this reason, concomitant medications with high risk for QTc prolongation will be excluded as will congenital QTc prolongation syndromes.
- Allergic rash: In approximately 1-5% of patients, an allergic rash develops. This pruritic eruption usually occurs after 1-2 weeks of dosing. Guidance will be provided to teams for managing allergic rash.
- Nausea/diarrhea: Gastrointestinal symptoms may occur with higher doses and sometimes with daily dosing of HCQ. Dividing daily dosing BID or TID is a commonly used strategy to improve tolerance. Guidance will be provided to teams for managing nausea and diarrhea.
- Severe hypoglycemia including loss of consciousness that could be life threatening has been reported in patients treated with or without antidiabetic medications.
- Neuropsychiatric events, including suicidal behavior have been reported.
- Other potential toxicities including bone marrow suppression, arrhythmia, and hypoglycemia. These are not likely with a finite course of therapy. Furthermore, there is no evidence that G6PD deficiency is a problem with HCQ. While different class of antimalarial causes hemolysis with G6PD deficiency, there are no reports of hemolysis with HCQ.

Risk lowering measures: Study procedures to manage and minimize risks include careful selection of the participants and monitoring over time to check on participants' health. Additional guidance to manage any risks will be provided to the study teams, as needed. In addition, an independent DSMB will monitor safety of the participants throughout the study.

2.3.2. Benefit Assessment

Participants who randomize to the treatment group may benefit from the prophylactic study drug administration. There is no direct benefit to participants randomized to the control group apart from participating in generating evidence that may ultimately support preventative therapy for SARS-CoV-2 infection. Participants will receive information about the best personal protective measures to prevent SARS-CoV-2 infection. In addition, they will benefit from involvement with the team following their health status during the study. The knowledge gained will be a benefit to others in the future. This is an opportunity to answer important questions for public health and prevention of SARS-CoV-2 infection for HCWs. Clarifying the adverse effect profile of HCQ in HCWs will also inform the public taking HCQ for prophylaxis of SARS-CoV-2 infection and potentially treatment of COVID-19.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	

• To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in HCWs	• Clinical infection with COVID-19:
	  ○ Confirmed: new-onset of fever or cough or dyspnea AND confirmed COVID-19 positive test result via local PCR testing, OR
	  ○ Suspected: new-onset fever or cough or dyspnea without local PCR testing due to local restrictions and/or testing policies

Secondary	
• To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs • Evaluate safety and tolerability of HCQ	• Viral shedding of SARS-CoV-2: ○ Central lab confirmed COVID-19 test • Safety and tolerability as determined by weekly DSMB assessment of subject reported serious adverse events (SAEs) and HCQ-associated Events of Special Interest (Section 9.1.4)
Exploratory	

• Evaluate SARS-CoV-2 seroconversion in participants taking HCQ
• Describe COVID-19 infectious complications in participants taking HCQ
• Describe time off from work for medical reasons in participants taking HCQ
• Describe QoL
• Describe experience of household contacts
	• Seroconversion at 1 month
	• COVID-19 complications:
	  ○ hospitalization
	  ○ ICU level care or ventilation
	• Days sick or lost work-time
	• Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress-Anxiety-Short Form, a Single Item Burnout Measure, Patient Health Questionnaire (PHQ-2)
	• Patient-reported clinical infections among household contacts and other impacts on household

4. Study Design

Refer to Section 1.2 for the Study Schema.

4.1. Overall Design

Potential participations will be pre-screened from the HERO Registry. Potentially eligible participants who indicate interest in trial participation in the HERO Registry and work at one of the 40 U.S. sites participating in this trial will be approached for participation in the HERO-HCQ trial. Please refer to Section 5.3 for more details about the recruitment and informed consent process. Approximately 2,000 HCWs from 40 U.S. sites will be enrolled in this trial and followed for ~60 days.

Eligible participants will be randomly assigned (1:1), stratified by site, to either treatment group (HCQ) or placebo in a double-blind fashion. After enrollment, baseline assessments will include nasopharyngeal swab for COVID-19 and a blood sample to assess baseline serology for SARS-CoV-2. For convenience, follow-up will be performed weekly through a direct to participant portal. A call center will provide support for any missed visits. Follow-up includes screening for COVID-19 clinical signs and/or symptoms, other respiratory infections, non-infectious clinical events, adverse events, and QoL assessments. For more details regarding follow-up procedures, please refer to Section 8.1.2.

A visit at approximately 30 days after randomization will be done on site to assess any subsequent clinical or safety events and adherence to study drug. A nasopharyngeal swab for COVID-19 and a blood sample will be obtained to assess for seroconversion for COVID-19 or other related tests.

An end of study visit will be conducted at approximately 60 days via the direct to participant portal or call center to assess for any subsequent clinical or safety events.

4.2. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Final Visit at 60 days.

The end of the study is defined as the date of the last visit of the last participant in the study. Data from interim analyses or recommendations by the DSMB may result in protocol modifications or early termination of the study.

5. Study Population

All Eligibility Criteria will be obtained per participant.

5.1. Inclusion Criteria

1. Completed Informed Consent
2. Age ≥ 18 years old
3. Currently working in any environment in which there is a risk of exposure to patients with COVID-19 infections ("healthcare worker") including, but not limited to, the following example work exposures:
    a. in the Intensive Care Unit (ICU), **or**
    b. in the Emergency department, **or**
    c. in Emergency services, **or**
    d. in a COVID-19 hospital unit/ward, **or**
    e. in respiratory services, **or**
    f. in COVID-19 testing location, **or**
    g. in a clinical or research laboratory handling COVID-19 patient samples, **or**
    h. in inpatient hospital unit/area, **or**
    i. in long-term care, assisted living or skilled nursing facilities, **or**
    j. in outpatient care, **or**
    k. in dental offices, **or**
    l. in home health care, **or**
    m. in health services for incarcerated populations, **or**
    n. in dialysis centers.

5.2. Exclusion Criteria

1. Prior diagnosis of COVID-19 infection
2. Participation in another COVID-19 prophylaxis trial within 30 days of consent
3. Respiratory illness with new-onset fever (Temperature > 100°F) or ongoing cough or dyspnea within 14 days
4. Known allergy to HCQ or chloroquine
5. Congenital prolonged QT syndrome
6. Current or planned use of QT prolonging drugs (e.g. procainamide, disopyramide, mexiletine, flecainide, propafenone, amiodarone, sotalol, cimetidine, dronedarone, dofetilide, levofloxacin, ciprofloxacin, moxifloxacin) and other contraindicated medications [see Manual of Procedures (MOP) for full list of contraindicated medications]
7. End stage renal disease
8. Pre-existing retinopathy
9. Current or planned use of HCQ (study drug) for any indication
10. Current or planned use of the following for treatment or prevention of COVID-19 infection:
    a. Chloroquine
    b. Azithromycin

11. Known cirrhosis or severe liver disease
12. History of severe skin reactions such as Steven-Johnson syndrome, toxic epidermal necrolysis
13. History of psoriasis or porphyria
14. Ventricular arrhythmias requiring medical treatment
15. Severe coronary artery disease or heart failure/cardiomyopathy with ongoing symptoms
16. Current or planned use of use of anti-seizure drugs
17. History of Glucose-6-phosphate dehydrogenase deficiency

5.3. Recruitment and Engagement

5.3.1. Participant Recruitment

To ensure HERO-HCQ accrues and retains the number and diversity of participants required to assess the primary and secondary endpoints, the HERO Registry will be used to facilliate participant recruitment. Sites may also recruit directly from their communities, with onboarding facilitated through the HERO Registry.

IRB-approved materials will be available on the HERO study website, including videos with English or Spanish subtitles, frequently asked questions (FAQs), and testimonials from participants. Potential participants who would like to learn more about the study will be directed to the study call center or the study website.

