APPROVED

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INSTITUTIONAL REVIEW BOARD

WHIP COVID-19 Study

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Will Hydroxychloroquine Impede or Prevent COVID-19

Study Administration

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Study Synopsis

Study Sponsor:	Henry Ford Hospital, Detroit, Michigan
Protocol Number:	1410401
Protocol Title:	Will Hydroxychloroquine Impede or Prevent COVID-19: WHIP COVID-19 Study
Indication:	This is a prospective, multi-site study designed to evaluate whether the use of hydroxychloroquine in healthcare workers (HCW), Nursing Home Workers (NHW), first responders (FR), and Detroit Department of Transportation bus drivers (DDOT) in SE, Michigan, can prevent the acquisition, symptoms and clinical COVID-19 infection.
Objective:	The primary objective of this study is to determine whether daily or weekly oral hydroxychloroquine (HCQ) therapy will prevent SARS-CoV-2 infection and COVID-19 disease in healthcare workers and first responders in SE, Michigan.
Study Design:	The study will randomize a total of 3,000 HCW, NHW, FR and DDOT bus drivers within Henry Ford Hospital System, the Detroit COVID Consortium in Southeast, Michigan. The participants will be randomized in a 1:1:1 blinded comparison of daily HCQ, weekly HCQ, or placebo. A fourth non-randomized comparator group of HCW, NHW, DDOT bus drivers, and FR who are currently on standard HCQ therapy will be recruited to assess the impact of weight-based daily dosing of HCQ as compared to the randomized arms. Eligible participants who are asymptomatic for pre-specified signs and symptoms suggestive of COVID-19 infection will have a whole blood specimen obtained at study entry. Participants will be provided with weekly dosing of hydroxychloroquine (HCQ) 400mg po q weekly, daily dosing of HCQ 200mg po q daily following a loading dose of 400mg day 1, or placebo. Participants will receive monitoring at each study week visit to assess for the development of COVID-19 related symptoms, COVID-19 clinical disease, and medication side effects. At week 8 or if diagnosed positive, participants will provide additional samples of whole blood and complete the final study questionnaire. Data including demographic, clinical results, work duties, location of main work area and possible exposures in the community will be collected through questionnaires and EMR review. Disease-specific, immunologic, and other serologic marker data will be obtained from stored samples.
Subject Population:	Approximately 3000 HCW, NHW, FR and DDOT bus drivers, age 18-75 years, presenting at participating clinical sites without symptoms of respiratory tract infection, as outlined in the Inclusion/Exclusion section of this protocol.

Duration of Subject Participation:	Each Participant's involvement in the study will last 8 weeks. Subject participation is required after consent for sample collection, questionnaires, and study calls and EMR review of clinical testing for respiratory infections.
Study Duration:	Up to 3 months for enrollment, 2 years for testing and publications, starting immediately following approval by the HFHS Institutional Review Board (IRB) and The United States Food and Drug Administration (FDA).

Abbreviations/Definitions

AE;	Adverse Event
°C:	Degrees Centigrade (Celsius)
CAP:	Community Acquired Pneumonia
CFR:	Code of Federal Regulations
COVID-19:	SARS-CoV-2 clinical coronavirus disease which may be diagnosed by clinical and/or laboratory methods
CRL:	Case Report Log
DDOT	Detroit Department of Transportation
EMR:	Electronic medical record
FDA:	Food and Drug Administration
FR:	First Responders
HCW:	Healthcare Workers
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IRB:	Nursing Home Workers
NHW:	Institutional Review Board
PI:	Principal Investigator
SAE:	Serious Adverse Event
SARS-CoVID -2:	Severe acute respiratory syndrome coronavirus 2 virus
SARS-CoVID-2 infection:	Detection of SARS-CoVID-2 infection by laboratory testing, can be symptomatic or asymptomatic presentation
SARS-CoVID-2 viremia:	Detection of SARS-CoVID-2 virus in blood, serum or plasma
SE:	South East

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1 BACKGROUND

Community-acquired pneumonias (CAPs) can be due to viral or bacterial pathogens, and are one of the most common infectious diseases. Viral CAPs are most commonly caused by influenza A and B and other common cold viruses such as RSV, especially during winter months. Although their presentations can vary, only microbiological testing techniques can definitively identify the pathogen involved. In December 2019, a novel disease caused by a new virus now known as SARS-CoV-2, commonly referred to as COVID-19, was identified in Wuhan, China. Since then, the infection has spread worldwide, with over 663,828 cases identified and 30,822 deaths as of March 28, 2020 (Johns Hopkins Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html). COVID-19 is a deadly pandemic which threatens the lives of millions of persons with mortality rates overall of 4.37%, but are highly very variable by region. For example, in Italy a crude mortality rate of 10.83% has been reported. In the United States, over 124,217 cases and 2,185 deaths have been reported, with the State of Michigan now representing the fourth most affected state, having 4,658 confirmed cases and 111 deaths reported (Johns Hopkins Coronavirus Resource Center, March 28, 2020; https://coronavirus.jhu.edu/map.html). HCW are at high risk of exposure given the close proximity in which they care for patients (Bureau of Labor Statistics, Occupational Employment Statistics) in addition to the growing shortages in personal protective equipment (PPE), which are paralleling the rise in COVID-19 cases (1,2). Recent COVID-19 outbreaks have demonstrated that up to 10-30% of HCW can become infected by the virus, and up to 85% may have asymptomatic/minimally symptomatic infection, promoting further spread of COVID-19 infection (2). Several epidemiological, societal and clinical interventions are currently ongoing to prevent the spread of COVID-19 disease, but to date, there are no published data on prevention strategies. This is a critical unmet need which must be addressed to preserve the population of active healthcare workers (HCW), nursing home workers (NHW), DDOT bus drivers, and first responders (FR) who are exposed to COVID-19 positive patients as part of their duties and represent the key component of our clinical response to this pandemic.

Chloroquine and hydroxychloroquine have demonstrated in-vitro efficacy in the treatment of COVID-19 (3). In 2005, Vincent *et al.* similarly demonstrated that chloroquine was effective in preventing the spread of SARS-CoV-2 in cell culture(4). Chloroquine interferes with the terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2, which is thought to impede the receptor binding and infection of the cell. Chloroquine was first discovered in 1934, and has been used for treatment of malaria since 1949 and other conditions such as systemic lupus erythematosus; and similarly, hydroxychloroquine (HCQ) has been used since 1955 (5,6).

These agents have a well-known safety profile. Multiple cohort studies have demonstrated the safety of HCQ in the lupus population, where it is routinely used even during pregnancy, with the only established contraindication for therapy being known retinopathy (7,8). Furthermore, the American College of Rheumatology does not recommend routine glucose-6-phosphate dehydrogenase screening, as clinical data have not demonstrated any significant risk of associated hemolysis in numerous cohort studies in both lupus and rheumatoid arthritis (8). Current dosing of HCQ for rheumatologic disease is weight-based, with the upper limit of dosing established at 5 mg/kg/day.

