Hackensack Meridian *Health*

Feasibility, Safety and Early Efficacy Trial of Hydroxychloroquine as Primary Prevention of Corona Virus Disease 2019 in high risk health care providers

Hackensack Meridian *Health* (HMH)

Principal Investigator: Jawad F. Kirmani, MD: HMH-JFK University Medical Center

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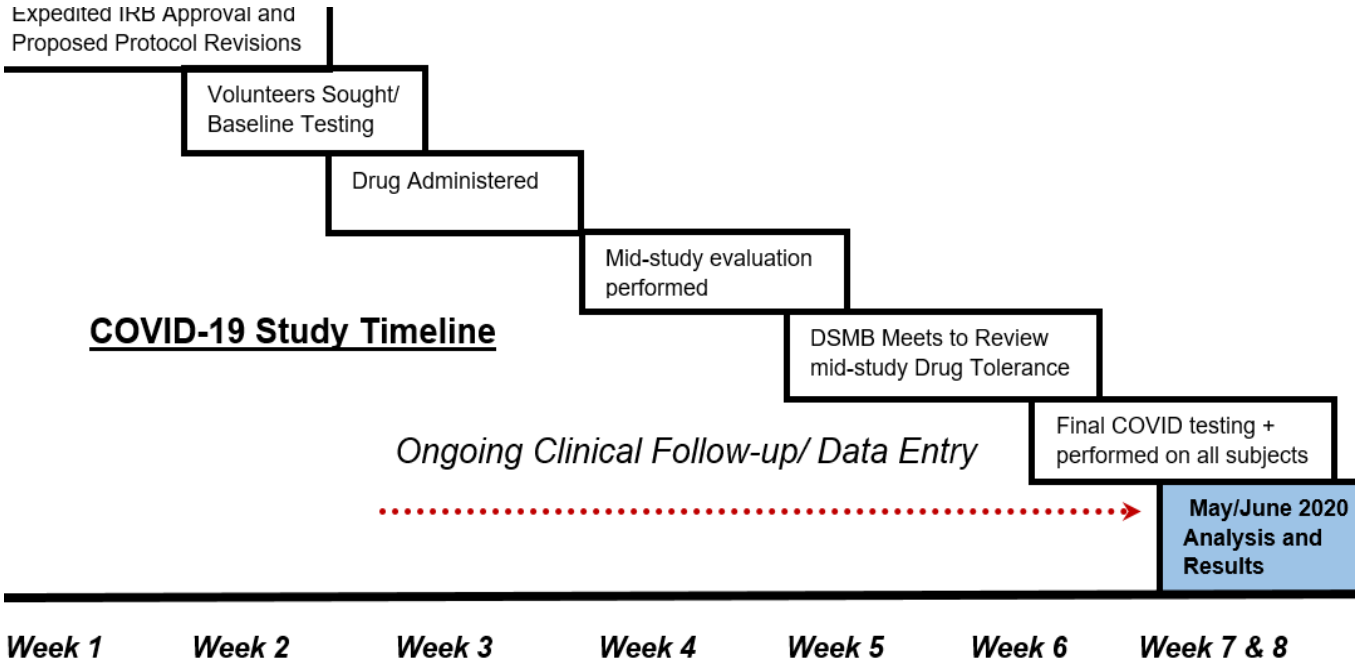
SUMMARY

We propose to conduct an open-label Phase II trial to evaluate the feasibility, safety and early efficacy of hydroxychloroquine (HCQ) administration in reduction of transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and development of Corona Virus Disease 2019 (COVID-19) in high-risk, healthy acute care provider participants exposed, directly or indirectly, to COVID-19 patients. There is a more than 50 years track record of safety of HCQ for treatment and prevention of various disease states. Early data on use of HCQ for COVID treatment suggests anti-viral activity and immunomodulatory properties for reducing inflammation associated with COVID-19. Given the lack of data regarding use of HCQ for COVID-19 prevention in healthy participants in midst of pandemic crisis, we propose an expedited feasibility study focusing on safety and early efficacy.

Prior to HCQ administration, baseline SARS-CoV-2 and other baseline biomarker testing will be conducted. During the 4-week study period, participants will be monitored for drug related adverse events and assessed for development of COVID. SARS-CoV-2 assay and biomarker testing will be repeated at the end of four-week study. Safety outcomes will be assessed by the number of adverse events (AEs) and their severity; and early efficacy as the number of participants who tested positive at the end of the 4-week period comparing to data collected by occupational Health regarding the total number of high-risk healthcare workers that were tested positive during the same period and historical controls from known high risk infection rates. An exploratory analysis of inflammatory regulation and immunomodulatory markers by HCQ and its effect on possible disease modification based on previously studied pathophysiological mechanism of COVID-19.

The broader aim of this study is to set a precedent to facilitate a large-scale emergent public health intervention. Purpose would be to mitigate, or abort further transmission of COVID-19. Given that COVID-19 transmission has occurred prior to initiation of this study, the rationale for this intervention is based on prior epidemiological evidence. Post-infectious or vaccination-induced immunity in at least 30% of population at-risk has been shown to mitigate or abort propagation of a local epidemics and global pandemic. This would help flatten the curve of the disease progression, until such time that a vaccine may become available. Data from this study will be used to design and implement a population-based phase IIb/III randomized clinical trial.

Study overview is provided on the next two pages. Study Timeline is summarized below.



Brief Title	HCQ in Health Care Providers for Primary Prevention of COVID-19
Official Title	Phase II: Feasibility, Safety and Early Efficacy Trial of HCQ as Primary Prevention of Corona Virus Disease 2019 (COVID-19) in high risk health care providers
Brief Summary	In vitro studies demonstrate that HCQ has anti-viral properties in Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2). HCQ is also widely used off-label in the acute treatment of COVID -19, including within the HMH network. However, there are no clinical studies for primary prevention of infection with HCQ for COVID-19. This study investigates whether HCQ reduces viral transmission in at-risk, healthy acute care provider participants.
Detailed Description	Open-label, consecutive at-risk subjects allocation with chemoprophylaxis with HCQ.
Study Type	Interventional
Study Phase	Phase II
Study Design	Allocation: Consecutive High-Risk Subjects Intervention Model: Voluntary assignment Intervention Model Description: Open-label, Feasibility, Safety and Early Efficacy trial Masking: None (open-label) Primary Purpose: Primary chemoprevention
Condition	COVID-19
Intervention	Drug: Hydroxychloroquine sulfate (Plaquenil™)
Study Arm	Intervention: Drug: HCQ sulfate HCQ 400mg (2x 200mg tablets) by mouth 6-12 hours apart on day 1, followed by 3 weeks of weekly 400mg (2x 200mg tablets) by mouth
Estimated Enrollment	45
Estimated Study Completion	May/June 2020
Estimated Primary Completion Date	May 2020 (Final data collection date for primary outcome measure)
Sex/Gender	All
Ages	18 to 99 years (Adult, Older Adult >60 years)