The HERO registry will be used to pre-screen potential HCWs for this study. Registry leadership will periodically review the list of registry participants to identify potential participants and ensure methods are used to populate the trial to achieve the objectives as well as diversity. Participants who appear to be eligible based on demographics (including geographic region), clinical characteristics, and interest in being contacted about trial participation will either be sent an email invitation or be contacted directly regarding the HERO-HCQ clinical trial. The email invitation will contain instructions for contacting the trial team to obtain more information and complete screening.

5.3.2. Participant Engagement

Participants will be engaged in the study through multiple channels. This includes, but is not limited to, ongoing participation in the HERO Registry and Patient Reported Outcomes via the online pariticipant portal. Additionally, participant engagement will include:

- creating a study-wide Healthcare Worker Advisory Group;
- developing participant-centered approaches that recognize the needs and preferences of healthcare workers locally and nationally; and
- multifaceted approaches that combine engagement tools, leverage the participant portal, use of social media, and representative healthcare worker associations or leaders.

5.3.3. Participant Randomization Process

Randomization will be stratified by site and occur onsite. Randomization will be monitored closely and the HERO registry for pre-screening will be used to ensure inclusion of key

subgroups and to ensure the trial results are applicable to an appropriately diverse population of HCWs who work in COVID-19 exposure areas. Both participants and the study team will remain blinded to assignment throughout the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, who fulfill inclusion and exclusion criteria, but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who are considered screen failures may not be re-screened.

6. Study Drug(s)

Study drug is defined as any investigational drug(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Hydroxychloroquine

6.1.1. Formulation, Appearance, Packaging, and Labeling

Hydroxychloroquine sulfate tablets are provided as white/off-white, film-coated, round tablets. Each tablet contains 200 mg of the active ingredient (HCQ sulfate). The non-active ingredients in the formulation include black ink, calcium hydrogenophosphate, carnauba wax, cornstarch, magnesium stearate, Opadry White YS-I-7443 and polyethylene glycol 400.

Study drug will be packaged and labeled in a masked manner and in compliance with regulatory requirements.

6.1.2. Drug Dispensing, Storage, and Stability

A quantity of study drug sufficient for 30-days will be provided to the participant at enrollment. Hydroxychloroquine should be stored at room temperature (15°C - 30°C).

6.1.3. Dosing and Administration

Participants will receive a 600 mg BID loading dose of study drug for the first day, followed by 400 mg QD for 29 days. All study drug doses will be oral self-administrations. Study drug will be supplied as 200 mg tablets.

6.1.4. Rationale for Selection of Dose

Hydroxychloroquine is an aminoquinolone antimalarial agent that is also approved and used for the treatment of autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus.

Studies have demonstrated *in vitro* activity of chloroquine against SARS-CoV. [17, 18] Both chloroquine and HCQ have been reported to have *in vitro* antiviral activity against SARS-CoV-2. [11, 12] *In vitro* testing using Vero cells vary; Yao et al demonstrated an EC50 of 23.90 and 5.47 uL for chloroquine at 24 and 48 hours respectively, compared to 6.14 and 0.72 for HCQ. [12] Liu et al reported on four multiplicities of infection (MOIs) (0.01, 0.02, 0.2, and 0.8); the 50% maximal effective concentration (EC50) for chloroquine was (2.71, 3.81, 7.14, and 7.36 μM) and for HCQ was (4.51, 4.06, 17.31, and 12.96 μM). Hydroxychloroquine may exhibit higher activity to chloroquine in protecting Vero cells from infection ("prophylaxis"); when Vero cells were pre-treated with drug before SARS-CoV-2 challenge, EC50 for chloroquine was >100 and 18.01 uL at 24 and 48 hours, respectively, compared to 6.25 and 5.85 for HCQ. [12] In animals, both drugs share similar tissue distribution patterns, with high concentrations in the liver, spleen, kidney, and lung reaching levels of 200–700 times higher than those in the plasma. [19]

The optimal dose of HCQ for treatment or prophylaxis is unknown. Absorption after oral dosing is incomplete and variable (~70% [range: 25 to 100%]). [20] Metabolism is primarily hepatic with metabolites including bidesethylchloroquine, desethylhydroxychloroquine, and desethylchloroquine. [21] The drug has long half-life elimination of approximately 40 days. [20]

Standard dosing in other medical conditions include: systemic lupus erythematosus (200-400 mg daily given once or divided BID), malaria treatment (800 x1, followed by 400 mg at 6, 24 & 48 h after initial dose), Q fever (600 mg/day in 1 to 3 divided doses) and rheumatoid arthritis (200-400 mg daily in 1-2 divided doses). The recommended maximum dose of HCQ is 5 mg/kg Actual Body Weight daily.

The dose chosen for this study is 600 mg orally BID on day 1 as a loading dose followed by 400 mg QD for an additional 29 days. This dose was chosen for several reasons:

- current *in vitro* studies report a wide range of EC50 for SARS-CoV-2,
- variability of absorption and of tissue distribution into the lung,
- due to a lack of phase 1b data for this drug in SARS-CoV-2 infection, the optimal pharmacokinetic/pharmacodynamic target is unknown.

Yao et al made assumptions regarding the absorption and tissue distribution that were optimistic and recommended as an optimal treatment dose 400 mg BID on day 1 as a loading dose followed by 200 mg BID daily for the remainder of the treatment course. [12] There is concern that this dose will not meet the necessary pharmacokinetic/pharmacodynamic targets for efficacy, in which case a negative study would not be due to failure of the antiviral efficacy but of suboptimal dosing. Yao et al also noted that the drug exposure was the same for 200 mg BID or 400 mg QD daily dosing. We propose a higher loading dose of 600 mg BID on day 1 to ensure more rapid steady state tissue distribution and 400 mg QD (versus BID) dosing for ease of dosing and adherence.

6.2. Placebo

6.2.1. Formulation, Appearance, Packaging, and Labeling

Placebo will be provided in a similar appearance as the study drug and be packaged and labeled in a masked manner in compliance with regulatory requirements.

6.2.2. Drug Dispensing, Storage, and Stability

A quantity of study drug sufficient for 30-days will be provided to the participant at enrollment. Placebo should be stored at room temperature (15°C - 30°C).

6.2.3. Dosing and Administration

All placebo doses will be oral self-administrations. Placebo tablets will be provided in a dose that mimics the pill count of the study drug (HCQ).

6.2.4. Rationale for Selection of Dose

N/A

6.3. Study Drug Accountability

Use of study drug will be tracked via the participant portal, call center, or final in-person study visit. Adherence to study drug as provided will be assumed unless reported otherwise.

Participants will dispose of any unused study drug as they would normally when stopping a medication.

6.4. Concomitant Therapy

Select concomitant medications of interest that the participant is receiving at the time of enrollment or receives during the course of the study will be recorded along with dosing information. Select concomitant medications of interest include the following:

- Therapeutics that are being used in other COVID clinical trials
- Antibiotics
- Antifungals
- Immunosuppressants including steroids
- Tylenol
- Nonsteroidal anti-inflammatory drugs
- Angiotensin-converting-enzyme (ACE)/angiotensin II receptor blockers (ARB)/angiotensin receptor neprilysin inhibitor (ARNI)
- Statin
- HIV protease inhibitors including lopinavir, ritonavir, atazanavir, darunavir
- ribavirin

Prohibited medications include those at high risk for QT prolongation including:

- procainamide,
- disopyramide,
- mexiletine,
- flecainide,
- propafenone.
- amiodarone,
- sotalol,
- cimetidine
- dronedarone,
- dofetilide
- fluoroquinolones including ciprofloxacin, levofloxacin, moxifloxacin
- see MOP for full list of contraindicated medications

6.5. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule. The maximal daily dosing should not exceed what is specified in the protocol.

If moderate or severe adverse event (AE) occurs, that is, in the opinion of the investigator, reasonably attributable to study intervention, then dose may be altered by changing from QD to BID dosing, may be temporarily halted, or may be reduced, in consultation with the study CCC. Relevant reporting and discussion with the CCC study personnel, must take place prior to dose modification.

