CLINICAL STUDY PROTOCOL

UTAH One (Understanding Treatment And Health in the Ongoing coroNa Epidemic): A Hydroxychloroquine Outpatient Study

Principal Investigators

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practice (GCP) and information privacy/security as required by the following:

- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46 (The Common Rule)
- International Council on Harmonization (ICH) E6 (R2)
- 45 CFR Part 160 and Part 164, Subparts A, C, and E

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

KEY ROLES

Individuals:

Principal Investigators: Adam Spivak, Rachel Hess

Data Coordinating Center Principal Investigators: Tom Greene, Rich Holubkov

Medical Monitor: Brandon Webb

Committees:

Trial Executive Committee: Adam Spivak, Rachel Hess, Tom Greene, Rich Holubkov, J. Michael Dean, Emily Spivak, Brandon Webb, Samuel Brown, Raj Srivastava, Ithan Peltan

Trial Advisory Committee: Willard Dere, Mark Briesacher, Angela Dunn

1.0 Definitions

Definitions

Eligible patients: All patients who meet all inclusion criteria and no exclusion criterion.

Consented participants: All eligible patients who have completed the consenting process.

Enrolled participants: All participants who have been randomized.

Intention-to-treat (ITT) Population: All enrolled participants, regardless of whether they received study drug or completed study procedures. This is the primary analysis population.

Study day: The calendar day of enrollment (randomization) is study day zero. The next day is study day one, and so on.

Assessment day: This corresponds to the survey instrument (day one survey is given on assessment day one).

Study Drug Discontinuation: Participant chooses to discontinue study drug, for any reason. Other study procedures may continue as decision of participant.

Study withdrawal: Participant discontinues study drug and does not wish to provide further study samples or data. Data recorded up to the time of withdrawal will be included in the study analysis.

Serious unexpected suspected adverse event (SUSAR)*.* A serious adverse event or drug reaction that is unexpected and believed related to participation in study.

2.0 Study Summary

2.1 Study title: Hydroxychloroquine for Outpatients with Confirmed COVID-19 (HCQ Trial).

2.2 Study objectives: Assess the efficacy and safety of hydroxychloroquine (HCQ) for reduction of viral shedding and hospitalization in outpatients with confirmed COVID-19.

2.3 Study hypothesis: Hydroxychloroquine is effective in reducing viral shedding and need for hospitalization in outpatients with confirmed COVID-19.

2.4 Study design: Phase 2, prospective, open-label, parallel group, randomized controlled trial

2.5 Inclusion criteria

Inclusion Criteria for Randomized Group:

- Patient age ≥18 years, competent to provide consent
- Within 72 hours of positive nucleic acid test for SARS-CoV-2

Inclusion Criteria for Household Contact Group:

- Individual age ≥18 living in the same house as someone diagnosed with COVID, competent to provide consent

2.6 Exclusion criteria

- Patient already prescribed chloroquine or hydroxychloroquine
- Allergy to hydroxychloroquine
- History of bone marrow or solid organ transplant
- Known G6PD deficiency
- Chronic hemodialysis, peritoneal dialysis, continuous renal replacement therapy or Glomerular Filtration Rate < 20ml/min/1.73m^2
- Known liver disease (e.g. Child Pugh score ≥ B or AST>2 times upper limit)
- Psoriasis
- Porphyria
- Known cardiac conduction delay (QTc > 500mSec)
- Concomitant use of digitalis, flecainide, amiodarone, procainamide, propafenone, or any other prescription medication known to prolong the QT interval
- Seizure disorder
- Prisoner
- Weight < 45kg
- Inability to follow-up – no cell phone or no address or not Spanish or English speaking
- Receipt of any experimental treatment for SARS-CoV-2 (off-label, compassionate use, or trial related) within the 30 days prior to the time of the screening evaluation
- Patient or another member of patient's household has been already enrolled in this study.
- History of ventricular arrhythmia

2.7 Sample size: The study will enroll up to approximately 200 participants in each arm (total 400 participants).

2.8 Primary Endpoint:

- Duration of viral shedding, as defined by time from randomization to the first of two consecutive negative swabs, measured on days 1 - 14.

2.9 Interim Monitoring:

Formal safety review by Data Safety Monitoring Board (DSMB) after 100, 200, and 300 subjects enrolled. No interim efficacy analyses or monitoring.