Accepts Healthy Volunteers	Yes (only healthy volunteers)
Eligibility Criteria	**Inclusion Criteria:** Volunteer High-Risk healthcare care providers in a hospital setting with active exposure to COVID-19 infection and negative test at baseline. **Exclusion Criteria:** • Inability to tolerate an oral medication or known allergy to chloroquine or hydroxychloroquine (HCQ) • Pregnancy or breast-feeding • Immunocompromised status, hepatic failure, electrolytic imbalance • Creatinine clearance (CCL) <30 mL/min • Prolonged QT interval (QTc > 450ms for males, QTc > 470 for females) • Confirmed COVID-19 infection on baseline testing • Has another known contraindication to treatment
Contacts	**Briana Decarvalho, MSN: Clinical Trials Coordinator**
Location Countries	United States
Medical Center	HMH-JFK University Medical Center HMH-Hackensack University Medical Center HMH- Jersey Shore University Medical Center
Statistics	Occurrence rates of well-known adverse events (side effects of hydroxychloroquine sulfate) in the intervention arm will be estimated by percentage and exact (Clopper-Pearson) 95% confidence interval. The observed rate of occurrence of these AEs will be compared with the upper limit of the confidence interval to assess if the observed rate is over and above the expected rate, per well-known rates on the pharmacy guidelines.
Has Data Safety Monitoring Committee (DSMC)	Hackensack University Medical Center DSMB (HUMC-DSMB)
U.S. FDA-regulated Product	FDA has been contacted and they have exempt this study from requiring an IND.
IPD Sharing Statement	Plan to Share IPD: No
Principal Investigator	Jawad F. Kirmani, MD: HMH-JFK University Medical Center
Study Sponsor	Hackensack Meridian *Health*

A. SPECIFIC AIMS

We propose to conduct a 4 week, emergent, single arm phase II, open-label, consecutive high-risk healthy subjects enrolled to evaluate safety, feasibility and early efficacy of hydroxychloroquine (HCQ) in volunteer Health Care Providers (HCP) participants, for primary chemoprevention of Coronavirus Disease 2019 (COVID-19)

Aim 1 (not hypothesis driven)

To evaluate the feasibility of this protocol including participants' compliance with HCQ, resource availability and resource utilization including performance of COVID-19 tests and biomarkers for safety in this emergent study with an expedited timeline.

Aim 2

To Determine the Safety profile for a previously well studied drug in this select group of HCP. Incidence of well described side effects would be studied over the course of the study and will be compared with the side effects and their prevalence as described in the Pharmacy manual for HCQ.

Hypothesis 1: it is postulated that the healthy volunteers would have similar safety profile than previously described in the literature for HCQ (2).

Aim 3

To evaluate the early efficacy of HCQ in high-risk, healthy volunteers in the prevention of acquiring COVID-19 while continuing to follow standard precautions that meet or exceed Centers of Disease Control (CDC) guidelines.

Hypothesis 2: The chemopreventative effect of HCQ confers protective effect against transmission of COVID-19 and less than or equal to 10% of study population would contract COVID-19 as compared to an expected 30% (1).

Exploratory Aims

To evaluate the effect of basic inflammatory regulation due to interventional drug and its effect on possible disease modification based on understood pathophysiological mechanism of COVID-19.

Hypothesis 3: COVID specific inflammatory response including cytokine IL-6 levels would be compared at the start and end of 4 week study with interventional drug (54).

B. BACKGROUND AND SIGNIFICANCE

B.1 COVID-19 Pandemic

The novel coronavirus was first detected in China and has spread to over 100 countries internationally, including in the United States, and as of March 24, 2020 about 400,000 patients were infected worldwide. The virus has been named Severe Acute Respiratory Syndrome- CoronaVirus-2, or SARS-CoV-2, and its disease process Coronavirus Disease 2019, abbreviated COVID-19 (5).

Coronaviruses are a large family of viruses common in humans and other animal species, including camels, cattle, cats, and bats. Rarely, non-human coronaviruses infect humans and are subsequently transmitted to other humans, which is the case in SARS-CoV-2. SARS-CoV-2 is a beta-coronavirus, similar to the Middle East Respiratory Syndrome CoronaVirus (MERS-CoV) and SARS-CoV. These viruses originate in bat species, which are the presumed reservoir or ancestral hosts for several CoronaViruses. The emerging natural history of the disease in the United States is similar to that described in isolated Chinese patients in the months prior to widespread dissemination. This suggests the reemergence of SARS-CoV-2 from a single animal disease vector (6).

Early on, patients at the epicenter of the outbreak in Wuhan, Hubei Province, China were linked to high-traffic seafood and live animal market, suggesting animal-to-person transmission. Later, a growing number of patients reportedly did not have exposure to animal markets, indicating subsequent person-to-person transmission. Person-to-person transmission was then reported outside the Hubei Province followed by countries outside China, including in the United States which has fast become the new epicenter (15). Almost all countries, are presently effected by community transmission of the virus that causes COVID-19, whereby how or where infected persons became exposed is unknown. Recently, novel, major epidemic foci of COVID-19, some without traceable origins, have been identified and rapidly expanding in Europe, North America, Asia, and the Middle East, with confirmed cases rapidly increasing in African and Latin American countries (5).

By Mid-March 2020, the number of COVID-19 cases outside of China increased significantly and the number of countries, states, or territories reporting infections to the World Health Organization (WHO) was 143 (5). On the basis of alarming rates of transmission, severity of disease, and level of inaction, on March 11, 2020, the Director-General of WHO characterized COVID-19 as a pandemic (7). The WHO Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH) regularly reviews and updates its risk assessments for COVID-19 to make recommendations to WHO Health Emergencies Program. STAG-IH's meeting on March 12, 2020 included an update of the global COVID-19 crisis and an overview of research priorities established by WHO Research and Development Blueprint Scientific Advisory Group (8).

B.2. COVID-19 Transmission

In response to COVID-19, many countries are using a combination of containment and mitigation actions with intention of delaying major surges of COVID-19 patients and stabilizing demand for hospital beds and ventilators, while protecting the most vulnerable populations from infection, including the elderly and immunocompromised persons with comorbidities (Figure 1). Actions taken to accomplish these goals vary and are based on national risk assessments that generally include estimated numbers of COVID-19 patients requiring hospitalization, availability of hospital beds, and ventilation support (9).

Most national response strategies include but are not limited to: variable levels of contact tracing as well as voluntary and involuntary self-isolation or quarantine; promotion of public health safety measures, including handwashing, respiratory etiquette, and social distancing; preparedness of health systems for a surge in critically-ill patients requiring isolation, oxygen, and mechanical ventilation; strengthening health facility infection prevention and control, with special attention to nursing home facilities; and postponement or cancellation of large-scale public gatherings. However, no preventative medication has been studied or is thought to be helpful (12).

Some lower-income and middle-income countries require technical and financial support to effectively respond to COVID-19, and many African, Asian, and Latin American countries are rapidly developing the capacity for PCR testing of COVID-19 (8). Based on more than 500 genetic sequences submitted to GISAID (Global Initiative on Sharing All Influenza Data), SARS-CoV-2 has undergone minimal RNA sequence changes and its transformation into another strain has not occurred (13). This is a nonetheless concerning, as successful mitigations efforts have been dependent upon this minimal sequence drift. If or when SARS-CoV-2 transformation occurs, pandemic mitigation efforts will be challenged. Presently, there is no evidence to link sequence information with transmissibility or virulence of SARS-CoV-2 and its disease process COVID-19. All of these factors highlight the importance of mitigation strategy through chemoprophylaxis for containment of rapid case increase until such time that a vaccine may become available (10).

From studies investigating viral shedding in patients with mild to severe presentations, viral shedding appears to be the greatest during the early phase of disease (Myoung-don Oh and Gabriel Leung, WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, Special Administrative Region, China, personal communication). The role, if any, of asymptomatic carriers in transmitting infection is not yet completely understood. Pre-symptomatic infectiveness is a significant concern (Myoung-don Oh and Gabriel Leung, personal communication) (14), and many countries are now using the first 48 hours of symptom onset as the marker for infected contact identification (16). Chemoprophylaxis with HCQ may play an important role in that early period.

B.3. Estimates of HCP infection rates during acute outbreak

Unfortunately, SARS-CoV-2, similar to other emerging high-threat pathogens, has disproportionately infected frontline health-care workers both in China and several other countries, including the United States (10, 11).