If the same SAE occurs consistently across participants, then dose or frequency of dosing may be reduced by trial leadership or per any DSMB recommendations.

6.6. Intervention After the End of the Study

No additional study drug will be provided to the participant following completion of the study.

7. Participant Withdrawal/Termination and Study Termination

7.1. Participant Withdrawal/Termination

Participants will be followed until participant closeout, withdrawal of consent, or death.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Those who request withdrawal from the study will be asked to continue on study follow-up with limited participation through the Final Visit (Section 8.1.3). Limited participation may include a call at 30 days and 60 days to assess safety.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2. Premature Termination or Suspension of the Study

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification will be provided documenting reason for study suspension or termination to the investigators, funding agency, and regulatory authorities, as appropriate. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility after a sufficient time has passed for accrual of the primary and secondary outcomes
- Recommendation by the DSMB

7.3. Lost to Follow-up

Participants will be asked for proxy contacts to assess vital status and/or other clinical events if a participant repeatedly fails to return for scheduled visits or does not participant in remote visits. A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits or does not participate in remote visits and neither the participant nor his or her proxy can be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic or participate in remote visits as required by the study:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule.
- The site or call center will contact the participant’s proxy to assess vital status or other clinical or safety events.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. If safe, and appropriate, participants who fail to respond to study contact should be contacted at work by the study team since these participants are employees of the facility.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

8. Study Assessments and Procedures

The study site will perform the baseline visit, which includes randomization, if eligible. The site will confirm suitability to receive study drug. Sites will be responsible for notifying the coordinating center for participant withdrawals, lost to follow-up, permanent cessation of study drug, study drug dose modifications, or change in vital status. Data is being collected directly from participant and supported by medical records, as needed.

8.1. Schedule of Events

Table 1: Schedule of Events

	Baseline: Onsite (Day 0)	**Follow-up: Remote (Day 7 ± 2 days)**	**Follow-up: Remote (Day 14 ± 2 days)**	**Follow-up: Remote (Day 21 ± 2 days)**	**Follow-up: Onsite (Day 30 + 5 days)**	**Final Visit: Remote (Day 60 + 5 days)**
Healthcare Worker Clinical Trial						
Consent	X					
Demographic Information	X					
Eligibility criteria confirmed	X					
Randomization	X					
Receipt of study drug or placebo	X					
Continued use study drug		Continuous				
Clinical Assessments						
Abbreviated medical history	X					
Concomitant Meds of Interest	X		X		X	X
Temperature	X					
COVID-19 Questionnaire		X	X	X	X	X
QoL Questionnaires	X		X		X	X
SAEs and Events of Special Interest[1]		Continuous via participant portal and at Onsite Visits				
Biospecimen Collection						
Nasopharyngeal swab for COVID-19	X				X	
Blood collection for exploratory analysis	X				X	

[1] Participant's medical record may be reviewed to confirm SAEs and Events of Special Interest (EOSIs).

8.1.1. Baseline (On-site, Day 0)

The following events will occur at the Baseline study visit:

- Consent: The consent process should be done in accordance with local IRB requirements. Phone consenting may be facilitated through the e-consent process via the online portal.
- Demographic information will be collected including, but not limited to, age, sex, race, ethnicity, and occupation
- Eligibility criteria confirmation
- Randomization: Participants must be randomized within 3 days of consent, which can be done in-person or by phone.
- Participant will receive 30-day supply of study drug or placebo
- Abbreviated medical history including smoking status, pre-existing underlying lung disease, underlying immunosuppression (transplant, malignancy, HIV, autoimmune disease), medical conditions that may increase risk of COVID-19 infections or complications (diabetes, cardiovascular disease)
- Concomitant medications of interest (Section 6.4)
- Temperature
- QoL questionnaires
- Nasopharyngeal swab for COVID-19 diagnosis
- Blood collection for exploratory analysis

8.1.2. Follow-Up

The following events will occur at the Follow-Up study visits:

Follow-up (Day 7 ± 2 days – Remote):

- COVID-19 Questionnaire
- Serious Adverse Event and EOSI collection

Follow-up (Day 14 ± 2 days – Remote):

- Concomitant medications of interest (Section 6.4)
- COVID-19 Questionnaire
- QoL questionnaires
- Serious Adverse Event and EOSI collection

Follow-up (Day 21 ± 2 days – Remote):

- COVID-19 Questionnaire
- Serious Adverse Event and EOSI collection

Follow-up (Day 30 + 5 days – Onsite):

- Concomitant medications of interest (Section 6.4)
- COVID-19 Questionnaire
- QoL questionnaires
- Serious Adverse Event and EOSI collection
- Nasopharyngeal swab for COVID-19 diagnosis

- Blood collection for exploratory analysis

8.1.3. Final Visit (Day 60 + 5 days - Remote)

The following events will occur at the Final Visit:

- Concomitant medications of interest (Section 6.4)
- COVID-19 Questionnaire
- QoL questionnaires
- Serious Adverse Event and EOSI collection

8.2. Clinical Assessments

Temperature: temperature will be assessed

Nasopharyngeal swab for COVID-19: Nasopharyngeal swabs are commonly used for the detection of respiratory viruses such as respiratory syncytial virus, influenza virus and coronavirus. A swab is inserted into the nostril and advanced along the floor of the nose until the posterior nasopharynx has been reached and gently rotated several times to collect sufficient specimen for testing.

The reference lab will notify sites of positive COVID-19 test results. Sites are expected to inform participants and the state health department of positive COVID-19 test results. The notification process will occur per local guidance and will **not** be tracked or documented by the study team.

8.3. Quality of Life and COVID Questionnaires

COVID-19 Questionnaire

The following QoL questionnaires will be used in this study:

- PROMIS Emotional Distress – Anxiety – Short Form: Patient-Reported Outcomes Measurement Information System (PROMIS) measures were developed through a collaborative process funded by the National Institutes of Health (NIH). [22] Anxiety has been identified by the PROMIS Steering Committee as a key domain of mental health and was defined as “autonomic arousal and experience of threat”, [23] which may compound the effects of stress in healthcare providers. [24] The PROMIS Emotional Distress – Anxiety-Short Form [25] has previously been shown to reliably assess anxiety in a variety of clinical populations. [26-28] The Anxiety short form consists of eight items each rated from 1-5 points (1=never and 5=always), with higher scores indicating greater anxiety.
- Single-item burnout measure: Prior work has demonstrated that burnout among medical professionals may adversely affect patient care. The current standard for burnout assessment is the Maslach Burnout Inventory (MBI), however, the full MBI consists of 22 items and may be burdensome to complete. Across previous studies, one emotional exhaustion (EE) question (“I feel burned out from my work”, rated on a 7-point Likert scale ranging from “Never” to “Daily”, with higher scores indicating more burnout) has exhibited high factor loading within its respective domain (MBI-EE). [29-32] A non-

proprietary adaptation of this item [33] has shown good performance relative to the full MBI in prior studies of medical students and physicians. [34, 35]

- Patient Health Questionnaire (PHQ-2): The Patient Health Questionnaire (PHQ-9) is a 9-item tool commonly used to assess depression severity. Given the need for a briefer measure to screen for depression in busy settings, a 2-item version of the depression module has been developed and validated. [36] The abbreviated scale, known as the PHQ-2, consists of questions about two domains: frequency of depressed mood and anhedonia, each scored from zero (not at all) to three (every day), with higher scores indicating greater depression severity. The measure has demonstrated good performance in diverse clinical [37-40] and healthcare provider populations. [41-44]

9. Safety Assessments

9.1. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. An AE can therefore be any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator.

A SAE or serious suspected adverse reaction or serious adverse reaction as determined by the investigator or the sponsor is an adverse event that results in any of the following serious outcomes:

- Death
- Life-threatening AE ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE. Hospitalization is defined as a stay in the hospital exceeding 24 hours.