3.0 STUDY DESCRIPTION

3.1 Background

COVID-19 is a pandemic illness caused by the SARS-CoV-2 virus and has a high mortality among hospitalized patients despite a benign course in the large majority of patients infected. Limited data are available from small outpatient studies and have not shown efficacy in preventing hospitalization. Hydroxychloroquine (HCQ) and chloroquine have antiviral and immune-modulating effects[1], but there are no data concerning their efficacy in reducing viral load and shedding in outpatients.

3.1.1 Evidence supporting possible efficacy for hydroxychloroquine.

In cell models, chloroquine both interferes with terminal glycosylation of the ACE2 receptor (the cell surface receptor by which SARS-CoV-2 enters human cells) and increases endosomal pH, which interferes (at least *in vitro*) with a crucial step in viral replication.[1,2] HCQ is 5x more potent than chloroquine in a Vero cell model of SARS-CoV-2 infection.[3] In independent experiments, chloroquine has confirmed in vitro activity against SARS-CoV-2.[4] Additionally, HCQ has in vitro efficacy against SARS-CoV-1.[5] According to news releases, an as-yet-unpublished set of case series in China (N reportedly 120) suggests the possibility of rapid viral clearance and low rates of progression to critical illness. In addition to in vitro anti-viral effects chloroquine and HCQ appear to have immune-modulatory effects, especially via suppression of release of TNF and IL6, especially in macrophages.[1,7-10]

3.1.2 Evidence against efficacy for hydroxychloroquine.

Chloroquine and HCQ have been promoted as extremely broad anti-infective agents for decades. The reported effects include suppression of fungi, atypical bacteria, and viruses. Other than the effects on ACE2 glycosylation, the mechanisms invoked as evidence for efficacy against SARS-CoV-2 have also been invoked for a wide range of viruses. However, when chloroquine and HCQ have been studied in humans, neither agent has demonstrated consistent efficacy in clinical trials, including in HIV, influenza, hepatitis, and Dengue.[11] In one trial, chloroquine resulted in increased viral replication in Chikungunya virus [Roques et al, *Viruses* 2018 May 17;10(5)] while in another hydroxychloroquine was associated with increased HIV viral load [Paton et al, JAMA 2012 Jul 25;308(4):353]. Expert opinion advises against HCQ for MERS, another serious coronavirus.[12] An underpowered (n=30) study of HCQ in COVID-19 recently published in China did not demonstrate any clinical benefit [Chen et al, J Zhejiang University, 2020 March 9]. The long history of clinical failure despite in vitro anti-viral activity suggests a low probability of efficacy.

3.1.3. Rationale for Trial

There is significant publicity concerning the potential use of HCQ in this pandemic, and many patients are seeking access to this unproven therapy. The ANZICS guidelines emphasize that novel treatments should be administered within clinical trials; the Surviving Sepsis Campaign guidelines (http://bit.ly/SSCCOVID-19) also affirm the lack of evidence to support the clinical use

of (hydroxy)chloroquine. WHO guidance (https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf) also strongly affirms that "investigational anti-COVID-19 therapeutics should be done under ethically approved, randomized, controlled trials." The evidence thus strongly favors equipoise.[13]

3.2 Study Design

Phase 2, prospective, placebo-controlled, parallel group, randomized trial

3.3 Study Objective

A novel coronavirus, SARS-CoV-2, is responsible for a rapidly spreading pandemic that has reached 160 countries, infecting over 500,000 individuals and killing more than 24,000 people. SARS-CoV-2 causes an acute and potentially lethal respiratory illness, known as COVID-19, that is threatening to overwhelm health care systems due to a dramatic surge in hospitalized and critically ill patients. Patients hospitalized with COVID-19 typically have been symptomatic for 5-7 days prior to admission, indicating that there is a window during which an effective intervention could significantly alter the course of illness, lessen disease spread, and alleviate the stress on hospital resources.

There is no known treatment for COVID-19, though in vitro and one poorly controlled study have identified a potential antiviral activity for HCQ. The rationale for this clinical trial is to measure the efficacy and safety of hydroxychloroquine for reducing viral load and shedding in adult outpatients with confirmed COVID-19.

3.4 Study Hypothesis

HCQ is effective in reducing viral shedding in outpatients with confirmed COVID-19.

3.5 Primary endpoint

- Duration of viral shedding, as defined by time from randomization to the first of two consecutive negative swabs, measured on days 1 - 14.