A comprehensive report published by the Chinese Center for Disease Control and Prevention on the epidemiological characteristics of 72,314 patients with COVID-19 confirmed our previous understanding that most known infective agents cause mild disease, with a case fatality rate ranging from 2.9% in the Hubei Province to 0.4% in other Chinese provinces (17). This report also suggested that elderly people, particularly those older than 80 years, and people with comorbidities, such as cardiac disease, hypertension, respiratory disease, diabetes, and immunocompromised status are at greatest risk of serious disease morbidity and mortality. Persons in healthcare facilities for older persons are at greater risk of serious disease as shown in the report of a series of deaths in elderly care facility in the US (18). Wang et al found that in their published cohort reported in JAMA, from Wuhan experience of 138 patients, 41% of the cases were considered to have been from hospital associated transmission a staggering 29% were healthcare workers (44). An estimated 3000 health care workers were confirmed to have been infected and at least 22 subsequently died. The estimates would indicate a staggering total of more than 30% of health care providers in Wuhan contracted COVID of vast majority remained undetected due to minor symptoms and were potential transmitter of COVID (61).

In Italy during the acute phase, 9% of the COVID-19 cases as of March 13 occurred in health-care workers (10). A total of 51 doctors who tested positive for COVID-19 have succumbed to the disease as of March 27, 2020 (44 in Lomabardy). At least 6,414 health care workers in Italy have reportedly contracted the virus as of March 27,2020 according to Italian Institute of Health. Out of over 86,000 cases in the country as of March 29, there were over 10,779 deaths and almost 13,030 recoveries (Case fatality rate: 11%). However, most of the death rates were in elederly and population with pre-existing co-mobidities. Case fatality rate of health care provider age group (20-65 years) was still 3.5%. The estimates would indicate a staggering total of more than **30%** of health care providers in Lombardy contracted COVID of whom almost 80% remained undetected due to minor symptoms (61).

As the Epicenter has now shifted from Wuhan, China to Lomabardy, Italy to now New York/New Jersey with an expected peak in mid to late April, a similar infection rate of greater than 30% could be expected in our HCW (64). For the study purpose high-risk HCW were chosen with a conservative estimate of COVID infection at 30% risk amongst the workers (61).

B.4. Role of Immune Response and Immunomodulation in COVID-19

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality (65). Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections (66) and occurs in 3·7–4·3% of sepsis cases (67) Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients (68). Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297·6 ng/ml in non-survivors' *vs* 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001), suggesting that mortality might be due to virally driven hyperinflammation (65).

B.5. WHO Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH) Call for Action

Evidence suggests that the pandemic of COVID-19 has entered the next stage with rapid transmission and dissemination of SARS-CoV-2 in countries outside China, with the incidence of disease exceeding that of China in many satellite countries. STAG-IH has made recommendations for response measures to prevent further transmission. More importantly, STAG-IH has identified deficiencies in our knowledge of SARS-CoV-2 and COVID-19 to facilitate the need for emergent research with special focus on areas outlined below (10):

1. Determine the best ways to apply knowledge about infection prevention and control in health-care settings (including identification of optimal personal protective equipment) and in the broader community.
2. Support standardized, best evidence-based approach for clinical management and better outcomes and implement randomized, controlled trials for therapeutics and vaccines as promising agents emerge.

B.6. Safety Profile and Pharmacological Properties of HCQ for Approved Indications

HCQ has adequate oral bioavailability and is widely used as an anti-malarial agent and treatment for autoimmune disease. From a pharmacokinetic standpoint, HCQ has long and heterogeneous plasma terminal elimination half-lives (approximately 40-60 days), high volume of distribution (44,000 liters) extending into aqueous and lipid compartments, and long mean residence time (1,300 hours). Approximately 50% of HCQ is bound to plasma proteins and hepatically metabolized into three active metabolites. The other half of drug metabolites undergo renal clearance. The pharmacokinetics, mechanism of action, and therapeutic properties of HCQ have been extensively studied. HCQis generally preferred over chloroquine given the latter's greater side effect profile and the former's analogous efficacy (20). HCQ clinical safety profile is better than that of chloroquine (during long-term use) and allows higher daily dose (45) and has fewer concerns about drug-drug interactions (46).

Malaria is the most prevalent parasitic infection in the world and not effected by actions of quinine. Resistance of malaria to chloroquine has rendered it ineffective. HCQ is an analogue of chloroquine with equivalent clinical efficacy against malaria whereby an N-ethyl group is substituted for a beta-hydroxylated group. HCQ mitigates ring formation, heme polymerization, and hemoglobin digestive pathways of the parasite. HCQ also may immunomodulate through cytokine reduction especially IL-6 and TNF-A. It has a down regulatory effect on Ferritin (20). HCQ has been used as chemoprophyalctic agent for prevention of malaria (20).

The mechanisms of action in HCQ and chloroquine in autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren's syndrome and their respective arthritides are only partially understood, thus, representing an enigma. Historically, HCQ has been employed successfully for the treatment of SLE and RA for over 70 years. HCQ is effective in preventing thrombosis in anti-phospholipid antibody (aPL) syndrome and controlling the dermatological complications in SLE. HCQ's strong binding to melanin reflects the dermatological properties of these drugs as well as the adverse ocular manifestations, which are less severe than that of chloroquine (20).

Commercially available package listed warnings and potential side effects are listed in **Appendix A**.

C. PRELIMINARY STUDIES

C.1. Preliminary Data for Use of HCQ and Feasibility for COVID-19 Patients

There are very few details available for effective treatment options for COVID-19 during this acute phase. Published reports stemming from the COVID-19 Chinese outbreak have evaluated the potential usefulness of HCQ for its antiviral properties and possibly for controlling cytokine release syndrome in patient with COVID-19 patients. (21)

HCQ was evaluated for SARS CoV-2 and shown to have significant anti-viral effectand viral clearance (13). The same in vitro study that stated Remdesivir's antiviral activity also showed chloroquine potent activity versus COVID-19 in human cells (13). It appears to block viral infection by increasing endosomal pH needed for virus/cell fusion, and interferes with the glycosylation of virus cellular receptors. The drug also has immune-modulating activity which is proposed to enhance its antiviral effect in vivo (22). Various other mechanism of anti-viral activity have also been proposed (47).

A Chinese clinical study evaluating 5 daily doses of 400 mg in adults who developed pneumonia from the COVID is scheduled to conclude in the latter half of 2020. The study is sponsored by the Shanghai Public Health Clinical Center, and it is unknown how long after study conclusion the information may be shared with other stakeholders. A large ongoing study is comparing HCQ'S clinical outcomes to Carrimycin, Lopinavir/Ritonavir, and Umifenovir, for patients with COVID. The study is not anticipated to conclude before February 2021. The most recent Chinese guidelines on COVID-19 recommend chloroquine phosphate 500 mg twice a day for up to 10 days for acute treatment (21).

Gautret et al. conducted a clinical trial aiming at assessing the effect of HCQ on SARS-CoV-2- infected patients in France (47). Gautret et al included total of 36 SARS-CoV-2-infected patients in the study. Twenty patients received HCQ and 16 patients were control. 6 patients treated with HCQ received Azithromycin for prevention of bacterial super-infection. Dosage of HCQ was 200 mg three times a day for 10 days. Mean HCQ serum concentration was 0.46 µg/ml+0.2 (N=20). Gautret et al were able to show that 70% of HCQ–treated patients were virologicaly cured compared to 12.5% of controls at Day 6 of treatment ($p < 0.001$). The significant difference was observed between the HCQ treated patients and controls starting even on day 3 post–inclusion (47). The results of this study are pivotal given that the mean duration of viral shedding in patients suffering from COVID-19 in China was 20 days (even 37 days for the longest duration) (48). Gautret et al did not include healthy subjects in their study to demonstrate a chemo prophylactic role of HCQ.