An unexpected adverse event is defined as any adverse event, the specificity or severity of which is not consistent with the package insert.

9.1.1. Collection Period for AE and SAE Information

Study participants (and their designated emergency proxies) will be instructed to report Events of Special Interest (EOSI) and SAEs through their access to the study's participant portal. Events of special interest and SAEs will also be elicited during each remote follow-up visit and during the Baseline and Day 30 onsite visits. Participants will have access to AE reporting via the electronic portal from the signing of the informed consent form (ICF) until the Final Visit (Day 60).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be considered an AE.

Non-serious AEs will not be collected unless the event meets the criteria of an EOSI.

Events of Special Interest will be collected from the start of study drug until Final Visit or until 30 days after the last dose if participant early terminates the study.

Serious adverse events will be collected from the start of study drug until Final Visit or until 30 days after the last dose if participant early terminates the study.

9.1.2. Assessing Causality of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

If a SUSAR occurs, the investigator/delegate will assess the relationship to study drug by using the following criteria:

- Related: The event has a relationship to study drug.
- Not related: The event has no temporal relationship to study drug or the AE has a much more likely alternate etiology or due to an underlying or concurrent illness or effect of another drug.

9.1.3. Reporting and Monitoring of SAEs

Although HCQ is approved for marketing in the United States, its investigational use for prevention of COVID-19 infection is not an approved indication, but will be under an IND and subject to IND regulations in 21 CFR 312. Listings of all SAEs, Events of Special Interest, and Unanticipated Problems that are reported will be compiled for frequent DSMB review. There will be no expedited reporting of individual SAEs as safety reports per 21 CFR 312.32(c)(1)(i)(A) or 21 CFR 312.32(c)(1)(i)(B). The DSMB chair will review SAEs weekly, and the convened DSMB will perform aggregate reviews of SAEs every two weeks. The convened DSMB will be responsible for determining if the safety reporting criteria are met per 21 CFR 312.32(c)(1)(i)(C) and 21 CFR 312.32(c)(1)(iv) so that the IND sponsor and study team remain blinded. The DSMB will prepare an aggregate report for submission to the FDA if the DSMB determines that an SAE occurs markedly more frequently in the drug treatment group than in the control group. An aggregate safety report will be submitted to FDA as soon as possible, but in no case later than 15 calendar days after the DSMB determination. If the DSMB determines that an unexpected fatal or life-threatening suspected adverse reaction occurs markedly more frequently in the drug treatment group than in the control group, an aggregate safety report will be submitted to the FDA as soon as possible, but in no case later than 7 calendar days after the DSMB determination. Information on individual SAEs will be available upon request from the Agency following the submission of any aggregate reports.

Individual SUSARs will be reported by the DSMB as expedited events to the FDA; 7-day reports for unexpected fatal or life-threatening adverse reactions and 15-day reports for serious and unexpected adverse reactions. If the DSMB or FDA note a clinically important increase in the rate of a SUSAR, the DSMB will notify investigators no later than 15 calendar days after determining that the information qualifies for reporting.

9.1.4. Events of Special Interest

The following are considered Events of Special Interest and should be recorded even if they do not meet the criteria above as Serious Adverse Events.

The following are EOSI that are possibly related to the use of HCQ:

- Arrhythmias (ventricular)
- Hepatic Failure
- Bone marrow failure
- Aplastic anemia

- Prolonged QT interval
- Angioedema
- Dermatitis exfoliative
- Acute generalized exanthematous pustulosis (AGEP)
- Psychosis
- Suicidal Ideation
- Seizure
- Methemoglobinemia

The following are also considered Events of Interest to the study:

- Fevers
- Sepsis
- Acute renal failure
- Disseminated Intravascular Coagulation (DIC)
- Secondary bacterial infection

The following are treatments or interventions associated with an event that will be collected:

- Supplemental oxygen use
- Non-invasive ventilation including BiPAP/CPAP
- Pressors
- Mechanical ventilation/intubation
- Intensive Care Unit (ICU) admission
- Extracorporeal Membrane Oxygenation (ECMO)

9.2. Unanticipated Problem (UP) and Terminations

9.2.1. Definition of Unanticipated Problem

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.2.2. Reporting of an Unanticipated Problem

The site investigator will report UPs for their participants to the Data Coordinating Center (DCC). The site may also be required to inform their reviewing IRB about an UP occurring at the local institution. The UP report to the DCC will include the following:

- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP
- The Coordinating Center will document and review all UPs. Details of the UP reporting process will be located in the MOP.

10. Statistical Considerations

10.1. Statistical Hypotheses

10.1.1. Primary Hypothesis

- Allocation to HCQ results in prevention of COVID-19 infection among HCWs at risk for COVID-19 infection.

10.1.2. Secondary Hypotheses

- Allocation to HCQ results in prevention of viral shedding of SARS-CoV-2 among HCWs at risk for COVID-19 infection.
- Hydroxychloroquine administration will be safe and well tolerated.

10.2. Sample Size Determination

The sample size of approximately 2,000 randomized participants was selected to yield reasonable power for testing the primary outcome of clinical infection with COVID-19. Several design factors and research objectives have been considered in developing an appropriate sample size for the HERO-HCQ study.

Based on several recent randomized clinical trials studying HCQ for inpatient COVID-19 disease conditions, a reduction in the clinical infection risk by a relative 50% is considered a clinically important treatment effect. For the primary outcome of clinical infection of COVID-19, the sample size will provide 80% power to detect a 50% relative decrease in the risk for the intervention group compared to usual care assuming that the placebo group risk is 5%. Similarly, the proposed sample size will provide 80% power to detect a difference of 6.5% (active) vs. 10% (placebo). These calculations assume a two-sided Type I error rate of 0.05 with 1:1 randomization and are based on a two-group continuity corrected chi-square test.

10.3. Randomization

HERO-HCQ is a multi-center, double blind, randomized, parallel group, superiority study. Randomization will occur at the level of the individual participant. Eligible participants will be randomized via the study website in a 1:1 ratio to either HCQ or matching placebo. Randomization will be stratified by clinical site using a permuted block design with random block sizes. [45]

10.4. Blinding

The HERO-HCQ Steering Committee along with site investigators, PCORI Program Staff, and study participants will remain blinded until database lock. Limited staff will be unblinded to handle randomization codes, deliver the interventions to sites, and prepare DSMB reports. The statistical staff responsible for preparing DSMB reports will not directly interact with the clinical team that delivers care to the study participants.

The Interactive Voice Response System/Interactive Web Response System will be programmed with blind-breaking instructions. Participant safety must always be the first consideration in making an unblinding determination. If the investigator decides that unblinding is warranted, the

investigator should contact the Coordinating Center for unblinding a participant's intervention assignment.

10.5. Populations for Analyses

The primary analyses will include all randomized participants with a baseline negative RT-PCR test.

Analyses of safety and clinical events will be based on the population of all randomized participants.

10.6. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses outlined in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.6.1. General Considerations

Statistical comparisons will be performed using two-sided significance tests. Baseline demographic and clinical variables will be summarized for each randomized arm of the study. Descriptive summaries of the distribution of continuous variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles) along with means and standard deviations. Categorical variables will be summarized in terms of frequencies and percentages.

The primary endpoint is clinical infection with COVID-19. Individual participants are expected to receive study drug for 30 days and will be followed for another 30 days for clinical events and patient-reported outcomes. Data collected during the 60-day follow-up will be included in the primary analyses.

Participants that develop symptoms of COVID-19 will follow local clinical and/or employee health protocols for testing and management. If testing is done per protocol, the results will be used for confirmation of the primary outcome. However, in some regions, testing may not be done for individuals with suspected COVID-19 symptoms and low risk factors for severe disease. Instead, these individuals may be told to self-isolate and monitor symptoms in lieu of testing. To reflect the different approaches expected for testing and management of healthcare workers who develop symptoms of COVID-19, the primary outcome includes both confirmed and suspected clinical COVID-19 infections.