3.6 Secondary endpoints

- Average level of select COVID-19-attributable symptoms
- Hospitalization within 14 days of enrollment.
- Persistence of viral shedding on day 28.
- Adult household contact viral acquisition

4.0 Study population

Ambulatory patients for whom SARS-CoV-2 testing is obtained at University of Utah testing sites after evaluation via telehealth services or by providers in University affiliated clinical facilities.

4.1 Screening

Patients undergoing testing for SARS-CoV-2 will be informed of this actively enrolling interventional trial and provided with informed consent documentation (hard copy or electronic) at the time of testing. Patients will be asked if they would be interested in considering trial participation if their test is positive. Investigators will monitor test results of individuals who indicate interest in the trial and contact those with positive tests to verify eligibility and provide remote informed consent by telephone, electronic consent, or videoconference. The consenting

process will be performed via a consenting mechanism that confirms the identity of the patient, provides access to the consent form, and obtains a signature to complete documentation, without requiring physical proximity of research staff and the study subject. The informed consent documentation will include HIPAA authorization for access to the medical record.

4.2 Inclusion and Exclusion Criteria

See sections 2.5 and 2.6.

5.0 Study Procedures

5.1 Intake medication review.

Prior to randomization, study personnel and/or clinical pharmacists will review medications being prescribed for patients on study to confirm eligibility. Study personnel will advise patients to contact the study team if any new medications are prescribed during the 5 day treatment course so that the medication may be reviewed for risk of prolonging QTc.

5.2 Cardiac review.

Prior to randomization, study personnel will review if patient has electrocardiograms (ECG) and will verify that prolongation of QTc has not been diagnosed clinically or on ECG.

5.3 Randomization.

After obtaining informed consent, participants will be randomized using variable block sizes stratified by patient age group (age ≤ 44, 45-59, 60-74, 75+ years). The randomization system at the Data Coordinating Center will require entry of patient initials, date of birth and sex. This will assure that patients do not attempt to enroll multiple times in order to secure active drug.

5.4 Study drug.

This is an open label, variable block randomized placebo controlled trial. If a participant is admitted to the hospital at any time during the active treatment period, the clinical team will decide whether or not to continue study drug treatment during hospitalization.

Participants randomized to the HCQ arm will receive HCQ 400mg po BID x 1 day, then 200mg po BID x 4 days[3]. The drug dose (2.4 gm over 5 days) falls at the lower end of doses proposed in various international trials, but it has proven in vitro efficacy, with a ratio of lung tissue trough concentrations to the EC50 (effective concentration to suppress 50% of viral activity) of >20.[3]

Those randomized to placebo will receive a placebo to be taken on the same schedule.

5.5 Study Assessments.

Coordinators will obtain baseline information at the time of randomization. This will include review of all medications being prescribed for patients on study. Study personnel will advise patients to contact the study team if any new medications are prescribed during the 5 day treatment course so that the medication may be reviewed for risk of prolonging QTc, or having a drug interaction with HCQ (see Appendix 3).

Daily assessments (assessment days 1 through 15) will include review for hospitalization and current symptoms. Daily assessments will also explicitly solicit occurrence of rash, symptomatic hypoglycemia, seizure, oxygen supplementation, nausea, vomiting, and impaired vision. Quality of life assessments will be made at baseline, day 28 - 2 days/+2 weeks, and six months - 1

week/+2 months, using the EQ-5D-5L, PHQ-9, GAD 7, and PLC 5. If the six-month survey is missed during the above outlined window, the study team may attempt to collect it for up to a year following the six-month timepoint.

Participants will be taught how to perform self-collection of oral swabs for SARS-CoV-2 on assessment days 1 – 14 and 28 +/- 2 (considering day 1 as day of study drug delivery). Oral swabs will not be required during hospitalizations, but patients will be asked to provide a swab on the day following discharge from the hospital, even if this occurs after day 28. These will be refrigerated after collection and collected by a courier associated with the study for transport to the central laboratory (ARUP) for testing. Training will be provided with written instructions, video, and discussion with the research coordinators.