Malaria prophylaxis dosing of HCQ is given as 400mg po once a week for the duration of the exposure (5). Recent work by Gautret P *et al* demonstrated that doses of 600mg of hydroxychloroquine showed significant reduction of viral carriage at day 6 as compared to controls in patients with COVID-19 (9). Other investigators demonstrated in-vitro activity of HCQ against SARS-COV-2 with an EC50= 5.47 uM (10). Unfortunately, no data exists on the efficacy of these medications as prophylaxis in the prevention of COVID-19.

The aim of this study is to demonstrate whether the use of hydroxychloroquine can prevent SARS-CoVID-2 infection and clinical COVID-19 disease in HCW, NHW, DDOT bus drivers and FR . Preventing COVID-19 transmission to HCW, FR, and DDOT bus drivers is a critical step in preserving the health care and first responder force, the prevention of COVID-19 transmission in health care facilities, with the potential to

preserve thousands of lives in addition to sustaining health care systems and civil services both nationally and globally. If efficacious, further studies on the use of hydroxychloroquine to prevent COVID-19 in the general population could be undertaken, with a potential impact on hundreds of thousands of lives.

2 STUDY OBJECTIVE

The primary objective of this study will be to determine if the use of either daily or weekly hydroxychloroquine will lead to the prevention of SARS-CoV-2 infections and COVID-19 disease in HCW, NHW, DDOT bus drivers and FR in SE, Michigan.

2.1 Primary Aim

1. To determine if the use of hydroxychloroquine as preventive therapy decreases the rate of acquisition of SARS-CoV 2 infections and clinical COVID-19 disease in Study Participants for each randomized treatment arm as compared to placebo.

2.2 Secondary Aims

1. Compare the rates of SARS-CoV 2 infections between the randomized treatment arms and the control arms to determine the effect of HCQ dose in the prevention of COVID-19 viremia and disease.

2. Compare the rates of SARS-CoV 2 infections in the non-randomized comparator arm to the randomized groups to assess the impact of chronic weight-based dosing of HCQ for COVID-19 prevention.

3. To compare the rate of SARS-CoV 2 infections as measured by IgM/IgG in study participants receiving HCQ versus placebo.

4. To compare the seroprevalence of SARS-CoV 2 IgM/IgG positive samples at study

entry and study conclusion in all participants receiving HCQ compared to those receiving placebo.

5. To compare the development of clinical symptoms or COVID-19 diagnosis in participants presenting asymptomatically at study entry but identified as seropositive by serology at entry between the randomized treatment arms and comparator arm.

6. To compare the clinical COVID-19 disease need for participants in each treatment arm to require emergency room visit, hospitalization or able to stay home without hospital care.

7. To determine the safety and tolerability of HCQ dosing for preventive strategy against COVID-19.

8. To examine other clinical determinants contributing to the risk of SARS-CoV 2 infection including demographics, work type and location, positive COVID-19 partners, possible exposures and clinical symptoms.

9. Examine the association between HCQ drug levels and development of COVID-19 symptoms or positive test results.

10. To identify immunologic, serological and inflammatory markers associated with acquisition and response to COVID-19 in both HCQ and placebo Participants developing laboratory or clinical confirmed disease.

2.3 Primary Endpoint

1. Difference in new cases of COVID-19 disease between randomized treatment arms.

2.4 Secondary Endpoints

1. The difference of SARS-CoV 2 infections between the randomized treatment arms and the control arms.

2. The difference of SARS-CoV 2 infections in the non-randomized comparator arm to the randomized groups.

3. The rate of SARS-CoV 2 infections as measured by IgM/IgG seroconversion in study participants receiving randomized HCQ versus placebo.

4. The seroprevalence of SARS-CoV 2 IgM/IgG positive samples at study entry and study conclusion in all participants receiving HCQ compared to those receiving placebo.

5. Emergence of clinical symptoms or COVID-19 diagnosis in participants presenting asymptomatically at study entry but identified as seropositive by serology at entry between the randomized treatment arms and comparator arm.

6. To examine the level of care needed by participants in each arm developing COVID-19 as measured as requiring emergency room visit, hospitalization or able to stay home without hospital care.

7. The safety and tolerability of HCQ dosing for preventive strategy against COVID-19 as measured by adverse events and serious adverse events.

2.5 List of Outcomes

1. Primary outcome: Clinical COVID-19 Disease with laboratory confirmation of infection

2. Secondary outcomes: SARS-CoV-2 infections, clinical COVID-19 disease without laboratory confirmation, serology (IgM and IgG) positivity, SARS-CoV-2 viremia, adverse events related to study medication or procedures, HCQ blood levels, immunologic and serologic markers associated with SARS-CoV-2 infection and COVID-19 and COVID-19 disease related ED visits and hospitalizations.

3. **STUDY LOCATIONS**

This study will be conducted through at Henry Ford Health System, Detroit COVID Consortium and the Detroit Public Health building. The applicable Institutional Review Board (IRB) for each participating site will review and approve the study protocol and informed consent documents prior to any Participant enrollment. All HCW and NHW will be enrolled at one of the participating Henry Ford Health System (HFHS), Detroit COVID Consortium clinical sites. First responders and DDOT bus drivers will be enrolled at either the Detroit Public Health Building located at 100 Mack St. Detroit, MI 48201 or at participating HFHS sites. The total study duration is expected to be up to 2 years, with Participants enrollment targeted to begin immediately following IRB and FDA approval.

4. **STUDY DESIGN**

The study will randomize a total of 3,000 HCW, FR, and DDOT bus drivers, age 18 to 75 years, through the Henry Ford Health System, Detroit COVID Consortium. HCW and NHW will include providers at both hospital/clinical settings and nursing homes. FR will include personnel working in both governmental, private or volunteer first responder services. DDOT bus drivers with the Detroit Department of Transportation. The participants who meeting study entry criteria and are not on HCQ prior to study enrollment will be randomized in a 1:1:1 blinded comparison of daily or weekly hydroxychloroquine versus placebo for 8 weeks.

A fourth non-randomized comparator group will be enrolled in the study comprising of HCW who are chronically on HCQ as part of their standard of care for their autoimmune disease(s). This will be an open enrollment group and will provide information of chronic weight-based daily therapy of HCQ effectiveness as a prophylactic/preventive strategy. These participants will continue on their therapy for the duration of the study.

The trial has implemented a pragmatic, adaptive enrichment design, where the efficacy analysis will be performed based on patients with negative screen for COVID-19 related symptoms at the baseline

and the safety analysis will be based on all randomized patients given there may be lag time to get any future COVID-19 test results back after the time of the study enrollment. The primary outcome of the study will be difference in development of COVID-19 disease between randomized arms. As new assays become available for research use for COVID-19 testing, these will be included in subsequent amendments if needed. The trial is also designed to have one interim look when a half of patients have completed the 8 weeks assessments for an early treatment efficacy, or a possible reassessment of study sample-size if the estimation of placebo rate is inadequate. A DSMB will be assembled to review interim analysis results. The DSMB Chair will also be provided a site SAE report weekly for safety review. Depending on response to the study intervention, the DSMB may decide it is necessary to stop/continue the trial if 1) there are safety concerns at any point in the trial or 2) there is evidence of treatment efficacy at the interim analysis; or recommendation for trial modification as it may be suggested, or 3) to continue the trial as designed. The primary aims of the DSMB are to decide if the study is safe to continue at the interim analysis timepoint and to monitor serious adverse events during the trial.