The pharmacological activity of chloroquine and HCQ was tested using SARS-CoV-2–infected Vero cells. Physiologically based pharmacokinetic models (PBPK) were conducted for each drug. HCQ was found to be more potent than chloroquine in vitro. Based on PBPK models, the authors recommend a loading dose of HCQ 400 mg PO BID, followed by 200 mg BID for 4 days for therapeutic steady state. (23)

Given that HCQ is already available in the US, comes in oral dosage forms, has a known safety profile, and is relatively inexpensive (compared to newer agents), it would not be as difficult to utilize this product as some of the other candidate agents, should the results of any studies confirm the findings of the in vitro study in a patient care setting. To date the use of this drug to achieve therapeutic levels in healthy individuals with an intent to use for chemoprevention for COVID 19 has not been studied (24).

C.2. Safety Consideration

The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years of continual usage (58). Cumulative dose of 1000g is generally considered safe for development of major side effects when studied in pharmacodynamics models (56). In our study total cumulative dose will be no more than 2g over a period of 4 weeks. A study of generally considered severe HCQ major adverse effect of retinopathy for HCQ <

9mg/kg for 3.25 years (cumulative dose of >800g) in human subjects confirmed safety of cumulative high dosages. The study also suggested a daily safe dose of <7.8 mg/kg for prolong use to minimize dose related side effects (53, 57).

C.3. Selection of Dosage

Dosage is based on the pharmacological activity HCQ tested using SARS-CoV-2–infected Vero cells. Physiologically-based pharmacokinetic models (PBPK) suggest loading dose of HCQ 400 mg PO BID, followed by 400 mg once weekly on the same day of each week continued for 4 weeks OR at least until one week of possible known exposure. Possible known exposure is to be defined as the active COVID patient or actively being treated at the health care setting of the health care provider (23). The loading dose (400 mg PO BID) has been shown through pharmacodynamic Phase 0 and Phase I studies to have an effective volume of distribution. Prophylactic dose range and steady state could be maintained with 400 mg weekly dosage in these studies (49, 50).

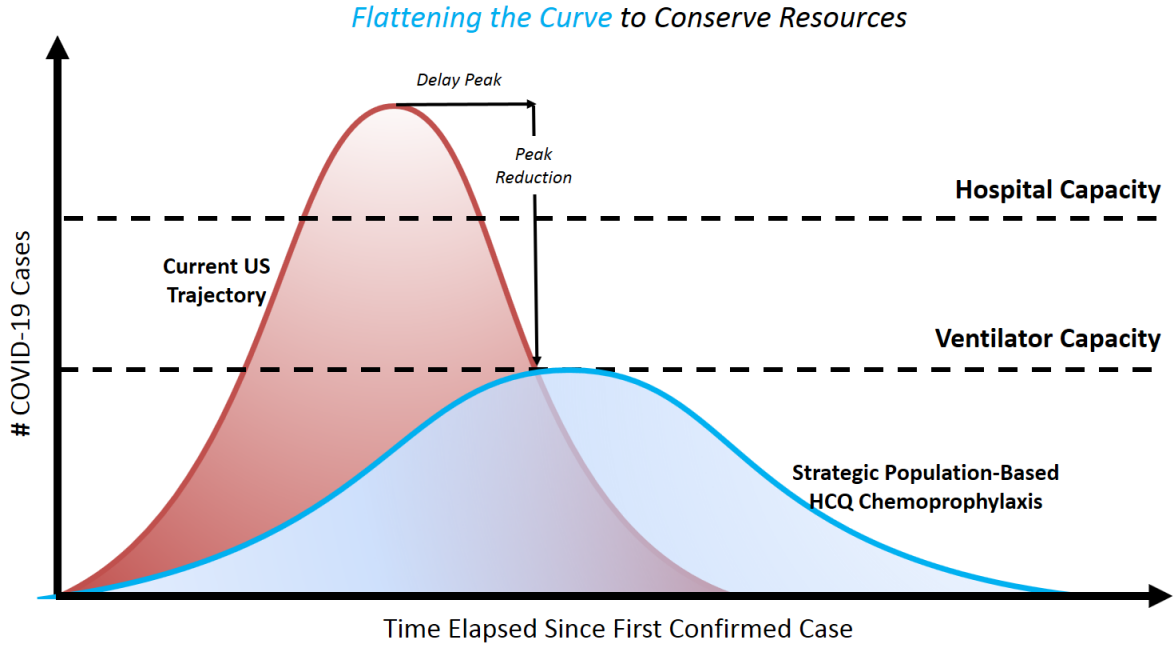
D. RESEARCH DESIGN

D.1. Study Objectives and Target Population

The **primary** objective of the study is to look at the early efficacy of hydroquinone and potential for providing primary prevention to target at-risk HCP population exposed directly or indirectly to COVID patients. The **secondary** objective of the study is to achieve a therapeutic steady state for chemoprevention yet achieve an acceptable safety and side effect profile as measured by objective testing at the end of the study and clinical evaluations monitored by Data Safety Monitoring Board (DSMB). **Tertiary** objective is to look at those that may contract the disease during the course of the study and measure severity of clinical outcomes and disease progression as measured by need for hospitalization or Intensive Care provision.

Broader goal of the study is to clear the path for major and urgent public health intervention that results in slowing or even aborting the spread of COVID-19. From the past experiences with viral infectious diseases if the preventative effect of immunity (either through infection or vaccination) exceeds 30%, a major pandemic could be prevented (3). See Figure 1.