The primary endpoint will be tested at the two-sided 0.05 level. All secondary endpoints will be tested at the 0.05 level.

10.6.2. Primary Endpoint

The primary analysis of the primary endpoint will be based on the Fisher's exact test. The difference in proportions and the associated 95% confidence interval will be the primary measure used to summarize the treatment effect.

A secondary analysis of the primary outcome of clinical infection with COVID-19 will be based on a logistic regression model with an indicator variable for the treatment group. The estimated

odds ratio and associated 95% confidence interval will be used to summarize the results from these analyses.

A sensitivity analysis will use the time-to-clinical infection with COVID-19 outcome. For that analysis, the treatment groups will be compared using a Cox proportional hazards regression model with the baseline hazard function stratified by site. [46, 47] The estimated hazard ratio and associated 95% confidence interval will be used to summarize the treatment effect.

10.6.3. Secondary Endpoint(s)

For the viral shedding of SARS-CoV-2 endpoint, a linear regression model with an indicator variable for the treatment group and additional pre-specified covariates will be applied. Analytic details about other secondary endpoints will be included in the Statistical Analysis Plan.

The statistical comparisons of the randomized arms with respect to the SAEs and EOSI interest will use chi-square or other appropriate 2-sample methods. Analysis of all-cause mortality will be conducted using a log-rank test with event curves presented as Kaplan-Meier estimates. A Cox proportional hazards will be used to estimate the hazard ratio associated with the HCQ intervention. Analyses of all-cause and cause-specific hospitalizations will use similar strategies.

10.6.4. Exploratory Analysis

Details of the exploratory analyses will be described in the Statistical Analysis Plan.

10.6.5. Subgroup Analyses

In addition to analyses of secondary outcomes in Section 10.6.3, a set of analyses will be reported to explore whether intervention effects on the primary and secondary outcomes are consistent across subgroups of interest defined according to baseline characteristics. These subgroups will be specified in the Statistical Analysis Plan. The planned sub-groups will include age, sex, race/ethnicity, occupation, and COVID-19 risk factors.

For each subgroup analysis, a logistic regression model (or linear model) will be used that is similar to the one described above, but with additional terms identifying subgroup membership and the intervention by subgroup interaction.

10.6.6. Adherence and Retention Analysis

Treatment dropouts and consent withdrawals will be tracked by verifiable means at each follow-up assessment. Participants will be asked about their use of study drug during telephone follow-up. Those reporting discontinuation or switching will be asked about the reasons for discontinuation/switching.

Because study participants are HCWs, it is expected that this study will have excellent retention. Measures of study retention to inform follow-up time will be based on a number of measures, weekly web-based check-ins for symptoms and exposure history or in-person visit.

10.7. Interim Analyses

Regular DSMB reviews will be conducted to ensure the safety of study participants and evaluate the accumulating endpoint data by treatment group. Regular DSMB meetings will monitor the following parameters at a minimum:

- Recruitment progress
- Enrollment overall and by subgroups
- Adherence, retention, and status of data collection
- Events of special interest
- Unanticipated problems
- Serious adverse events (SAEs)

Interim examination of clinical endpoints will be based on the accrual of primary endpoint data. It is expected that reviews of the data will occur approximately weekly following the enrollment of the first participants.

For ethical reasons, interim examinations of key safety and process data will be performed at regular intervals during the course of the trial. The DCC will create reports to track participant enrollment, rates of adherence with the assigned treatment strategy, and frequency of protocol violations. Prior to each meeting, the DCC will conduct any requested statistical analyses and prepare a summary report along with the following information: participant enrollment reports, rates of adherence with the assigned treatment, and description of SAEs.

Safety reports will be prepared for the DSMB approximately weekly once enrollment begins. For futility monitoring, HERO-HCQ will employ a flexible approach based on the prediction interval methods of Evans, Li, and Wei. [48] These flexible methods allow for the assessment of treatment differences as well as the precision related to those estimates. The futility reviews may include predicted interval plots as a tool to summarize the information. To implement these methods, we will predict the confidence intervals at the end of the study conditional on a range of reasonable assumptions including the null hypothesis, the alternative hypothesis, and the observed trend. The upper and lower limits of these prediction intervals will be compared with 'acceptable' treatment group differences that allow for the incorporation of other information including the safety profile of the intervention. It is expected that the first futility assessment will occur once the first 1000 randomized participants have completed their 30-day visit. Additionally, conditional power calculations will be used to assess the futility of continuation in the presence of a small or negative treatment effect.

The method of Haybittle and Peto will be proposed as the primary guide for interpreting interim efficacy analyses. [49, 50] The four interim efficacy analyses are expected to occur after the first 1000, 1250, 1500, and 1750 participants have completed their 30-day visits. The proposed efficacy monitoring guideline uses large critical values ($p \leq 0.001$) for the treatment group comparison of the outcome of clinical infection with COVID-19 at each assessment until the planned final analysis. A two-sided stopping boundary for all-cause mortality with $p<0.001$ will be recommended for all reviews.

Monitoring boundaries are intended to guide the interpretation of interim analyses and are not a strict rule for early termination. It is expected that both internal and external factors will

influence the decisions of the DSMB. The Statistical Analysis Plan will describe the planned interim analyses and futility monitoring in greater detail.

10.8. Data Safety Monitoring Board (DSMB)

The DSMB will monitor participant safety and study performance. A DSMB charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the DCC and agreed upon by the DSMB. Reports will be prepared by the DCC in accordance with the plan outlined in the charter, or as requested by the DSMB chair, and will include interim analyses of primary and secondary endpoints, additional safety events, and other information as requested by the committee. After each scheduled closed meeting, the DSMB will send a recommendation to the IND sponsor to continue, modify, or terminate the study. After approval, the recommendations will be forwarded by the CCC to investigators for submission to their local, regional and national IRB/Ethic Committees, as applicable. DSMB reports will be the primary mechanism for reporting safety concerns to FDA, as needed. The DSMB will establish links with the FDA and other appropriate DSMBs as possible to ensure rapid communication of important safety findings as needed. Please refer to the DSMB Charter for further details.

11. Ethical Standards

11.1. Institutional Review Board (IRB)

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB(s) of record for review and approval. This approval must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB(s) before being implemented in the study. All changes to the consent form will also be IRB-approved and a determination will be made regarding whether previously consented participants need to be re-consented.

11.2. Informed Consent Process

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and documentation of informed consent is required prior to starting study procedures. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator (or their delegate) will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study team will distinguish between the desire to discontinue study drug and the desire to withdraw consent for study follow-up. In the event that a participant withdraws consent, the investigator or his designee will clarify with the participant and document whether the withdrawal is a temporary or permanent, and if a full or partial withdrawal.

11.3. Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical and private information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information will be securely stored in the clinical study database.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Duke Clinical Research Institute. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

11.4. Intended and Future Use of Stored Biosamples and Data

Samples and data will be available for use to understand COVID-19 exposure or related conditions. De-identified biological samples will be stored at the central lab. The central lab will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant. Access to stored samples will be reviewed using a biospecimen ancillary proposal application and review process. Data collected for this study will be stored at the DCRI. Data generated from the use of the biospecimens will be tracked and saved in password-protected computers.

After the study is completed, the de-identified, archived biospecimens and biospecimen data will be sent to the Coordinating Center. These samples could be used for research into COVID-19 or other health outcomes in this population. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed; however, samples already distributed to investigators will not be recalled and data generated from those samples will be retained.