Phlebotomy will be performed at day 1, day 7 (+/-2 day),day 28 (+/-2 day) and 6 months- 1 week/+2 months. This will require personal protective equipment (PPE) for the phlebotomy-certified research staff. Note that the 6 months blood draw is being added mid-study, after subjects have been enrolled, Therefore, already enrolled participants will be notified of the 6 months blood draw, provided with a new copy of the consent form, and told that they do not have to participate in the 6 month blood draw. If the six-month blood draw is missed during the above outlined window, the study team may attempt to collect it for up to a year following the six-month timepoint.
Blood samples will be used to assess the immune response to SARS-CoV-2, drug screening, investigation of viral biology, cardiac biomarkers, and development of diagnostic assays. Plasma and peripheral blood mononuclear cells (PBMCs) will be stored in the University of Utah Center for Clinical and Translational Science (CCTS) biospecimen repository. If there is remaining sample after these analyses, they may be used to study other diseases.

Six months after enrollment, study staff will verify subsequent hospitalizations and vital status of the participant.

5.6 Household Contacts
Household contacts 18 years or older will be asked to self-collect oral swabs in the same manner and same daily schedule as the study participant. Provision of the oral swabs will be considered implied consent, waiving the need for consent documentation.

5.7 Data collection.
Research coordinators and/or investigators will collect data and record them on paper and/or electronic CRF provided by the Data Coordinating Center (DCC). Data quality will be monitored by clinical data managers at the DCC. Note that given concerns for contagion during the pandemic, coordinators will practice “no-touch” practices for data collection and entry.

6.0 Analysis and interpretation of data.
A formal statistical analysis plan (SAP) will be written and finalized before the conclusion of enrollment and prior to the beginning of data analysis. The principles of this SAP are outlined here.

We note that in the unique circumstances of this trial setting, it is possible that information may become available that would lead to modifications of prespecified analysis. A hypothetical example would be evidence from multiple global studies that a particular underlying condition is strongly associated with outcomes such as shedding or hospitalization rates in response to hydroxychloroquine. In such circumstances, a modification to this study’s analysis plan could

be considered, if possible with the investigators blinded to the effect of the modification on the analysis, and in consultation with the DSMB. If the statistical analysis plan were to be modified, the analytic plan would be updated, with the previous version retained, and the modification explicitly noted in the presentation of the trial results.

The primary prespecified analysis for efficacy is a comparison of duration of viral shedding during the first 14 days after randomization between the two treatment arms. For each participant, this outcome will be defined as the number of days until an oral swab sample shows no shedding, as confirmed by a sample from the subsequent day. Thus, for example, a participant with their first negative samples on days 7 and 8 would be treated as having stopped shedding on Day 7. The requirement for confirmation will be waived for patients who are negative for shedding on Day 14.

Due to the nature of the data collected over a 14-day interval, and uncertainty about the distribution of shedding duration and the resulting hazard function, our primary analysis will apply the stratified log-rank test to compare the distribution of shedding duration between the hydroxychloroquine and control groups, with administrative right censoring at day 14. The primary analysis will be conducted using a 2-sided $\alpha=0.05$. The log-rank test will be stratified by the age group randomization stratum. The Efron approach will be used to account for tied shedding duration times. Kaplan-Meier curves will summarize the shedding time distributions in the two randomized groups.

Special handling will be required in our primary analysis of shedding duration for periods in which patients are hospitalized because swabs will not be obtained during hospitalizations. In our primary analysis, we will apply a last value carried forward imputation approach during hospitalization, and assume continued viral shedding during hospitalizations for patients whose last pre-hospitalization assessment is positive. A sensitivity analysis will right censor follow-up on the day of hospital admission. These two analyses represent the range of plausible scenarios for shedding during hospitalization under the assumption that any association between hospitalization and shedding must be positive; i.e., conditional on past history, the risk of viral shedding on any given day is at least as large for hospitalized as for non-hospitalized patients. We expect a relatively small proportion of subjects to be hospitalized, limiting the impact of assumptions concerning shedding during hospitalizations on the primary analysis. Additional sensitivity analyses, including analyses in which the end date of shedding is modeled as a latent variable will be considered.

Quantification of the magnitude of “treatment effect”, and indeed the interpretation of the trial results, will depend on the specific patterns of the shedding distribution. For example, in the unexpected scenario where the cumulative incidence curves for the ending of shedding actually cross during the 14-day evaluation period, the treatment arm with lower 14-day shedding rate would likely be preferred regardless of any shorter-term benefit observed in the other arm. Assuming, however, that the assumption of proportional hazards is found to be consistent with the data, the effect of the treatment will be expressed as a hazard ratio with 95% confidence interval. We will also report the differences between the randomized groups in truncated mean shedding duration to 14 days and in median shedding duration with 95% confidence intervals based on estimates derived from Kaplan-Meier curves.