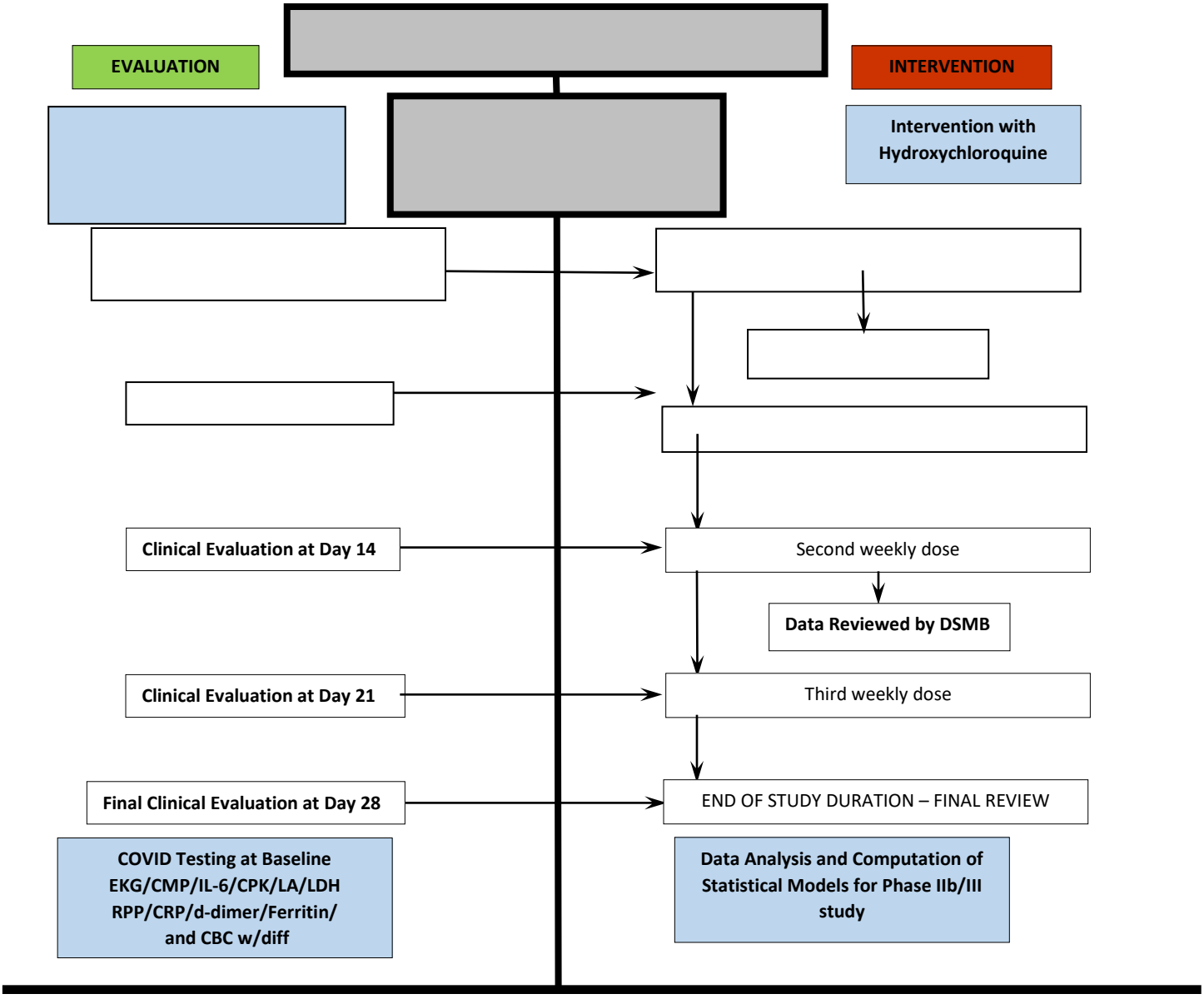
Figure 1: The Effect of HCQ Chemoprophylaxis on COVID-19 Case Peak in US



D.2. Overview of the study design

Phase II Trial of HCQ as Primary Prevention of Corona Virus Disease 2019 (COVID-19) is an open-labeled study to evaluate prevention feasibility and early efficacy with HCQ for COVID-19. In addition to the feasibility of this proposal, this study investigates whether HCQ is safe when used as chemoprophylaxis and whether it reduces transmission in volunteers as measured with a baseline SARS-CoV-2 test, and at 4 weeks from start of the medication administration in high risk healthy health care workers exposed directly or indirectly to patients with COVID-19. A comparative analysis of disease transmission in the ED versus Intensive Care setting would also be performed as an exploratory analysis. It is postulated that emergency room contact is higher risk while the environment in the Intensive Care Setting is generally more controlled (2). See Figure 2 that summarizes the sequence of Evaluation and Intervention.

Figure 2: Overview of the Single Arm Study Design. Summarizing the Evaluation and Intervention Sequence



Continuing larger corroborative study would be designed based on safety and feasibility data of this study to answer an urgent issue of extreme importance for public health intervention. If the drug intervention is able to differentially protect 30% or more individuals when compared to the controls (Relative risk reduction), it could

mitigate or abort the spread of virus until such time that a vaccine becomes available (See Figure 1). HCQ use has over 50 years of experience and proven safety even for vulnerable population such as for children and pregnant women (25, 26, 27, 28). It is available in generic form. Ready availability, cheap cost and relative safety would allow the drug to be administered widely across the general population.

D.3. Inclusion Criteria

Volunteers ages 18 to 99 years, able to sign own informed consent form, considered high-risk healthcare care providers in a hospital setting with active exposure to COVID-19 infection. High-risk HCP's are defined as those actively working during the study duration in the Emergency Department and in the Intensive Care Setting, for the purpose of this study.

D.4. Exclusion Criteria

- Inability to tolerate an oral medication or known allergy to chloroquine or hydroxychloroquine
- Pregnancy or breast-feeding[a]
- Immunocompromised status, hepatic failure, electrolytic imbalance
- Creatinine clearance (CCL) <30 mL/min
- Prolonged QT interval (QTc > 450ms for males and QTc > 470 for females)
- Confirmed COVID-19 infection on baseline testing
- Has another known contraindication to treatment with the study drug, including retinopathy.

[a] Female participants of childbearing potential must have pregnancy testing performed at screening if not on hormonal contraception.

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods.

D.5. Conduct of the Study

D.5.a. Screening Procedure

All subjects would be screened according to the inclusion/exclusion criteria set for per the study protocol. A screening log will be maintained to record the screening of each subject. The study team will evaluate the subjects.

Once a subject is enrolled and clinical data collection would be initiated (See Appendix B, C and D for the Clinical Evaluation Intake forms). The participant would undergo a baseline CBC, CMP, EKG and SARS CoV-2 testing. As soon as test results are confirmed, protocol is initiated and study drug administered.

D.5.b. Subject Identification

To protect participant confidentiality, each participant is identified by a 3-digit unique code.

D.5.c. Deviation from the Protocol

The investigation team will not deviate from the protocol. The Institutional Review Board (IRB will be informed of all protocol changes by the investigator in accordance with the IRB/Ethics Committee's established institutional procedures.

D.6. Clinical and Laboratory Assessment

There will be a detailed baseline assessment. Clinical assessment would consist of two parts. There is a component of self-assessment followed by objective measures assessment. This includes laboratory and cardiac assessment. Assessment is designed to screen appropriate subjects for the study and would ensure the

monitoring from the safety perspective. The assessments are described below and detailed forms attached in Appendix B, C and D. Appendix B contains the self-assessment and objective assessment evaluation at baseline. Appendix C has the mid study evaluation and Appendix D is the final evaluation form.

D.6.a. Subject Assessment

D.6.a.i. Self-Assessment

Subjects are given self-assessment forms at the beginning, half-way mark and end of the study for screening of potential exclusions. The questionnaire also addresses immunocompromised status, as well as any active COVID symptoms (Appendix B, C and D).

D.6.a.ii. Objective Assessment

Objective assessment would include a physical exam to check the Heart rate, Respiratory rate, Temperature and Blood Pressure at Baseline, at half-way mark and at the end of 4-week study period.

CBC with differential, CMP, CPK, LA, LDH, RPP, CRP, d-dimer, Ferritin, IL-6 and EKG would be performed at baseline and at conclusion of 28-day study.

SARS CoV-2 testing has been developed by HMH. The network received preliminary Emergency Use Authorization from the Food and Drug Administration to start using the test on March, 12, 2020. The New Jersey Department of Health has also approved the test. The panel is designed for specific detection of the SARS-CoV-2 (two primer/probe sets). An additional primer/probe set to detect the human RNase P gene (RP) in control samples and clinical specimens is also included in the panel. RNA isolated and purified from upper and lower respiratory specimens is reverse transcribed to cDNA and subsequently amplified in the Bio Molecular Systems Mic qPCR cycler with micPCR software v2.8.0. Turnaround time is 4-5 hours. The testing is qualitative. Subjects would be tested at baseline and then at the conclusion of the study.

D.7. Ascertainment of Outcomes

The results of any study are determined by the accuracy of outcome, it is important for a study to have an outcome that is objectively defined and reproducibly ascertained. The primary objective of the study is easily verified using a very objective measure of SARS-CoV-2 negative test at the end of the study period. In the event that subject does contract COVID, clinical outcome that results in hospitalization or intensive care management would be an outcome measure. Objective measures of derangement of electrolytic abnormalities, EKG and Blood counts would be performed for safety profile evaluation of HCQ before and at the conclusion of the study period. Safety profile of the medication would be obtained as self-reported events by the HCPs. Expected adverse events exceeding historically reported safety and adverse events will be noted and monitored closely DSMC.