11.5. Site Management and Quality Assurance

The study team will work in tandem to ensure that the data collected in this study are as complete and correct as possible. We will implement a four-step, multi-functional approach to quality control:

- Training: Prior to the start of enrollment, the clinician investigators and study coordinators at each site will be trained with the clinical protocol and data collection procedures, including how to use the Electronic Data Capture (EDC) system. Follow-up training and training for new study personnel will be conducted as needed.
- Monitoring: The CCC, along with the DCC, will ensure that data collection is handled properly, will provide in-service training, and will address questions from site investigators and coordinators. Review of data quality and completeness will occur on a regular and ongoing basis. Any issues will be addressed. There will be no on-site monitoring or source document verification.
- Managing data: After the data have been transferred for statistical summarization, data description, and data analysis, further crosschecking of the data will be performed with discrepant observations being flagged and appropriately resolved through a data query system.
- Reviewing data: Events of interest will be reviewed to ensure an appropriate standardized classification of the component events comprising the primary composite endpoint.

11.6. Site Monitoring

This study will employ a centralized risk-based approach to monitoring with routine and periodic review of participant-submitted data to validate informed consent process, identify and follow-up on missing data, inconsistent data, data outliers, etc. and ensure completion of administrative and regulatory processes. The study team will facilitate regular communication through training sessions, teleconferences, videoconferencing, email, etc. Using quality-by-design principles, steps will be taken at the study design stage to foresee and limit problems that might occur during the study conduct. Participant selection facilitated by the HERO registry should lead to efficient identification and enrollment of those who satisfy study eligibility and enrichment criteria. Follow-up from the portal and call center is expected to keep participants engaged and help them maintain their assigned treatment by regularly asking them about the treatment they take. Minimal levels of intervention and a focus on observing rather than influencing the study participants greatly increases the likelihood that Good Clinical Practices will be followed. Central statistical monitoring is particularly useful for identifying unusual patterns in data. We will deploy an integrated approach to quality surveillance, which will be detailed in the appropriate study management plans.

12. Data Handling and Record Keeping

12.1. Data Collection and Management Responsibilities

The data management platform for this study is primarily focused on a single web-based portal that will support all data collection and interactions with participants and study sites. Related operational systems supporting the Coordinating Center activities and services provided partners (e.g. lab, drug supply) will be embedded within each of those organizations and interfaced via a routine set of data transfers or application interfaces. The figure below (Figure 1) illustrates the systems and interactions required to enable a well-coordinated study delivery plan. Study participants accessing the system directly and the emphasis on self-reported data does require primary identifiers to be maintained within a limited number of systems. These data will be secured such that it is only maintained in the minimum required systems and accessible to the minimum number of people to perform the study procedures described in this protocol. The primary method of identifying a participant will be with a unique participant identification number.

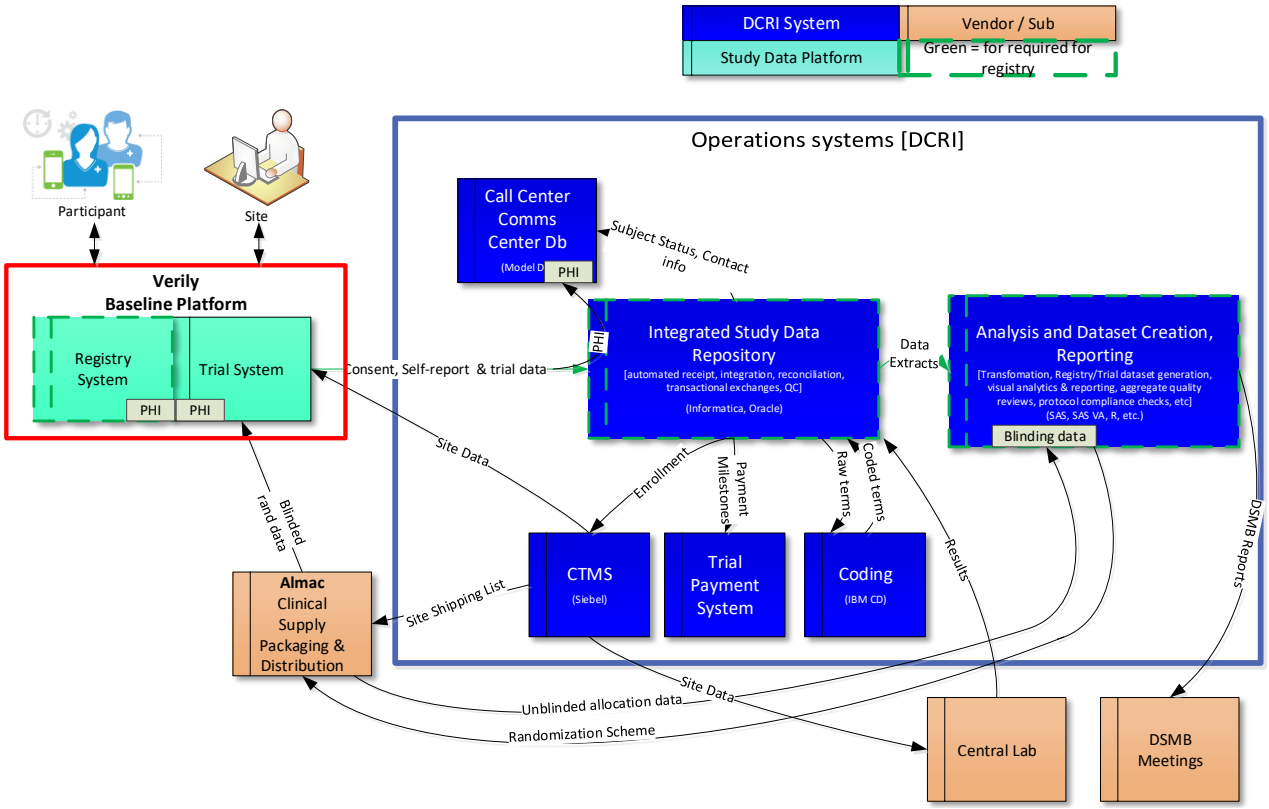


Figure 1: Data Flow Diagram

Participants will use a study portal developed by Verily for the consent, data reporting and scheduling activities in this study. The Verily system leverages the Google infrastructure, including hosting, security, user account management and the study-specific data system. Leveraging this infrastructure ensures very high levels of system security and support are embedded in the portal. Although leveraging Google infrastructure this is a stand-alone portal

and no data is shared from other sources with the study, and no study data will be shared with any other Google systems.

The study systems at the DCRI DCC support the orchestration of work across partners/vendors, integration of study data for operational reporting and statistical analysis, and business processes like tracking regulatory documents and processing site payments. All systems are 21CFR11 compliant and adhere to the Duke Information Security Office policies. All **e**xternal data transfers are exchanged via SSH File Transfer Protocol (SFTP) or encrypted application programming interface (API) directly between systems.

The call center staff will contact study participants directly, as described in the study consent form, to obtain precious follow-up information should a participant not respond directly within the portal. The participant contact information will be transferred from the portal into the communications system used by the call center for these contacts. This system manages call queues, scheduling, and call processing information. The study data obtained by the call center will be entered directly into the study portal.

The study data is managed using a set of tools including Oracle (relational database management system), Informatica (data exchange/extract-transform-load procedures), Cognos (operational reporting), SAS, and SAS Visual Analytics (statistics).

Data quality is managed at each stage of its lifecycle. Data collected in the portal conforms at inception to highly structured data elements and protocol-specific rules, subsequent data transfers are checked to conform to format and semantic specifications and all data is assessed for referential integrity across sources through a set of reconciliation practices upon integration then followed by a variety of logical checks within a participant and in aggregate.

12.2. Study Records Retention

Study documents should be retained for a minimum of six years after the study has ended. However, if required by local regulations, these documents should be retained for a longer period. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3. Protocol Deviations

A protocol deviation is defined as non-compliance with the clinical study protocol, GCP, or MOP requirements. The non-compliance may be on the part of the participant, site investigator, or the site staff.

A major protocol deviation is a significant divergence from the protocol that may have significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data. Major protocol deviations must be sent to the study IRB and local IRB per their guidelines, recorded in source documents, and reported to the coordinating center. Major protocol deviations will be tracked.