Participant eligibility will be assessed prior to study entry, and a screening questionnaire will be completed. Eligible asymptomatic participants will have study sample collections (whole blood) obtained at study entry. Clinical symptom data will be obtained at study screening and entry, to assess study eligibility focusing on the presence or absence of symptoms suggestive of COVID-19 infection.

The study's purpose and its potential risks and benefits will be explained to potential study Participants. Enrollment of study Participants will be done only after informed consent is obtained and a copy of the consent document is returned to the potential Participant. Consented Participants will be assigned a unique Subject ID that corresponds to the unique identifier assigned to the participant upon completion and submission of the online screening form.

In the event a Participant decides to withdraw consent before the baseline blood or study specimens can be collected, this Participant will be excluded from the study before they are randomized.

Participants will have 8 scheduled study encounters (see schedule of events, section 7.2). Screening/baseline visit will include study screening, informed consent, and initial study questionnaires and specimen collections. At this visit, enrolled Participants will be provided with 8 weeks of hydroxychloroquine (HCQ) or placebo pills based on their randomized study group. Participants will be asked to contact the study team if COVID-19 infection is established at any time during the study. For study weeks 1,2,3,5,6 &7, Participants will receive a monitoring questionnaire to assess for COVID-19 symptoms/diagnosis, adherence and medication side effects. These monitoring visits will be done by telephone and/or electronic encounters (virtual visits, email), whichever method the patient prefers to encourage adherence to the monitoring. Every effort will be made to obtain the weekly information from Participants and avoid missing timepoint information. Participants will have a +/- 3 day window to complete their scheduled study visits. As recommended in the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic, updated on March 27, 2020, the approach of using electronic or virtual visits for study safety assessments will support study monitoring while increasing the safety for participants by reducing potential exposures to SARS-COV-2 while attempting to come to clinical areas for study visits, where no direct contact is needed as part of trial design.

The study Participant will have an in-house, face-to-face visit on week 4 of the study to obtain monitoring questionnaires to assess for COVID-19 symptoms/diagnosis, adherence and medication side effects, and collect study blood samples. At study week 8, participants will present for the final study visit and will provide additional samples of whole blood, as well as complete an end of study questionnaire. Participants who are determined to be positive for

COVID-19 by either study or clinical testing will complete the study at that timepoint. Every effort to obtain confirmatory test results for COVID-19 will be done, including patient self-report, at study evaluations if presenting with symptoms, and from supportive medical records or study testing. At this point, participants having been diagnosed with COVID-19 will be asked if they would be willing, within 30 days of recovery, to present for a study visit to provide a blood sample and answer an end of study questionnaire than can be scheduled at a later time. All participants will be monitored for safety 30 days post study completion.

Any potential study Participant who screens positive for COVID-19 symptoms or tests positive for SARS-CoV 2 during screening or subsequently during the trial, will be referred to their respective providers for further testing and care. HFHS employees will be directly referred to employee health for further evaluation.

Study questionnaires will obtain information on Participant demographics, clinical background, clinical symptoms, employment, work activities, location of main work area, known possible exposures to COVID-19 patients, potential medication side effects and adherence to study treatment regimens. Complete questionnaires are located in the appendix section.

Additional laboratory studies will include plasma serologies, cellular & systemic inflammatory markers as well as other disease associated markers. Samples will be stored for future studies as new markers of SARS-COV-2 infection and COVID-19 disease may be yet to be identified.

Samples will also be stored for potential future HCQ level testing. The testing will be done for samples from both randomized treatment arms and comparator arm subset of patients to assess their study compliance as compared to the medication adherence indicated in the study questionnaires. HCQ drug levels will provide further information regarding drug levels and their association with the effectiveness of the treatment strategies on prevention of symptom development and clinical & laboratory confirmed disease.

All collected specimens will be sent directly to the research laboratory for processing, analyses and storage. Patients who develop clinical symptoms for SARS-CoV-2 will have both clinical referral for testing and study blood collected. Additional testing for serology, immunology and other markers will be done later in the study. Samples will be stored in appropriately monitored – 80°C freezers or liquid nitrogen containers in the Division of Infectious Diseases and/or Translational and Clinical Research Center laboratories for testing.

4.1 Use of Data

The results of the investigational study will be used for the determination of the efficacy of the intervention strategy.

The data generated during this study will support clinical trials for the prevention and monitoring of COVID-19 in HCW, FR, & DDOT bus drivers and will expand our knowledge of this disease. Any data obtained during the course of the study that may potentially significantly impact the management and/or outcomes of the proposed therapies and monitoring for COVID-10 will be made immediately available to the general health community with all related data. Barring these findings, data sharing will be planned at the completion of the study after all study plan analyses and sub-analyses have been completed.

No personally identifiable testing for human DNA will be performed on any samples obtained from this study.

4.2 Study Duration

Each Participant's involvement in the study will include direct contacts with study investigators which includes the following: Baseline screening, enrollment and sample acquisition; week 2-7 monitoring questionnaire, and blood samples on week 4; and week 8 study termination questionnaire and blood sample acquisition. The Participant will receive their randomized 8 week study medication supply following enrollment and randomization. The research pharmacy will

dispense medication to a dedicated study coordinator, who will then dispense the medication to the participant. All transfer of medication will be recorded on a drug accountability log for the site and in the participants' source binder. The total time for each participant in the study will be for 8 weeks from enrollment. For Participants with COVID-19 diagnosis will have an unplanned study visit after 4 weeks from diagnosis for final study assessment and blood draw. All patients may be contacted up to 30 days post completion of the study medication for safety monitoring. The study duration is estimated at 2 years for the completion of enrollment, data collection and analyses, laboratory testing to be completed, and dissemination/publication. Initial findings of the study are expected to be completed within 6 months of study initiation.

5 STUDY MATERIALS

5.1 The following materials will be needed at enrollment (in dedicated research exam room):

5.1.1 Vials of Universal Transport Media

5.1.2 Pre-printed labels with the site's assigned sample identification numbers for labeling the blood samples.

5.1.3 Blood collection kits with appropriate whole blood vials.

5.1.4 Cooler for sample transport to the laboratory for processing.

5.1.5 Study screening questionnaire

5.1.6 Informed consent

5.1.7 Thermometers

5.1.8 Medication Safety Sheet

5.2 The following materials are required for the randomization visit:

5.2.1 Study medication dispensed in pill blister pack

5.2.2 Placebo medication dispensed in pill blister pack

5.2.3 Randomization form

5.2.4 Drug accountability log

5.3 The following materials needed for the week monitoring visits:

Weeks 1,2,3,5,6 & 7 will be virtual visits (via telephone, telemedicine, electronic mail as preferred by the Participant)

5.3.1 Questionnaire for adverse events and COVID-19 symptomatology

5.3.2 Call Log and Call Dialogue

5.3.3 Referral if symptomatic and/or the participant has a significant AE/SAE (as indicated in Pharmacy section).

5.3.4 AE/SAE monitoring document.

5.3.5 Drug accountability log

Week 4 visit will be a face-to-face visit in a dedicated research room/area.