D.8. Procedure for Safety Monitoring

HUMC designated DSMC will be responsible for monitoring of safety of data and subjects. The study PI, and designated staff will teleconference in for open session meetings of the DSMC and will present the progress reports every week.

D.9. Statistical Consideration

The main objective of this open-label Phase II trial is to evaluate feasibility, safety and early evidence efficacy of hydroxychloroquine administration in the reduction of viral transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and development of Corona Virus Disease 2019 (COVID-19) in at-risk, healthy acute care provider participants exposed, directly or indirectly, to COVID-19 patients.

See Table. 1 for Summary of primary and secondary objectives and end points on the next page.

Table. 1 Summary of Objectives and Endpoints			
Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
Primary Objective			
Rate of COVID-19 negative intervention arms	Rate of negative COVID-19 results	Rate of COVID-19 negative as indicated by micPCR	28 days
To Determine the Safety profile for a previously well studied drug in this select group of HCP.	Incidence rate of AEs of HCQ prophylaxis, 1) Visual Disturbances 2) Cardiac 3) Anemia 4) Electrolytic Disturbances 5) Hepatorenal abnormalities 6) Other less serious side effects listed below	Incidence rate of AE of HCQ prophylaxis, 1)Participant Evaluation reports 2) EKG prolongation of QTc on pre and post-test 3) CBC pre and post evaluation 4) Electrolyte profile with pre and post test 5) Renal function and Liver function tests pre and post 6) Participant Evaluation reports	28 days
Secondary Objective			
• To evaluate the effect of basic inflammatory regulation due to interventional drug and its effect on possible disease modification based on understood pathophysiological mechanism of COVID-19.	LA, LDH, RPP, CRP, d-dimer, Ferritin and IL-6 would be performed at baseline.	LA, LDH, RPP, CRP, d-dimer, Ferritin and IL-6 would be performed at the conclusion of 4 week study period.	Up to 28 Days And phase II/III study design implementation if the above findings support continuation.

D.9.a. Sample size determination

The study will enroll 45 health care workers (HCWs). We anticipate to enroll 45 over a week period at the rate 11-12 per day. The JFK medical center has at least 270 at-risk HCWs, that is, healthy acute care providers exposed, directly or indirectly, to COVID-19 patients. We anticipate 25% of these HCWs will be willing to participate in this study. Additional healthcare workers will be recruited in HUMC and Jersey Sore University Medical Center.

Assume that the proportion HCWs that is COVID-19 during the period of outbreak during its peak without prophylaxis positive is 30% (Ref). We anticipate that treating the HCWs with HCQ will be protective so that 10% will be COVID-19 positive by Day 28. That is, we anticipate 90.0% of HCWs with HCQ will be COVID-19 free by Day 28. We seek to examine early evidence of efficacy in using a Phase II single arm trial (Table. 2).

Table 2. Sample size calculation of proportion HCWs COVID-19-free Day 28 at 80% and 90% power

Type of Test	Po	Pa	Effective size	Type I error	Power	Achieved Power	Sample size	Rounded up size
One-sided	0.70	0.90	0.5157	0.025	0.80	0.8065	29.5	30
One-sided	0.70	0.90	0.5157	0.025	0.90	0.9035	39.49	40
Po= rate of HCWs if not given HCQ that develop COVID-19 by day 28; Pa= rate of HCWs given HCQ that develop COVID-19 by day 28;								

Assume that if the HCWs were not given HCQ as a prophylaxis, the proportion of HCWs that develop COVID-19 by Day 28. For a target improvement to 90%, the test will be seeking to detect a moderate effect size of 0.5157. The study will use a one-sided one sample proportion test to examine this against the alternative the proportion of HCWs that develop COVID-19 Day 28 is 0.90, using 0.025 as a probability of Type I error (the probability of rejecting P=0.70, incorrectly). To detect the moderate effect size with 80% power, the study would require 30 HCWs to be enrolled in the study and this sample size will achieve power of 80.7%. To detect the moderate effect size with 90% power, the study would require 40 HCWs to be enrolled in the study and this sample size will achieve power of 90.4%. Adjust for 5% drop out rate [this is 30/.95=31.5 or 32 HCWs; 40/.95=42.1 or 43, rounded to 45 HCWs]. The sample size calculation was obtained using a binomial test, based on the arcsine transformation, utilizing the P*wr* sample in R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

D.9.b. Primary Safety endpoint analysis

Occurrence rates of well-known adverse events (side effects of hydroxychloroquine sulfate) in the intervention arm will be estimated by percentage and exact (Clopper-Pearson) 95% confidence interval. The observed rate of occurrence of these AEs will be compared with the upper limit of the confidence interval to assess if the observed rate is over and above the expected rate, per well-known rates on the pharmacy guidelines.

Nausea, Headache, dizziness, vertigo, mood disorders including irritability, fatigue, abdominal pain muscle aches and pains, alopecia, weight loss, skin pigmentation are categorized as minor adverse events based on FDA labelled adverse event profile for the purpose of the study (37, 42). Minor adverse effects do not exceed 15% for each individual side effect (42, 57, 58). Current psychological pressure and workload related stress of high-risk HCWs is also a consideration (63). Global pandemic and local severe outbreak of COVID-19 has stretched the health care resources globally and locally (63). The cumulative effect may result in higher reported constitutional symptoms that may not be directly related to the drug (63). This will be adjudicated by DSMC during weekly study evaluation calls. All of these adverse events have been described as dose dependent and reversible upon discontinuation of medication (57).

The table below shows the established rates of occurrence of major adverse events. Idiosyncratic major adverse events or major allergic reactions have not been associated with HCQ in the literature. All of these side effects are dependent on duration and cumulative dose The dose used for the purpose of the study and is limited in duration similar for malaria prohylaxis dose (37,42). This compares favorably to the high dosages used for much longer duration in autoimmune disease states such as SLE or Rheumatoid Arthritis (57). Most of the reports of major adverse events in literature are reported for patients receiving high dosages for long duration. For instance, the visual disturbance related to retinopathy have been reported after more than 5 years of routine daily usage of chloroquine and not been validated for HCQ in phase IV studies (58). The reports

for major adverse are all reported to be less than 1% when given in smaller spaced out dosage as suggested in our study (Table. 3).

Table. 3: Major Adverse Events	Established Rate of occurrence
Visual Disturbances confirmed by objective findings	<1%
Cardiac Arrythmias requiring intervention	<1%
Anemia (Drop >2gm/dl or less than 8gm/dl)	<1%
clinically significant Electrolyte Disturbances	<1%
Hepatorenal abnormalities requiring intervention	<1%

D.9.c. Stopping Guidelines

Using repeated significant testing (Jennison and Turnbull) with 3% as lower proportion and 5% as higher proportion, 5% alpha level, and 80% power to for early termination, shape parameter of the boundary, delta=0.0, the following stopping guidelines were computed by the toxbdry function in the Clinfun package in R version 3.6.3.

The trial will be terminated if out of the first 25 HCWs that receive HCQ as prophylaxis, 1 experience one of the major adverse events. If out of the first 45 patients, 2 or more HCWs experience one of the major adverse events then trial will be stopped. (Table. 4)

Table 4. Stopping Boundaries for each of major AEs (retinopathy, cardiac arrhythmias, anemia, Electrolyte disturbances, hepatorenal abnormalities requiring intervention)		
Monitoring Look	Number of Patients at the Monitoring Look	Stop if Number of Patients with Repeat Scans is at least
1	26	1
2	45	2

The operating characteristics in Table 5 indicate that the rule has 79.1% probability of stopping early at an expected sample of 19.5.