12.4. Publication and Data Sharing Policy

This study will comply with the PCORI Public Access Policy, which ensures that the public has access to the results of PCORI-funded research. Methods of data sharing for HERO-HCQ will include 1) archiving de-identified data in a data repository and 2) sharing of limited datasets under a Data Use Agreement (DUA) and IRB approval. Data will be made available to qualified investigators by archiving a fully de-identified dataset in a platform to be determined at the end of the trial. Both repositories allow users to search, view study information, and then submit an application to receive data. Prior to archiving study data, the DCC will produce a final dataset that will be stripped of all personal health information (PHI), including full date elements, in compliance with the Health Insurance Portability and Accountability Act (HIPAA) privacy rule. The relative timing of an event will be retained in the dataset converting to study days instead of dates.

The study result will be returned, including some participant specific results, to enhance value from participation. Study results will be disseminated to the public and the medical community through presentations at scientific meetings and publishing manuscripts in high impact peer-reviewed journals. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical studies registration policy as a condition for publication. The ICMJE defines a clinical study as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical studies be registered in a public registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the study in an acceptable registry, so the research results may be considered for publication in ICMJE member journals.

13. Study Leadership

The Steering Committee is a multi-stakeholder committee that oversees the study and includes representatives from clinical sites, the trial coordinating center, the PCORnet Coordinating center, HCWs and chaired by a member selected by the funding agency, PCORI.

The HCW Committee is composed of HCWs who represent potential participants of the trial to provide perspective of those who will ultimately benefit the most from the learnings or results of the trial. The HCW Committee will have input into the design, conduct, interpretation and dissemination of the trial.

The Executive Committee is a subset of the Steering Committee and consists of the Principal Investigators of the Clinical Coordinating Center (CCC), the DCC, and the Steering Committee Co-Chair. The Executive Committee is charged with overseeing the day-to-day operations of the trial as an extension of the Steering Committee, to ensure efficient and high-quality performance.

The Coordinating Center is composed of a CCC and a DCC, each overseen by principal investigator(s). The CCC is responsible for study coordination, site management, communication, and financial administration. The DCC is responsible for treatment allocations, receipt and processing of data, quality control programs, and statistical analysis and reporting.

An independent DSMB will oversee the safety and welfare of trial participants as well as provide recommendations for continuation, discontinuation or revision of the trial.

Figure 2: Operational Structure Diagram

14. Summary of Changes

Protocol Version (version #, date)	Summary of Changes
Version 0.2, 4/07/2020	Changed all study dates from weeks to days; updated Key Exclusion Criteria in the synopsis to be consistent with the Exclusion Criteria in the eligibility section (Section 5.2); updated schema to correct events that will occur in HERO Registry vs. HERO-HCQ Clinical trial (Section 1.2); clarified that all Eligibility Criteria will be obtained per participant (Section 5); modified inclusion criteria to allow HCWs in "related healthcare services" and those who work in a COVID-19 testing location or inpatient hospital unit/area with potential COVID-19 cases (Section 5.1); added cirrhosis as an Exclusion Criteria (Section 5.2); clarified that participant recruitment will be exclusively from the HERO Registry (Section 5.3.1); clarified that participants may be called at 30 and 60 days for follow-up after early withdrawal (Section 7.1); added that participants may be contacted at work for follow-up (Section 7.3); added windows to Study Visits (Section 8.1); added "Serious" to the AE collection line and a footnote to details medical record review at Final Visit for SAEs and Events of Special Interest (Table 1); added language that positive COVID-19 test results be communicated to sites and they are expected to report to the participant and state health department per local regulations (Section 8.2); provided more details about safety reporting to FDA (Section 9.1.3); removed specified document requirements for unblinding (Section 10.4); participants with suspected COVID-19 will be included in the primary outcome (Section 10.6.1); updated Interim Analysis Plan (Section 10.7); specified that the DSMB will send study recommendations to the IND sponsor only (Section 10.8); clarified that blood samples will be sent to a central lab (Section 11.4); updated the Data Flow Diagram to reflect

	changes in data flow (Figure 1); clarified that PCORI is the funding agency (Section 13); removed PCORI from the Operational Structure Diagram (Figure 2).
Version 1.0, 4/10/2020	Changed Randomization Section under Study Population to Participation Randomization Process sub-heading (Section 5.3.3) to avoid confusion with Randomization section in the Statistical Section (Section 10.3); corrected HCQ table shape from peanut-shaped to round (Section 6.1.1); added the following exclusion criteria per FDA recommendation (Section 5.2): history of severe skin reactions, history of psoriasis or porphyria, ventricular arrhythmias requiring medical treatment, severe coronary artery disease or heart failure/cardiomyopathy with ongoing symptoms, known cirrhosis or severe liver disease, current or planned use of anti-seizure drugs, history of Glucose-6-phosphate dehydrogenase deficiency; adding hypoglycemia and neuropsychiatric events as risks of taking HCQ (Section 2.3.1); updated the primary analysis population to include only randomized participants with a baseline negative RT-PCR test per FDA recommendation (Section 10.5); removed ITT population analysis (Sections 10.5 and 10.6.1); added all-cause mortality analysis (Section 10.6.3); changed proportional hazards to logistic regression (Section 10.6.5).
Version 2.0, 5/01/2020	Updated Key Inclusion and Exclusion Criteria in the Synopsis (Section 1); numbered eligibility criteria (Sections 5.1 and 5.2); added the following to Inclusion Criteria: broadened definition of HCW and removed “able to speak and read English or Spanish” (Section 5.1); added the following Exclusion Criteria: current or planned use of HCQ (study drug) for any indication and removed HCQ from the subsequent bullet due to redundancy with the added criteria (Section 5.2); updated participant recruitment and engagement strategies (Sections 5.3.1 and

	5.3.2); COVID-19 questionnaire and AE collection removed at baseline (Table 1 and Section 8.1.1); clarified that data may be collected from participant's medical record (Section 8 and Table 1); sites should notify CC of HCW dose modifications (Section 8); added that randomization should occur within 3 days of consent and may be done in-person or by phone (Section 8.1.1); AE collection changed to SAE and EOSI collection as only SAEs and EOSIs will be collection (Sections 8.1.1, 8.1.2, and 8.1.3); added SUSAR causality and expedited reporting of SUSARs to FDA (Section 9); corrected Quality Insurance to Quality Assurance (Section 11.5); other administrative changes.
Version 3.0, 7/07/2020	Updated Study Rationale and Background (Sections 1.2, 2.1, 2.2). Changed the definition of confirmed and suspected clinical infection with COVID-19 for the primary endpoints (Section 3). The rationale for this update is as follows: Initial reports of COVID like illness identified fever as the most common symptom, reported as occurring in >80% of cases; thus, in an attempt to increase the specificity of the definition for suspected clinical infection, the originally primary endpoint required 2 symptoms of fever plus either cough or dyspnea. Data from a recent publication [51] resulted in calculations that showed only 40% of lab confirmed cases reported fever, 30% reported fever plus cough and only 10% reported fever plus shortness of breath. Similarly, only 38% of probably cases reported fever, 25% reported fever plus cough and only 8% reported fever plus shortness of breath. This data indicates that the more stringent definition of suspected COVID infection would underestimate actual case rate. Thus the endpoint is being amended to redefine suspected clinical COVID infection as only one of three new-onset symptoms (fever or cough or dyspnea).

	Updated sample size (Sections 1.1, 1.2, 4.1 and 10.2), updated the statistical analysis plan for the primary objective and the interim analysis (Sections 1.1, 10.6.1, 10.6.2, 10.7), updated inclusion to broaden definition of HCW (Sections 1.1 and 5.1), clarified End of Study Visit as completing the Final Visit at 60 days (Section 4.2), and other minor administrative changes.