5.3.6 Week 4 will require the addition of blood draw materials as in section 5.1.

5.4 The following materials needed for the week 8 end of study visit (in dedicated research exam room):

5.4.1 Questionnaire for adverse events and COVID-19

symptomatology.

5.4.2 Referral if symptomatic and/or the participant has a significant AE/SAE (as indicated in Pharmacy section).

5.4.3 AE/SAE monitoring document.

5.4.4 Laboratory material as in 5.1 for sample collection and processing.

5.4.5 Drug accountability log

6 STUDY SUBJECTS

6.1 Number of Subjects

Approximately 3000 HCW, FR, and DDOT bus drivers, age 18 to 75 years, without symptoms of respiratory tract infections and without a history of testing positive for SARS-CoV-2 will be prospectively enrolled and randomized at Henry Ford Health System, Detroit COVID Consortium or the Detroit Public Health Building. The fourth non-randomized comparator arm will include Participants on chronic maintenance therapy with weight-based HCQ twice a day dosing for their autoimmune disease, which will be continued throughout the study. Enrollment in this group will be open as it will be a non-randomized treatment arm, with total numbers of HCW enrolled will be expected to be lower than the randomized groups. The total study duration is expected to be up to 2 years, with Participant enrollment targeted to begin in April 2020.

Randomization Schema will be generated by the Biostatistician at Department of Public Health Sciences (PHS) at HFHS prior to the study enrollment. Randomization will be stratified by study site and level of risk of exposure in two levels. High risk includes healthcare personnel working in either hospital or nursing home settings (including environmental service) who

work in COVID-19 care areas, emergency rooms and intensive care units caring for COVID-19 patients, nursing home HCW providing any direct patient care, first responders (FR) and DDOT bus drivers. Low risk group will include healthcare and supportive personnel who work in non-COVID-19 care areas, without direct patient contact, and those involved in administrative roles. All physicians and clinical staff who are involved in the patient's enrollment and follow-ups will be blinded to the study treatments. Once enrolled, each Participant will be assigned a unique identifier. This number, along with the assigned site number, will constitute the Subject ID. This process is defined by using the following format:

□□□ - □□□□□
Site # Subject #

Site # = 3-digit code for the site assigned by the investigators

Subject # = 5-digit sequential number assigned by site personnel/investigators

All subject-specific material (i.e., case report log and samples) must be labeled in accordance with this ID.

6.2 Inclusion/Exclusion Criteria

To be enrolled in the study, each Participant must meet all of the following inclusion criteria and none of the following exclusion criteria:

6.2.1 Inclusion Criteria

1. Participant is willing and able to provide informed consent.
2. Participant is 18-75 years of age.
3. Participant does not have symptoms of respiratory infection, including cough, fevers (temperature >38.0C), difficulty breathing, shortness of breath, chest pains, malaise, myalgia, headaches, nausea or vomiting, or other symptoms associated with COVID-19.

4. Participant is willing to provide blood samples for the study.
5. Subject agrees to all aspects of the study.
6. The participant has no known allergies or contraindications (as stated in the consent form) to the use of hydroxychloroquine (HCQ) as noted in the exclusion criteria and Pharmacy sections.

6.2.2 Exclusion Criteria

1. Does not meet inclusion criteria.
2. Participant unable or unwilling to provide informed consent.
3. Participant has any of the symptoms above or screens positive for possible COVID-19 disease.
4. Participant is currently enrolled in a study to evaluate an investigational drug.
5. Vulnerable populations deemed inappropriate for study by the site Principal Investigator.
6. The participant has a known allergy/hypersensitivity or has a medication or co-morbidity (including history of gastric bypass, epilepsy, cardiovascular disease or renal failure) that prevents the use of HCQ (see pharmacy section).
7. The participant is a woman of childbearing age whose pregnancy status is unknown and is not willing to use 2 methods of contraception.
8. The participant is pregnant or nursing.
9. The participant was diagnosed with retinopathy prior to study entry.
10. The participant has a diagnosis of porphyria prior to study entry.

11. The participant has renal failure with a creatinine clearance of <10 ml/min, pre-dialysis or requiring dialysis.
12. The Participant has a family history of Sudden Cardiac Death.
13. The participant is currently on diuretic therapy using loop-diuretics.
14. The participant has a history of known Prolonged QT Syndrome.
15. The participant is already taking any of the following medications: Abiraterone acetate, Agalsidase, Amodiaquine, Azithromycin, Conivaptan, Dabrafenib, Dacomitinib, Dapsone (Systemic), Digoxin, Enzalutamide, Fusidic Acid (Systemic), Idelalisib, Lanthanum, Lumefantrine, Mefloquine, Mifepristone, Mitotane, Pimozide, QT-prolonging Agents, Stiripentol). See Pharmacy section.

6.3 Participant Discontinuation

Participants may discontinue their participation in the study at any time. A Participant may be withdrawn from the study at any time at the discretion of the Investigator. Participants withdrawn from the study prior to randomization will not be included in the study. Using the intention to treat (ITT) approach, participants randomized but not completing the study will be included in the study analyses based on the treatment they were assigned and worse case (test positive) will be considered for those who withdraw early and clinical COVID-19 disease status cannot be confirmed.

For this study, Participants may be discontinued from the randomized study drug if deemed to have developed a study drug related SAE. Safety follow up for up to 4 weeks after discontinuation will be done to determine clinical outcomes via direct communication with the Participant. Similarly, Participants who discontinue medications will be approached to assess any clinical outcomes during their planned 8 study week participation. Participants that are

discontinued from the study by the Investigator, are lost to follow up or decline further study involvement and withdraw their consent will not be approached after study discontinuation.

6.4 Participant Withdrawal

A Participant will be considered unevaluable for the purposes of this study if:

- Participant withdraws consent for study participation before designated baseline samples have been obtained.
- Participant refuses specimen collection at study baseline.

Subjects who are unevaluable will be withdrawn from the study and will not be included in the study analyses.

7 STUDY PROCEDURES

7.1 Screening and Enrollment

Research site staff will be notified of potential Participants (i.e., Participants meeting all inclusion criteria) through screening forms filled out by potential participants on the study website, or indirect contact (in person, electronic or telephone). Research site staff will be located at different sites within participating clinical institutions to facilitate Participant enrollment (e.g., points of entry). FR and DDOT bus drivers will be informed of the study through IRB approved communications received through their work or union resources or health department flyer. All FR and DDOT bus drivers will be screened and enrolled at a participating clinical institution or health department. Research site staff trained in basic Human Research Subjects Protection will obtain informed consent from each Participant prior to enrollment and specimen collection in accordance with all applicable regulatory requirements. Those Participants wishing to participate will be asked to sign the Informed Consent Form (ICF) and will be provided with a copy for their records. The original form(s) will be maintained with the Participant's study records. Study

investigators will receive reports on eligible and enrolled study Participants on a regular basis to monitor study enrollment and accrual.

Consented Participants will be assigned a Subject ID that is recorded on the Case Report Log provided by the site investigator team. The Principal Investigator (PI) at each clinical site will maintain a Participant Master Log that will associate the Subject ID to the Subject's name and contact information. This log will remain at the clinical site and will remain confidential to the clinical site.