Table 5. Operating characteristics for the stopping boundaries for Major AE occurrence						
Probability Of Toxicity	Probability of crossing low bndry	Probability of stopping low bndry	Expected sample size low bndry	Probability of crossing high bndry	Probability of stopping high bndry	Expected sample size high bdnry
0.030	0.597	0.592	26.6	0.589	0.584	26.8
0.034	0.648	0.643	24.9	0.641	0.636	25.1
0.038	0.694	0.689	23.3	0.687	0.682	23.5
0.042	0.734	0.729	21.9	0.728	0.728	22.1

D.9.d. Primary Efficacy endpoint analysis

The proportion of at-risk health care workers HCW given hydroxychloroquine that develop COVID-19 by Day 28 will calculated and its corresponding exact (Clopper-Pearson) 95% confidence interval will be computed and reported. To examine if the HCQ is COVID-19 protective to HCWs by Day 28 , a one-sided one sample binomial test will performed to test observed rate against the assumed rate of 70% in unprotected HCW population. If the test's p-value is less than 0.025 then the result will be considered statistically significant.

D.9.e. Secondary Endpoint analysis

The aim of the secondary objective is estimate time to COVID-19 positive case in HCWs that will be given HCQ as a prophylaxis. Time to COVID-19 infection (confirmed positive result) in HCWs on hydroxychloroquine therapy will be estimated using a Kaplan –Meier method. The rate of incidence COVID-19 (based on symptom development) at specific time 14 days and 21 days will be reported based KM estimates and corresponding 95% confidence intervals.

It is possible that HCWs treated with HCQ as a prophylaxis would withdraw from the study or drop out due to symptomatic COVID-19 or other disease states and/or unrelated death. They may also drop out if other more promising prophylaxis become available during the study period or HCQ is shown to not be a promising chemoprophylactic agent (see section D.10.a.). In those participants KM plots for 14 days' incidence rates would be reported if available.

D.9.f. Exploratory Endpoint analysis

The aim of the exploratory analysis will be to examine the changes for inflammatory/immune biomarkers in serum samples from baseline, at the start of HCQ prophylaxis regimen, to Day 28 (54).

Change in level of biomarkers from serum samples will be analyzed using a two-sided paired t-test if the paired data are normally distributed or two-sided Wilcoxon signed rank test in the paired data are not normally distributed. Assumption of the normality of the date will be assessed using a Shapiro- Wilk test.

D.9.g. General Data analysis

Descriptive statistics will be performed in the following manner. Continuous variables will summarized as mean (standard deviation) if data are normally distributed or median (interquartile range) if the data are not normally distributed. The assumption of the normality of data will be assessed using Shapiro-Wilk test of normality. Categorical variables will be summarized as frequency (percentage). Comparison of continuous variables will be performed using two-sided t test or Wilcoxon rank sum test, as appropriate. Comparison of categorical variables will be conducted using two-sided Fisher's exact test or Pearson Chi-Square. Unless specified otherwise, any $p<0.05$ will be considered statistically significant. All data analysis will be conducted using the software SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

D.10. Other Considerations in Study Design

D.10.a. Drop-out rate

We expect the drop-out rate through drug tolerance and/or side effects to be less than 5%. It is also possible that some subjects may have to change medications if they become symptomatic and require hospitalization, in that case they would have reached an endpoint and would no longer receive the intervention medication in the pre-specified dose or for duration of the study.

D.10.b. Treatment failure

Overall treatment failure would be assessed at the half way mark of the study at which DSMC may decide to halt further enrollment. The assessment of failure would be based on development of symptomatic COVID disease.

D.11. Study Organization and Staff

Hydroxychloroquine for COVID-19 Study would have its own DSMC driven by Clinical Pharmacy and Infectious Diseases Departments. It will also rely on clinical information being received through CDC and HMH Command Center as new developments for COVID pandemic becomes available.

D.12. Strategies for Recruitment, Retention and Adherence to Study Protocol

Critical to successful recruitment and retention in the study would be sharing of interim results with participants. Any such announcements would come with the direction of DSMC. Similarly calls for recruitment would be given by HMH Command Center. Also, at onset of the study it would be ensured resources exist to help provide translators for the subjects, if needed. There is no gender related differences in regards to bioavailability and steady state achieved with use of HCQ.

E. HUMAN SUBJECTS / ETHICAL ASPECTS

E.1. Ethical Considerations

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

E.2. Institutional Review Board (IRB) Review

The final study protocol, consent form, HIPAA form, and all forms including and collection tool/diary will be approved by an OHRP accredited Institutional Review Board (IRB). Approval will be received in writing before study initiation.

Any changes to the study design will be formally documented in amendments and be approved by the IRB prior to implementation.

E.2. Informed Consent

The PI will ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Consent will be documented by the participants' dated signature and the PI or study team member that conducts the informed consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB's approval in advance of use. The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature.

E.3. Participant Confidentiality

The participant collected data, and all analysis of the data will adhere to HIPAA & institutional confidentiality requirements.

More specifically, a coding system will be used for which a unique identifier (study ID number) will be assigned to each patient name and contact details. Only the study number will be included in the data collection tool, data analysis software and potential publications.

The list with the direct identifiers (for the purposes of linking data and keeping track of participants) will be stored separately in a secure server.

Should results of the study be published or reported, individual names or other identifying information will not be used.

E.4. Data Collection

All physical data will be collected and stored at the PI location in a locked office in a locked cabinet. Electronic data will be kept on password protected computer only accessible to the PI and study team.

F.5. Retention of Records

Records will be retained in accordance with regulatory, organizational and sponsor requirements, but no less than six (6) years following the completion of the research. Disposal of records will be done in such a manner that no identifying information can be linked to research data.

E.6. Study Monitoring

The study will be monitored on an ongoing basis by the PI and by the Hackensack Meridian Health Data Safety Monitoring Committee (HMH-DSMC), see below.

E.7. Data Safety Monitoring Plan

The Hackensack Meridian Health Data Safety Monitoring Committee (HMH-DSMC) will be responsible for the data and safety monitoring of this study. As this study is an investigator initiated Feasibility study utilizing an off label FDA approved drug the study requires real-time monitoring by the PI and study team and will be reviewed monthly by the Data and Safety Monitoring Committee (DSMC). Once enrollment and treatment are completed, review will take place annually.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible.