15. References

1. *COVID-19 Map FAQ*. 2020 [cited 2020; Available from: https://coronavirus.jhu.edu/map-faq.html.
2. McIntosh, K. *Coronavirus disease 2019*. 2020 [cited 2020 March 24].
3. Burton, T.a.L., P, *Human Testing Begins Earlier Than Expected For U.S. Coronavirus Vaccine.* The Wall Street Journal, 2020.
4. Minder, R.a.P., E, *Virus Knocks Thousands of Health Workers Out of Action in Europe.* The New York Times, 2020.
5. Wang, X., X. Zhang, and J. He, *Challenges to the system of reserve medical supplies for public health emergencies: reflections on the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in China.* Biosci Trends, 2020. **14**(1): p. 3-8.
6. Grein, J., et al., *Compassionate Use of Remdesivir for Patients with Severe Covid-19.* New England Journal of Medicine, 2020. **382**(24): p. 2327-2336.
7. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Preliminary Report.* New England Journal of Medicine, 2020.
8. McCreary, E.K., J.M. Pogue, and o.b.o.t.S.o.I.D. Pharmacists, *COVID-19 Treatment: A Review of Early and Emerging Options.* Open Forum Infectious Diseases, 2020.
9. Kalil, A.C., *Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics.* JAMA, 2020.
10. Wang, M., et al., *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.* Cell Research, 2020. **30**(3): p. 269-271.
11. Liu, J., et al., *Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro.* Cell Discovery, 2020. **6**(1): p. 16.
12. Yao, X., et al., *In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).* Clin Infect Dis, 2020.
13. Sturman, L.S., C.S. Ricard, and K.V. Holmes, *Conformational change of the coronavirus peplomer glycoprotein at pH 8.0 and 37 degrees C correlates with virus aggregation and virus-induced cell fusion.* J Virol, 1990. **64**(6): p. 3042-50.
14. Zhou, D., S.-M. Dai, and Q. Tong, *COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression.* Journal of Antimicrobial Chemotherapy, 2020.
15. Wang, D., et al., *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China.* JAMA, 2020. **323**(11): p. 1061-1069.
16. Wu, C., et al., *Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.* JAMA Internal Medicine, 2020.

17. Keyaerts, E., et al., *In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine.* Biochem Biophys Res Commun, 2004. **323**(1): p. 264-8.

18. Vincent, M.J., et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread.* Virol J, 2005. **2**: p. 69.

19. Fox, R.I., *Mechanism of action of hydroxychloroquine as an antirheumatic drug.* Semin Arthritis Rheum, 1993. **23**(2 Suppl 1): p. 82-91.

20. Tett, S.E., *Clinical pharmacokinetics of slow-acting antirheumatic drugs.* Clin Pharmacokinet, 1993. **25**(5): p. 392-407.

21. McChesney, E.W., et al., *Studies of the metabolism of some compounds of the 4-amino-7-chloroquinoline series.* J Pharmacol Exp Ther, 1966. **151**(3): p. 482-93.

22. Cella, D., et al., *The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years.* Med Care, 2007. **45**(5 Suppl 1): p. S3-S11.

23. *The Patient Reported Outcomes Measurement Information System (PROMIS): A Walk Through the First Four Years, (2009).*

24. Dyrbye, L.N., et al., *Association of Clinical Specialty With Symptoms of Burnout and Career Choice Regret Among US Resident Physicians.* JAMA, 2018. **320**(11): p. 1114-1130.

25. Pilkonis, P.A., et al., *Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger.* Assessment, 2011. **18**(3): p. 263-83.

26. Batterham, P.J., et al., *Psychometric Properties of 7- and 30-Day Versions of the PROMIS Emotional Distress Item Banks in an Australian Adult Sample.* Assessment, 2019. **26**(2): p. 249-259.

27. Teresi, J.A., et al., *Measurement Equivalence of the Patient Reported Outcomes Measurement Information System((R)) (PROMIS((R))) Pain Interference Short Form Items: Application to Ethnically Diverse Cancer and Palliative Care Populations.* Psychol Test Assess Model, 2016. **58**(2): p. 309-352.

28. Schalet, B.D., et al., *Clinical validity of PROMIS Depression, Anxiety, and Anger across diverse clinical samples.* J Clin Epidemiol, 2016. **73**: p. 119-27.

29. *Maslach C, Jackson SE. The measurement of experienced burnout. J Occ Behav. 1981;2:99–113.*

30. Gil-Monte, P.R., *Factorial validity of the Maslach Burnout Inventory (MBI-HSS) among Spanish professionals.* Rev Saude Publica, 2005. **39**(1): p. 1-8.

31. Kanste, O., J. Miettunen, and H. Kyngas, *Factor structure of the Maslach Burnout Inventory among Finnish nursing staff.* Nurs Health Sci, 2006. **8**(4): p. 201-7.

32. West, C.P., et al., *Single item measures of emotional exhaustion and depersonalization are useful for assessing burnout in medical professionals.* J Gen Intern Med, 2009. **24**(12): p. 1318-21.

33. *Rohland BM, Kruse GR, Rohrer JE. Validation of a single-item measure of burnout against the Maslach Burnout Inventory among physicians. Stress and Health. 2004;20(2):75–9. doi: 10.1002/smi.1002.*

34. McMurray, J.E., et al., *The work lives of women physicians results from the physician work life study. The SGIM Career Satisfaction Study Group.* J Gen Intern Med, 2000. **15**(6): p. 372-80.

35. Dolan, E.D., et al., *Using a single item to measure burnout in primary care staff: a psychometric evaluation.* J Gen Intern Med, 2015. **30**(5): p. 582-7.

36. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The Patient Health Questionnaire-2: validity of a two-item depression screener.* Med Care, 2003. **41**(11): p. 1284-92.

37. Arroll, B., et al., *Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population.* Ann Fam Med, 2010. **8**(4): p. 348-53.

38. Chagas, M.H., et al., *Validity of the PHQ-2 for the screening of major depression in Parkinson's disease: two questions and one important answer.* Aging Ment Health, 2011. **15**(7): p. 838-43.

39. Richardson, L.P., et al., *Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents.* Pediatrics, 2010. **125**(5): p. e1097-103.

40. Corson, K., M.S. Gerrity, and S.K. Dobscha, *Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item.* Am J Manag Care, 2004. **10**(11 Pt 2): p. 839-45.

41. Unrath, M., et al., *The mental health of primary care physicians in Rhineland-Palatinate, Germany: the prevalence of problems and identification of possible risk factors.* Dtsch Arztebl Int, 2012. **109**(11): p. 201-7.

42. *Brennan, J., McGrady, A., Whearty, K. et al. Emotional Status of Third Year Medical Students and Their Responses to a Brief Intervention. ANN BEHAV SCI MED EDUC 18, 10–14 (2012).* https://doi.org/10.1007/BF03355199.

43. Sen, S., et al., *A prospective cohort study investigating factors associated with depression during medical internship.* Arch Gen Psychiatry, 2010. **67**(6): p. 557-65.

44. Earle, L. and L. Kelly, *Coping strategies, depression, and anxiety among Ontario family medicine residents.* Can Fam Physician, 2005. **51**: p. 242-3.

45. Broglio, K., *Randomization in Clinical Trials: Permuted Blocks and Stratification.* Jama, 2018. **319**(21): p. 2223-2224.

46. Cox, D.R., *Regression Models and Life-Tables.* Journal of the Royal Statistical Society. Series B (Methodological), 1972. **34**(2): p. 187-220.

47. Glidden, D.V. and E. Vittinghoff, *Modelling clustered survival data from multicentre clinical trials.* Stat Med, 2004. **23**(3): p. 369-88.

48. Evans, S.R., L. Li, and L. Wei, *Data Monitoring in Clinical Trials Using Prediction.* Drug Information Journal, 2007. **41**(6): p. 733-742.

49. Haybittle, J.L., *Repeated assessment of results in clinical trials of cancer treatment.* Br J Radiol, 1971. **44**(526): p. 793-7.

50. Peto, R., et al., *Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design.* Br J Cancer, 1976. **34**(6): p. 585-612.

51. Boulware, D.R., et al., *A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19.* New England Journal of Medicine, 2020.