Clinically asymptomatic Participants not on HCQ chronic therapy will be randomized into one of the three randomized arms of the study. At that time, the research pharmacy will be notified of the subject randomization and they will prepare the 8-week supply of study medication. This will be recorded on a drug accountability log in the pharmacy. Pharmacy will notify study coordinators when medication is available for pick up and dispensing. Research coordinator will pick up the study medication and schedule a drug dispensing study visit (baseline) with the subject. At the drug dispensing study visit (baseline visit), the Participant will be given their 8-week supply of medication, which will be recorded on their individual drug accountability log. Subjects will be instructed to keep their medication blister pack and return it at the week 4 study visit and at the end of the study for a study drug reconciliation. Participants will be asked about medication adherence during their virtual monitoring visits. Participants will have a +/- 3 day window to complete their scheduled study visits. If a subject stops the study drug for any reason during the trial, the subject will be instructed to keep the remainder of their medication and return it to study personnel within 1 month for study drug reconciliation.

Asymptomatic Participants on chronic HCQ therapy will continue on their current medication for the duration of the study. If during the study period, the Participant is unable to refill their

prescription, the Study team will assess the possibility of providing the HCQ treatment for period that the Participant is unable to fill their prescription or to the end of the study (whichever occurs first).

7.2 Study Schedule of Events

Case Report Forms	Screening / Baseline	Randomization[d]	Monitoring Weeks							Study Withdrawal or Positive COVID-19 Diagnosis	Week 8 End of Study	As Needed
			1	2	3	4	5	6	7			
Pre-Screening Checklist	X											
Eligibility	X											
Baseline Survey – Pt reported	X											
Laboratory – Blood Draw	X					X				X[c]	X	
Randomization Form	X											
Weekly Assessment			X	X	X	X	X	X	X	X[b]	X	
Blinded Drug Accountability Log		X	X	X	X	X	X	X	X	X	X	
AE/SAE Log			X	X	X	X	X	X	X	X[c]	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	
Protocol Deviation Log												X
Unblinding												X
Final Status										x[e]	X[e]	

Note: [a] Virtual visits for monitoring will be done via telephone, video visits or electronic mail encounters, as preferred by the study participant to promote study compliance and reduce risks for participants to coming to the clinical settings and become exposed to COVID-19. [b] Study withdrawal evaluations due to COVID-19 infection, patient preference or other reasons may be done either by virtual visits or clinic visits, depending on the participant clinical situation. [c] A study questionnaire and blood draw will be attempted on each HCW/FR who test or screen positive for COVID-19 by either study or clinical screening & testing. If study testing identifies potential active SARS-COV-2 infection during the study, the investigators will notify the Participant of the results and ensure that the Participant has access to appropriate follow up care. Participants will have a +/- 3 day window to complete their scheduled study visits. [d] If the participant cannot receive his blister pack immediately after enrollment, the participant may return later on the date of enrollment or next day to receive their study medication. Clinical assessment will be the evaluation for symptoms during the encounter with the research personnel, any potential/ active participant describing, presenting or with clear symptoms of viral infection will be referred to their medical provider for care. [e] The final status form will be completed at week 8 or upon withdrawal or early termination.

7.3 SAMPLE COLLECTION AND HANDLING

Five (5) 10 ml blood tubes consisting of 4 EDTA and 1 Shield tubes of whole blood will be collected from each participant at the baseline/enrollment, week 4 and week 8 timepoints. The samples will be collected using standard aseptic procedures and will be stored in a 4°C refrigerator or cooler until transport to the research laboratory where the samples will be processed. Samples will be processed to serum plasma or cell components. Testing for SARS-CoV 2 will be done for study entry samples. Remainder of the samples will be stored in -80°C for whole blood/serum plasma and cell samples will be stored in liquid nitrogen for future testing.

8 Statistics and Reports

8.1 Case Report Form (CRF) and Questionnaires

Study investigators will provide CRLs to sites and must include the following information:

- Participant demographics, date/time of symptoms onset, and sample collection date must be recorded.
- The study entry/enrollment (baseline visit), drug dispensing visit, week 4 and 8 visit, or at study withdrawal or confirmation of COVID-19 infection, questionnaire for each participant and submit for data entry upon completion.

If a recording error is made, cross out the error will be crossed through with one stroke, initialed and dated, with the correct information entered next to the erroneous entry.

The information required for completion of the CRL is as follows:

Subject Information:

- Subject ID (3-digit site number and 4 digit4-digit Subject number)
- Subject Gender
- Subject age

- Subject Consent Obtained (Yes/No)
- Date of Subject Consent (DD/MMM/YYYY)
- Diagnostic testing performed during the clinical visit and assay results if available
- Inclusion Criteria (Yes/No) -all criteria must be checked "yes" or Subject is not eligible
- Exclusion Criteria (Yes/No)-if any criteria is checked "yes", the Subject is not eligible
- Date of Onset of Symptom (DD/MMM/YYYY) if present
- Complete Questionnaire for each timepoint

Sample Collection Information:

- Sample Collection Date (DD/MMM/YYYY)
- Standard of Care Method/ Results
- Comments (Print Comments)

PI Signature and Date

- PI or Designee Signature and Date

8.2 Reporting AE and SAE – Frequency

Completed as participant reports for SAE and in the questionnaire for mild to moderate AEs only reported during planned study timepoints.

8.3 Statistical Analyses and Sample Size

The ITT will be used for testing the treatment efficacy based on patients who are SARS-CoVID-2 viremia negative at the baseline. The primary analysis will be to compare the rate of COVID-19 disease for each treatment group to the placebo group with a Mantel-Haenszel chi-square test with multiplicity adjustment using the Dunnett's step up method(11,12). The stratifying

variables will be those used for the randomization, site and High vs. Low risk groups. The high risk group include healthcare personnel (including environmental service) who work in COVID-19 care areas, emergency rooms and intensive care units caring for COVID-19 patients. First responders and DDOT bus drivers will be included as a high risk group. Low risk groups will include healthcare workers who work in non-COVID-19 care areas, without direct patient contact and those involved in administrative roles.

The DSMB chair will be provided with a weekly site SAE report to monitor safety. An interim analysis will be done when a half of patients have completed the 8 weeks assessments for an early treatment efficacy or a possible reassessment of study sample-size if the estimation of placebo rate is inadequate. Depending on response to the study intervention, the DSMB may decide it is necessary to stop/continue the trial if 1) there are safety concerns at any point in the trial or 2) there is evidence of treatment efficacy at the interim analysis; or recommendation for trial modification as it may be suggested, or 3) to continue the trial as designed. The DSMB will only stop the clinical trial for safety reasons.

Secondary analyses will be performed to evaluate the comparisons between the randomized arms and the chronic HCQ treatment comparator arm. Additional analyses will include assessments of inflammatory markers in both plasma and leukocytes, clinical characteristics associated with risk for COVID-19 acquisition, disease specific markers and clinical symptoms, as well as virologic markers and sequencing of positive COVID-19 patients during the study. Safety and AE reporting will also be done as part of the study. A detailed statistical analysis plan (SAP) will be written before the study is closed.