The comparison of proportion of patients hospitalized by day 14 between the randomized hydroxychloroquine and placebo groups will be performed with a two-sided Mantel-Cochran-Haenszel test stratifying by the age categories as used for randomization, with 2-sided

alpha=0.05. In the unlikely event that some patients die within 14 days after randomization without being hospitalized, these patients will be assigned to the hospitalization category in the analysis. Results will be presented as relative risks with 95% confidence intervals within each age stratum, and then pooled across strata.

The average symptom level for assessment days 1 through 15 will be compared between treatment groups, as described in the Statistical Analysis Plan. The duration of COVID-19 attributable symptoms through assessment day 15 will be summarized graphically across evaluation time points using Kaplan-Meier curves, and compared between randomized groups by applying the log rank test with stratification by the age randomization strata. Participants who are hospitalized by assessment day 15 will be treated as having symptoms each day they are in the hospital. Follow-up time will be right censored at assessment day 15

Our main analysis of adult household contact viral acquisition will be restricted to households with at least 2 adults for which no other adult besides the index study subject tests positive for COVID-19 at baseline. We will evaluate the effect of the hydroxychloroquine intervention on the risk of adult household viral acquisition by applying a Mantel-Cochran-Haenszel test stratifying by the randomization age categories and total number of adults within the household. Results will be presented as relative risks with 95% confidence intervals within each stratum, and then pooled across strata. A secondary analysis will assess the effect of treatment arm on rate of household viral acquisition rates averaged across all adults within the household by using a modified Poisson regression model incorporating correlation between participants in the same household, and controlling for age category and number of household members.

The Statistical Analysis plan will detail additional analyses to be performed, including additional exploratory analysis as well as reporting of six-month outcomes among participants.

Safety—already well established in studies of thousands of patients and in post-marketing surveillance—will be assessed through counts (proportions) of adverse events, with special attention to those listed in the package insert for hydroxychloroquine and careful investigation of any SUSARs. As noted elsewhere in this protocol, safety data will be reported to the trial DSMB after every (approximately) 100 subjects have been enrolled in the trial.

We do not anticipate applying formal stopping rules for either efficacy or futility in this trial. It is expected that the trial will remain open for up to 12 months, as the cyclic nature of the illness is not well understood. Thus, if enrollment is not accomplished in this first wave of infection, the trial will not be suspended for futility, anticipating that subsequent waves may occur and enable full enrollment.

6.1 Power and sample size analysis

For a survival analysis, statistical power is readily expressed as a function of the number of events or event rate. Table 2 below shows minimum increases in the hazard rate due to hydroxychloroquine detectable with 80% power, under different overall event rates by 14 days in the trial (calculations done in PASS assuming a conventional proportional hazards model with treatment arm as a single predictor, using a two-sided test with alpha=0.05). With 400 enrolled participants, within our expected range of observed shedding rates, we expect the trial to have substantial power to detect a treatment effect if hydroxychloroquine increases the “successful

outcome" rate (at each timepoint) 1.4-fold or greater compared to the rates observed with placebo.

Table 2. Minimum Increase in Hazard Rate Yielding 80% Power with 2-sided α=0.05, with N=400 randomized and evaluable subjects

Assumed Overall Rate of No Shedding by 14 Days	**Minimum Hazard Ratio for "No Shedding" Outcome due to Hydroxychloroquine for which Power is 80%**
50%	1.49
55%	1.46
60%	1.44
65%	1.42
70%	1.40
75%	1.38
80%	1.37

7.0 Human Subjects Considerations.

If a person without insurance is hospitalized for illness related to COVID-19, he or she is eligible for emergency Medicaid. This is beyond usual Medicaid eligibility and related to special rules related to COVID-19 illness. In 2019, the United States government issued new rules in the form of an executive order restricting the ability for immigrants who use public benefits, including Medicaid, from obtaining permanent residency. For many individuals who are not citizens or permanent residents of the United States—whether they are documented or not—this has made them reluctant to use public programs for which they are eligible, including Medicaid and COVID-19 related health benefits.

In order to uphold principle of justice for all research participants, and to ensure that everyone who participates in this study will be appropriately respected for volunteering, we have partnered with U Health to offer participants who are uninsured **and** for whom completing paperwork regarding financial assistance would put them at risk in their judgement, the ability to receive the same level of care for COVID-19 as other people, should this be needed during their participation.