Sample size/power calculation:

With one planned interim analysis when 50% of the participants have completed their 8 week treatment and using an O'Brien-Fleming alpha spending method to ensure an overall type 1

error of 0.05, the critical value for the interim analysis will be 0.0054 and the final critical value will be 0.0492. With a sample size of 900 per group and alpha=0.0492, the power to detect a 32% reduction in COVID-19 disease rate (10% vs 6.8%) between the placebo group and each HCQ treated group would be 87%. Power calculations are also given for placebo rates of 8% and 15% with a 32% reduction in COVID-19 disease rates for the HCQ treated groups. Assuming 5-10% of patients will have SARS-CoVID-2 viremia positive at the baseline, we need 1000 per group with a total of 3000 patients to complete the trial.

Power calculations using simulations for Dunnett's step up method

Assuming 900 per group and alpha=0.0492

COVID-19 disease rate in placebo	COVID-19 disease rate in treatment	Power
8%	5.4%	80%
10%	6.8%	87%
15%	10%	98%

9 PARTICIPANT INVOLVEMENT ENDPOINT/FOLLOW-UP

All Participants who sign the Consent and Authorization Form and provide three (3) blood sample draws, complete the baseline and week 1- 8 assessments, or after acquiring COVID-19 infection at any point during the study period are considered to have completed participation in this study. Participants will be followed for 30 days after meeting study endpoint for safety purposes. No further follow-up by the study Investigator is planned for Participants involved in this study thereafter. Electronic medical records will be accessed to obtain information on any diagnostic testing done for COVID-19 as part of the Participants' routine care which may lead to diagnosis of COVID infection, including but not limited to PCR, serologies, rapid diagnostic tests, and other related tests.

10 SAFETY CONSIDERATIONS

10.1 Definitions of Adverse Events

An **Adverse Event (AE)** is any untoward medical occurrence in a Participant administered an investigational product or undergoing a procedure, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not it is related to the investigational product. *Development of COVID-19 disease will not be considered an adverse event as it is considered the study primary endpoint.*

A **Serious Adverse Events (SAE)** is any untoward medical occurrence that may present itself during a Subject's participation in a clinical trial that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the Participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Medical care and hospitalization secondary to development of COVID-19 disease are considered study endpoints for this prevention study.

It should be noted that AEs that lead to hospitalization are considered SAEs. However, elective

hospital admissions not in response to an adverse event are not SAEs.

Life-threatening means that the Participant was, in the view of the PI, at immediate risk of death from the reaction as it occurred. This definition does not include a reaction that, had it occurred in a more serious form, might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

AEs will be considered to be **study-related** if the event follows a reasonable temporal sequence from a study-specific procedure and could readily have been produced by that study or medication procedure. Deaths, organ failures and other complications related to the Participants underlying conditions (including the disease or problem that caused the Participant to seek medical care), should **not** be considered study-related AEs.

10.2 Possible Risks & Benefits Associated with Study Procedures

There is a potential health benefit to Participants by participating in this study, as the medication may help to prevent the acquisition or ameliorate the manifestations of COVID-19 infection. The COVID-19 testing results obtained from testing completed by the study investigators will be made available to the Participants when available to the investigator. If any Participant has a positive COVID-19 test during the study, the Participant will be referred to their respective healthcare provider for additional testing and treatment as recommended by the local guidelines. HFHS employees will be referred directly to employee health. First responders and DDOT bus drivers will be referred to their respective employee health services. Participants may also be referred to their primary care provider, if they choose so. Additional, secondary endpoint analyses and results will not be returned to the participating site and will not be used in the management of Participants. No personally identifiable testing for human

DNA will be performed on any samples obtained from this study. DNA testing on de-identified samples will be planned as a secondary study analyses to assess potential DNA markers of increased susceptibility to COVID-19 infection in our study population.

Hydroxychloroquine (HCQ) is considered a safe and effective drug in the treatment of Rheumatoid arthritis, Systemic Lupus Erythematosus and other autoimmune diseases, as well as for the prevention of Malaria infection (6). The 2015 American College of Rheumatology guidelines do not recommend any routine laboratory testing or electrocardiogram monitoring for patients taking HCQ standard doses (up to 400mg maintenance dose) daily (8). Side effects of the medication are varied including gastrointestinal symptoms, skin and hair changes, muscle pains, an irregular heartbeat, and others as listed in Pharmacy section 10.3, with most being mild and of unknown incidence. Severe but rare side effects include drug allergic reaction, cardiac arrythmias with risk of death, hypoglycemia with concomitant hypoglycemic medications, visual changes, retinal disease and rarely blood cell count anomalies may occur. Participants with any potential medication associated drug-drug side effects and/or with any elevated risk factors associated with any significant HCQ side effects or toxicities, will be excluded from the study.

The only study-related procedure that could impact Participant safety is the collection of three (3) planned blood draws. The anticipated risks of collecting a blood sample specimen may include slight pain, discomfort, and/or the possibility of bleeding or bruising at the site.

Possible risk of loss of confidentiality could occur by obtaining study questionnaires and accessing the Participants' electronic medical records to determine assay results from any clinical testing for COVID-19 that may have been performed during their clinic or emergency room visit includes potential exposure of confidential medical information. Investigators will keep a separate patient key linking MRN to the study ID and will not provide this information to the study sponsor unless required by law. All study and clinical information will be kept in

secure electronic servers and in locked cabinets. Investigators will ensure that only the minimal amount of information needed for the study is accessed and recorded for study purposes. (See Confidentiality, section 11.3)

10.3 Pharmacy

DOSE

The once weekly randomized treatment arm will receive the proposed dose of hydroxychloroquine for prophylaxis of malaria is 6.5 mg/kg per dose (maximum of 400mg per dose) administered orally weekly on the same day of each week. This is based on the recommended dose for prophylaxis of malaria(13).

The daily hydroxychloroquine treatment arm will receive a 200mg oral dose daily following day 1 dose of 400mg orally once. This dose represents approximately half the standard weight-based dosing recommended for management of autoimmune diseases and therefore less likely to produce side effects than standard of care. All treatment groups will receive placebo pills to have the patients take 2 pills a day.

The randomized placebo arm will receive placebo pills made to resemble the daily dosing of HCQ. Similarly, the once a week treatment arm will receive placebo pills for the days not on HCQ medication.

No specific dosage adjustments are required in patients with renal dysfunction or hepatic disease due to the lower dosing regimen in the intervention arms (14).

Note, the elimination half-life of hydroxychloroquine sulfate estimated from 172 hours to 50 days (15). Subjects may have prolonged exposure to hydroxychloroquine even after discontinuing the medication.

PRECAUTIONS AND CONTRAINDICATIONS

Hydroxychloroquine is contraindicated in patients with hypersensitivity to hydroxychloroquine or related compounds.

Caution should be exercised when using hydroxychloroquine in Participants with any of the following underlying conditions or risks:

- Cardiovascular disease: cardiomyopathy, with fatalities, has been reported. QT prolongation, ventricular arrhythmias, and torsades de pointes have been reported. Avoid use with other drugs that prolong QT interval.
- Dermatologic: severe exacerbation of psoriasis may occur. Other dermatologic reaction may occur.
- Endocrine and metabolic: severe hypoglycemia may occur in patients treated with antidiabetic medications.
- Hematologic: Aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia may occur, more commonly with prolonged use.
- Hepatic: Use with caution in patients with liver disease, alcoholism, or use of other hepatotoxic drugs. Dose adjustment may be necessary; however no specific dose guidelines are available.
- Musculoskeletal: proximal myopathy has been reported. Neurologic: neuropathy has been reported.
- Ophthalmic: Irreversible retinal damage has been reported as a rare complication of therapy. Increased risks include doses larger than 6.5mg/kg, duration of over 5 years, renal insufficiency, concomitant use of tamoxifen, or concurrent macular disease.
- Psychiatric: suicidal behavior has been rarely reported.

DRUG-DRUG INTERACTIONS

Hydroxychloroquine should not be used with certain drugs that are known to prolong QT syndrome. These include but are not limited to:

Common drugs known to cause Torsades de Pointes	
Class	Examples
Antiarrhythmics	Disopyramide, procainamide, quinidine, sotalol
Macrolides	Azithromycin, clarithromycin, erythromycin
Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin
Antifungals	Fluconazole, ketoconazole, pentamidine, voriconazole
Antipsychotics	Haloperidol, thioridazine, ziprasidone
Antidepressants	Citalopram, escitalopram,
Antiemetics	Dolasetron, droperidol, granisetron, ondansetron
Opioids	Methadone
Miscellaneous	Cocaine, cilostazole, donepezil

Other moderate drug interactions:

Digoxin: may increase serum digoxin concentrations.

Antacids or PPI may reduce HCQ absorption.

PATIENT COUNSELING

Counsel Participants that side effects of this medication may include vertigo, tinnitus, visual field defects, color vision abnormalities, nausea, vomiting, fatigue, decreased appetite, headaches, dizziness, and irritability. Participants taking antidiabetic medications will be counseled on the

risk of hypoglycemia and the associated symptoms. Symptoms of toxicity (e.g. rash, visual changes) should be reported to a healthcare provider and to the investigators. Participants will be made aware of the need to keep their study medications out of the reach of children.

10.4 Reporting Requirements

Any medical occurrences that are observed during the study that the Investigator believes are **serious AND qualify as either an unanticipated adverse event OR are related to study-specific procedures** as defined above must be reported (by telephone or FAX) to the Study PI or Co-PI **within 10 days** to:

Laurie Marshall-Nightengale, MD, MSc

Research Coordinator

Tel: 313-916-4835

The applicable IRB must also be informed of the event in accordance with their procedures. The Investigator will then submit a detailed written report to Study Sponsor and the IRB no later than ten (10) days after the Investigator discovers the event.

Study investigators will be responsible for reporting any reportable serious, unexpected, study-related AEs from this study to the FDA and other applicable regulatory agencies.

11 INVESTIGATOR OBLIGATIONS

11.1 Guidelines for the Conduct of the Study

The Investigator is responsible for ensuring that the study is conducted in accordance with the clinical protocol and in compliance with FDA regulatory requirements outlined in 21 CFR Parts 11, 50, 54, 56 and 812, the Guidance for Industry - Good Clinical Practice: Consolidated Guidance (ICH-E6) April 1996, and the Declaration of Helsinki.

The Investigator is also responsible for protecting the rights, safety and welfare of Participants under the Investigator's care.

11.2 Informed Consent

In accordance with guidelines as outlined in CFR 21, Part 50, the Investigator or designee will ensure that the Participant/Subject is provided full and adequate verbal and written information about the nature, purpose, possible risks and benefits, and costs of this investigational study. A written informed consent form (ICF) will be provided to each participant describing this information. This form must be reviewed and approved by Study Sponsor, Investigators and the IRB before its use in the study. Each Participant must sign and date this form prior to their participation in the study.

An original consent form for each Participant will be kept on file at the clinical site. A copy will also be given to the Participant or parent/legal guardian signing the form.

11.3 Confidentiality

The Investigator and designees, employees, and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy and security of Participant's health information. Study data disclosures will be limited to the Sponsor, IRB, FDA or other authorized recipients as appropriate for the execution, analysis, review and reporting of this study. Such information shall not be used for any other purposes and will remain

confidential.

11.4 Protocol Modification/Amendments

Deviations from the protocol will be documented throughout the duration of the study. Protocol deviations may include, but are not limited to the following:

- Participant is enrolled without meeting all inclusion criteria and/or meets one or more exclusion criteria; or
- Participant samples are not stored or handled within protocol specified timeframes and/or temperature requirements.
- Participant questionnaires are not fully completed prior to study entry.

If preliminary or interim review of study data indicates that a revision to the protocol is required, an amendment to this protocol will be prepared and implemented upon agreement of the study investigators. If these changes or deviations affect the scientific accuracy of the investigational plan or the rights, safety, or welfare of human Participants, the IRB must be notified. Deviations from the protocol will must be documented on the Protocol Deviation Log.

Protocol amendments may be introduced by the lead investigator team at any time after the start of the study to include new procedures or address new findings in the field.

11.5 Recording & Monitoring of Study Data

All required study data will be recorded on a Source Document and later transcribed to the Case Report Logs provided by study investigators. The data recorded on the Case Report Logs is derived from study related source documents. The Investigator shall ensure that all data on the

Study Report Logs is complete and accurate and consistent with source documentation.

All data collections will be recorded/or legibly printed in indelible black or blue ink. Any errors will be crossed out with a single line and the correct entry made in indelible ink and initialed and dated by site personnel making the correction.

A monitor may review the Case Report Forms for completeness and accuracy. Study data on the Study Report Forms may be verified against information on original source documents. Source documentation may include, but is not limited to, clinical records, intake forms, test result print outs, laboratory logs and may differ by site. The source documentation reviewed will be noted by the study monitor in each monitoring report. The monitor will also check written informed consent forms and all study specific logs for completeness, accuracy and plausibility.

11.6 Direct Access to Source Data & Study Documents

The Investigator and study site will permit trial-related monitoring, audits, IRB review and regulatory inspection by providing authorized personnel from Study Sponsor, its representatives, the IRB, the FDA and other appropriate regulatory agency direct access to all trial related data.

Direct access is the permission to examine, analyze, verify and reproduce any records, source documents or reports that are important to the evaluation of a clinical study. Any party with direct access should take reasonable precautions to maintain the confidentiality of the study Participants.

11.7 Record Retention

Copies of Study Report Forms, original ICFs, original source documents, study records, and reports must be maintained by the Investigator for a period of five (5) years after the investigation is terminated or completed, or for a period of two (2) years after the records are no longer required for the purposes of supporting a pre-market approval application or a notice of completion of a product development protocol. Study sponsor should be notified in writing at least 30 days prior to the disposal or transfer to another location or party, of any study records related to this protocol.

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APPENDIX A: INVESTIGATOR

Study Document 1

Investigator Signature & Date: _____

Investigator Name & Title (print): _____

Name(s) of Co-Investigators: _____

Address of Study Center: _____

_____

Telephone Number: _____

APPENDIX B: APPROPRIATE TECHNIQUE FOR BLOOD DRAW

Proper collection of a quality throat specimen from each Participant is critical.