All participants will be provided with information during their first visit by the study nurse that if they require hospitalization, are uninsured, and if in their judgement completing paperwork regarding financial assistance would put them at risk, they should, upon presenting to a U Health emergency department, identify themselves to the registrar and financial counselor. The financial counselor will identify their participation in the electronic health record and note this in the hospital billing system.

Participants will be provided with a card identifying them as study participants and with instructions on it so as to remind them of what to do if they need to be hospitalized. They will also be provided with a handout to keep at home in case they are unable to speak to the financial counselor and hospital rules restrict visitors so the person contacted regarding the patient at home has the same information.

7.1 Institutional Review Board oversight.
Institutional Review Board (IRB) approval is required and will be secured before any subject is enrolled at the study site. The DCC will not enable access to the electronic data capture or randomization systems until IRB documentation is received.

7.2 Informed consent.
Informed consent will be obtained from participants prior to randomization. Proxy consent will not be used. Informed consent will be obtained without an original paper signature because of the contagious nature of the virus. Adult household contacts who agree to provide daily swabs are presumed to be consenting, and documentation of consent will be waived for them.

7.3 Potential risks
Risks associated with participation in this study include risks associated with HCQ administration and potential loss of confidentiality.

The package insert for HCQ lists visual impairment, cardiac impairment, QTc prolongation, worsening of psoriasis or porphyria, proximal myoneuropathy, suicidality, and hypoglycemia. All of these risks are quite rare and where observed are seen after prolonged administration, generally in the range of years. While ocular examinations are recommended after a year (and for acute symptoms), routine ocular examinations have never been recommended for brief duration of therapy. While QTc prolongation has been described with HCQ, it is generally modest, and routine EKG monitoring is not normally practiced even during long-term administration of hydroxychloroquine. HCQ may be associated with prolongation of QTc. We chose a conservative threshold of 500msec as an exclusion criterion after consultation with electrophysiology cardiologists.

7.4 Mitigation of risks
In order to mitigate the risk of prolongation of QTc, we have chosen a conservative exclusion threshold of 500 msec after consultation with electrophysiology cardiologists. Daily assessments will specifically ask about the adverse events listed above on a daily basis. Our eligibility criteria exclude patients with elevated risk of HCQ toxicity, and we have selected dosages in the lower end of the therapeutic range. Further, treatment is restricted to 5 days.

Risk of loss of confidentiality is mitigated by securing all paper materials used by coordinators for data collection, and IT security maintained at the DCC. Direct patient identifiers (names, contact information, medical record numbers) will not be recorded at the DCC, but will be secured at the study sites. The study sites will maintain lists that correlate medical record numbers with study ID numbers recorded in the DCC electronic data capture system.

7.5 Discontinuance of HCQ
Patients may choose to discontinue HCQ for any reason, and HCQ will be discontinued if a known contraindication arises. Study procedures should otherwise continue. This is not the same as withdrawal from the study.

7.6 Withdrawal from study.
Patients may withdraw from the study at any time. Data recorded up to the time of withdrawal will be included in the study analysis.

7.7 Protocol deviations and violations.

The investigator will not implement any deviation from, or changes of the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or research personnel,, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of telephone number(s)). Protocol deviations will be reported to the DCC within 24 hours of the site becoming aware of the deviation. The study team will provide explanation of the deviation to the DCC. The DCC will notify the IRB of protocol deviations that have potential impact on human subjects safety or trial integrity. The investigator may implement a deviation from, or a change of, the protocol to eliminate immediate hazard(s) to trial subjects without prior IRB approval/favorable opinion. As soon as possible, the implemented deviation must be reported to the DCC, which will notify the medical monitor and the IRB.

8.0 Adverse Events

Patient safety is central to this study protocol.

8.1 Adverse event reporting.

Adverse events will be recorded from randomization through day 14 or hospitalization, whichever occurs first. The following adverse events will be collected in the adverse event case report forms and entered into the DCC electronic data capture system:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study drug or study procedures or of uncertain relationship
- Adverse events that lead to permanent discontinuation of the study drug.

The following adverse events will be collected prospectively as part of the study-specific outcomes and do not require additional adverse event reporting with the DCC unless they meet criteria for being serious (defined below):

- Rash
- Symptomatic hypoglycemia
- Seizure
- Cardiac arrhythmias
- Worsening requirement for oxygen supplementation and support
- Nausea/vomiting
- Impaired vision

8.2 Serious Adverse Events

All serious adverse events (SAE) will be reported to the DCC. As per federal definitions (primarily in 21 CFR 312.32(a)), a **serious** adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening event, one that places the subject at immediate risk of death (this does not include an event that, had it been more serious, would have placed the subject at immediate risk of death)
- Prolonged inpatient hospitalization or rehospitalization

- Persistent or significant disability/incapacity, indicating a substantial disruption of a person's ability to conduct normal life functions (i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life).

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

SAEs must be reported to the DCC within 24 hours of becoming aware of the SAE. This may be accomplished by telephone call or email and can be succinct notification.

Investigators must assess serious adverse events for expectedness and relatedness. Expected SAE include known side effects of study drug as well as clinical events consistent with worsening of COVID, or consistent with pre-existing co-morbidities of individual patients. Relatedness must be assessed by an investigator, and is based on clinical judgment that the event is related to having participated in this study. This is assessed as not related, possibly related, and related. This information must be provided to the DCC within 48 hours of becoming aware of the SAE.

Deaths from worsening of viral infection or underlying co-morbidities are expected, and do not automatically require expedited reporting. Sudden deaths or deaths believed related to cardiac arrhythmias must be reported to the DCC within 24 hours of becoming aware of the death. The DCC or medical monitor will report these deaths to the DSMB chair within 24 hours of notification. As these are expected complications of study drug, these do not require expedited reporting to the FDA or IRB as described in the next paragraph.

Serious adverse events that are unexpected and related to study participation must be reported to the FDA and the IRB within 7 days of the DCC becoming aware of the classification of the SAE. The DSMB chair will also be notified. All other SAE do not need to reported to the IRB or FDA. All SAE will be tabulated by study arm and presented to the DSMB at its regular meetings.

8.3 Unanticipated Problems

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

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research. 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; it is not intended to identify the event as possibly related imply because it cannot be proven to be unrelated.

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.0 Miscellaneous Topics

9.1 Reporting and Regulatory Compliance.

All relevant information will be reported in compliance with relevant regulations and Good Clinical Practice. This is not a registrational trial but will be performed under an IND exemption.

9.2 ClinicalTrials.gov registration.

This trial is registered with ClinicalTrials.gov (NCT04342169). Updates to the Clinicaltrials.gov entry will be made in compliance with relevant regulations.

9.3 Records retention. Study sites will arrange for the retention of raw data as per institutional protocol but for a minimum of 3 years after publication of the primary paper. All data and documents will be made available when requested by appropriate authorities. Records will be maintained to verify the existence of each patient in the study, as per standard protocol.

APPENDICES

Appendix 1. Visit schedule

	Visit					
Procedure	**Baseline**	**Daily through 15 days**	**14 days**	**Hospitalization**	**28 days**	**6 months**
Screening procedures	X					
Informed consent	X					
Data collection	X	X	X	X	X	X
Active Adverse Event review		X				
Passive Adverse Event review				X		
EQ-5D-5L, PHQ-9, GAD 7, PLC 5	X				X	X
EQ-5D-5L: EuroQol-5 dimensions-5 level; PHQ-9: Patient Health Questionnaire-9, GAD 7: Generalized Anxiety Disorder 7-item scale, PLC 5: PTSD Checklist for DSMB-5 scale						

Appendix 2: Biospecimen collection schedule:

Study Events	Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	28	6 months
			HCQ or Placebo															
COVID-19 PCR swab positive		1																
Inclusion / Exclusion criteria		1																
Informed consent discussion / signatures		1	1															
Adverse event review			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Surveys (EQ-5D-5L / PHQ-9 / GAD7 / PLC5)			1														1	1
HCQ or Placebo administration			1	1	1	1	1											
Research Specimen Collection																		
Oropharyngeal self-swab for SARS-CoV-2			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Household contact over age 18 oropharyngeal self-swab for SARS-CoV-2			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Peripheral blood (PBMC / plasma biobank)	40 mL (five yellow top ACD tubes)		1						1								1	1

Appendix 3. Potential medication interactions with hydroxychloroquine

A. Medications considered contraindicated, which if ordered on a subject during the 5-day study period will prompt study personnel or clinical pharmacists to discuss with treating clinicians whether stopping the study drug is appropriate or whether this medication could be stopped or substituted: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol.

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

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