Three (3) blood specimens will be collected from each Participant using the sterile procedure as routine standard of care. A total of five (5) 10 mL tubes of whole blood will be collected at each timepoint. Avoid contaminating the specimens when collecting samples. Do not touch the top of the tubes or the sample collection site without gloves and protective equipment.

A. Procedures/Study Protocol

1. The phlebotomist or trained research assistant to perform the venous blood draw will inspect the participant's arms and hands for a vein of a reasonable size. This is most often the medial cubital vein, although other veins on the forearm and back of the hand can be used.

2. Once a suitable vein has been selected by the phlebotomist, the participant will be asked to sit or lie down in a position that provides the phlebotomist access to the vein and that is comfortable for the participant.

3. The skin superficial to the vein will be cleaned with an alcohol wipe.

4. A tourniquet will be applied 5-10 cm above the intended site of the venous puncture.

5. Blood samples will be collected using a closed, vacutainer system. The grey rubber end of the vacutainer needle is exposed and screwed onto the vacutainer tube holder. The needle is then unsheathed and inserted through the skin and into the vein at an angle of 15-30 degrees.

6. Blood tubes can then be inserted into the tube holder and onto the hold. The vacuum in the tube will draw the blood. A full tube can be disengaged, and a new tube can be added. The number of tubes to be used varies depending on the number and type of analyses to be performed.

7. Upon completion of the blood draw, the tourniquet will be removed, and the needle will be withdrawn from the vein quickly.

8. Cotton will be pressed on the site of venous puncture.

9. Participant will be asked to sit still and apply pressure to stop the bleeding and reduce the risk of bruising.

10. The phlebotomist will disengage the needle from the holder directly into the sharp's disposal.

11. If a plasma sample is being collected the blood samples will be gently inverted to mix anticoagulant.

12. Once the bleeding has subsided or stopped (approximately 2-3 min), a bandage will be applied over the puncture and the participant will be asked to sit quietly for up to 10 minutes.

13. The phlebotomist will inform the participant there may be bruising at the site of the puncture for the next few days, to keep the puncture area clean and dry to promote rapid healing, and no heavy lifting for 24 hours to prevent further bruising.

14. The participant will be thanked for their participation.

B. EQUIPMENT

• 21 gauge needle for each participant with closed vacutainer system

• Blood collection tubes for each participant

• Tourniquet

• Box of nitrile/vinyl gloves (Do not use latex gloves due to allergies/sensitivities.)

• Alcohol wipes, cotton balls/swabs, bandages

• Pillow/pad for raising arm to comfortable elevation

• Apple/orange juice and snacks for fasting participants

• Disposable, single use materials or equipment are to be used whenever possible

• Any reusable materials or equipment must be cleaned and disinfected with alcohol-based sanitizers before use with another participant

C. DESCRIPTION TO STUDY PARTICIPANTS

1. Each individual (i.e., study participant) is to be asked in-person, by telephone, or by email if they are:

    • comfortable having blood drawn, and allergic/have sensitivities to rubbing alcohol.

2. Individuals who indicate in any way they are uncomfortable with the procedure and/or are allergic/sensitive to rubbing alcohol will be asked not to participate in the study.

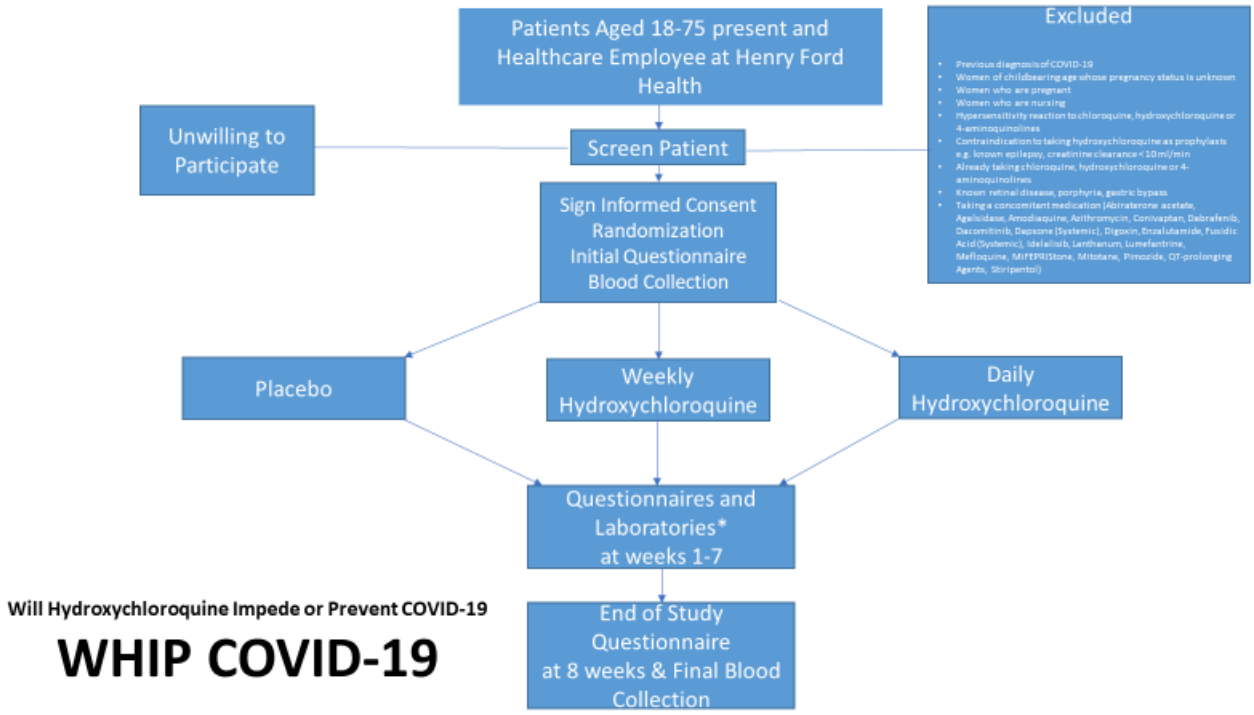
3. In the information-consent letter participants must be informed:

- the blood will only be drawn by a trained and experienced phlebotomist who has been delegated to conduct the procedure by a physician.
- the phlebotomist will insert a needle into a vein in their arm similar to giving a blood sample in a lab that may be requested by their family physician/doctor during a routine physical or a check-up.
- the procedure requires wiping an area of the skin with rubbing alcohol and puncturing a suitable vein on the inside surface of their elbow with a 21-gauge needle.
- Participant will be instructed to wear a loose shirt or a short sleeve shirt as the most commonly used vein

for blood collection is located on the inside surface of their elbow.

- Participant may ask any questions that they may have about the procedures at any time or ask to stop the procedure at any time.

APPENDIX D: STUDY FLOW CHART



Note: * Only study week 4 will be a clinic research visit with blood draw performed at that visit and refill of the participant randomized medications. Weeks 1,2,3,5,6 & 7 will be done via telephone, virtual visit or electronic mail, as preferred by the patient.