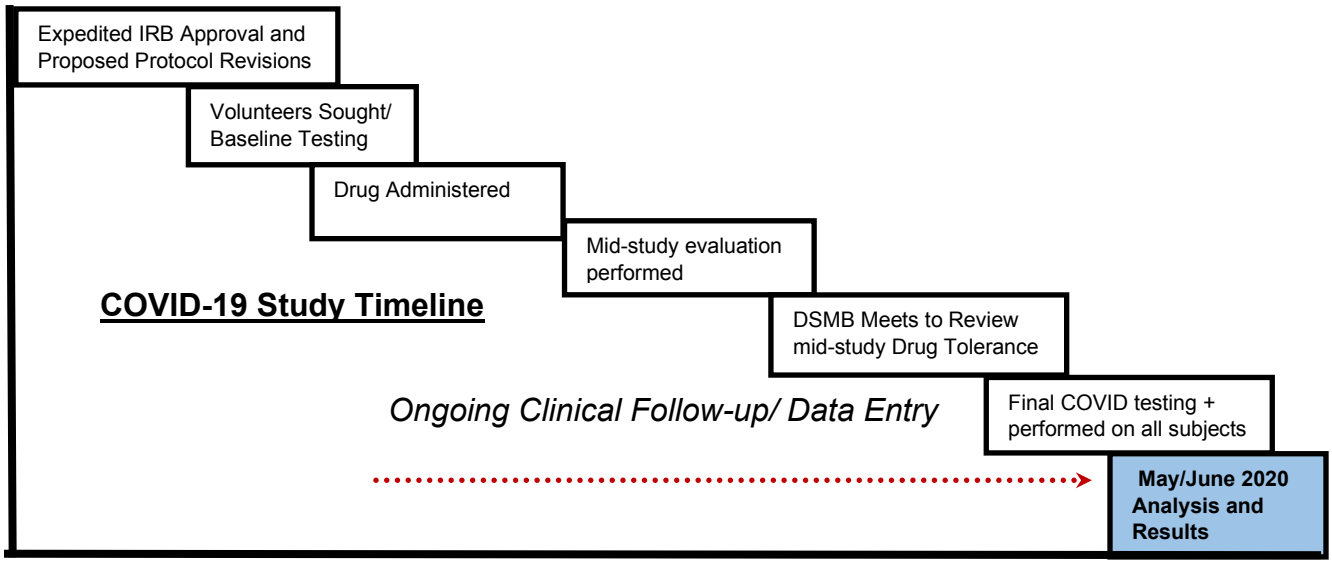
E.8. Study Discontinuation

The study will be discontinued if there are a significant number of side effects or significant numbers of symptomatic COVID-19 development.

E.9. Publication Plan

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

F. EXPEDITED TIMELINE:



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APPENDIX: A

1. Potential Side Effects of Hydroxychloroquine:

Ocular:

Irreversible retinal damage has been observed in some patients who had received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease. A baseline ocular examination is recommended within the first year of starting hydroxychloroquine. The baseline exam should include: best corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral domain ocular coherence tomography (SD-OCT). For individuals with significant risk factors (daily dose of hydroxychloroquine sulfate greater than 5.0 mg/kg base of actual body weight, subnormal glomerular filtration, use of tamoxifen citrate or concurrent macular disease) monitoring should include annual examinations which include BCVA, VF and SD-OCT. For individuals without significant risk factors, annual exams can usually be deferred until five years of treatment. In individuals of Asian descent, retinal toxicity may first be noticed outside the macula. In patients of Asian descent, it is recommended that visual field testing be performed in the central 24 degrees instead of the central 10 degrees. It is recommended that hydroxychloroquine be discontinued if ocular toxicity is suspected and the patient should be closely observed given that retinal changes (and visual disturbances) may progress even after cessation of therapy (28).

Cardiac:

Cardiac Effects, including Cardiomyopathy and QT prolongation: Post-marketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine as well as with use of chloroquine. Patients may present with atrioventricular block, pulmonary hypertension, sick sinus syndrome or with cardiac complications. ECG findings may include atrioventricular, right or left bundle branch block. Signs or symptoms of cardiac compromise have appeared during acute and chronic treatment. Clinical monitoring for signs and symptoms of cardiomyopathy is advised, including use of appropriate diagnostic tools such as ECG to monitor patients for cardiomyopathy during hydroxychloroquine therapy. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) or biventricular hypertrophy are diagnosed. If cardiotoxicity is suspected, prompt discontinuation of hydroxychloroquine may prevent life-threatening complications. hydroxychloroquine prolongs the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking hydroxychloroquine (see OVERDOSAGE). Therefore, hydroxychloroquine should not be administered with other drugs that have the potential to prolong the QT interval. (29)

Worsening of Psoriasis:

Use of PLAQUINIL in patients with psoriasis may precipitate a severe attack of psoriasis. Although, PLAQUINIL is used in the treatment of porphyria, PLAQUINIL-induced psoriasis is worsened secondary to porphyria. The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard (30, 31).

Proximal Myopathy and Neuropathy:

Skeletal muscle myopathy or neuropathy leading to progressive weakness and atrophy of proximal muscle groups, depressed tendon reflexes, and abnormal nerve conduction, have been reported. Muscle and nerve biopsies have been associated with curvilinear bodies and muscle fiber atrophy with vacuolar changes. Assess muscle strength and deep tendon reflexes periodically in patients on long-term therapy (32, 33).

Neuropsychiatric events, including suicidality:

Suicidal behavior has been rarely reported in patients treated with hydroxychloroquine (34, 35).

Hypoglycemia:

hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications (see DRUG INTERACTIONS and ADVERSE REACTIONS). Patients treated with hydroxychloroquine should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with hydroxychloroquine should have their blood glucose checked and treatment reviewed as necessary (36).

2. PRECAUTIONS

General: Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine (37).

Hepatic/Renal Disease: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. A reduction in dosage may be necessary in patients with hepatic or renal disease, as well as in those taking medicines known to affect these organs (38, 39).

Hematologic Effects/Laboratory Tests: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Periodic blood cell counts should be performed if patients are given prolonged therapy. If any severe blood disorder such as aplastic anemia, agranulocytosis, leukopenia, or thrombocytopenia, appears which is not attributable to the disease under treatment, consider discontinuation of hydroxychloroquine. Hydroxychloroquine should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (40). We will not obtain labs for all patients checking for G-6-PD deficiency, since there is no evidence to support routine lab evaluation before use of Hydroxychloroquine (51).

Dermatologic Effects:

Dermatologic reactions to hydroxychloroquine may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis (41).

3. Drug Interactions

Digoxin: Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Insulin or antidiabetic drugs: As hydroxychloroquine may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Drugs that prolong QT interval and other arrhythmogenic drugs: hydroxychloroquine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.

Mefloquine and other drugs known to lower the convulsive threshold: hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anti-malarial agents known to lower the convulsion threshold (e.g., mefloquine) may increase the risk of convulsions.

Anti-epileptics: The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Methotrexate: Combined use of methotrexate with hydroxychloroquine has not been studied and may increase the incidence of adverse effects.

Cyclosporine: An increased plasma cyclosporine level was reported when cyclosporine and hydroxychloroquine were co-administered. The following interactions have been observed on treatment with the structurally related substance chloroquine phosphate, and therefore cannot be ruled out for hydroxychloroquine.

Praziquantel: Chloroquine has been reported to reduce the bioavailability of praziquantel.

Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.

Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability

of ampicillin (42).

APPENDIX: B

Initial Clinical Evaluation Form **Date evaluation form filled:**

(fields with an * are identifiers and will be kept separately after original data collection)

*Name:

*Date of birth (mm/dd/yyyy):

Sex:

*Address:

*Phone no:

*Email:

Interpreter used? Yes/No (If Yes, then name of interpreter with spoken language.

Job position (nurse/CTA/Tech./Physician, etc.):

Exposure: a) Numbers of Contact with known COVID19 patients
b) Numbers of Contact with COVID19 suspect patients
c) Estimated Time in minutes or hours of exposure
d) Others (specify)

Pre-existing conditions:

No risk for medical condition	Yes	No	unknown
Cardiac disease (not simple hypertension)	Yes	No	unknown
Chronic lung disease	Yes	No	unknown
Diabetes	Yes	No	unknown
Hemoglobinopathies	Yes	No	unknown
Immunosuppressive condition	Yes	No	unknown
Liver disease	Yes	No	unknown
Renal disease	Yes	No	unknown
Dialysis	Yes	No	unknown
Metabolic disease	Yes	No	unknown

Neurological disorder Yes No unknown

Other medical condition? Yes No unknown

If yes, then specify:

Other risk factors:

Are you a current smoker? Yes No unknown

If yes, number of pack years:

Do you drink alcohol? Yes No unknown

If yes, average number of drinks per week:

Pregnancy Yes No unknown

Current Medications: Yes No unknown

If yes, specify medications:

Allergies: Yes No unknown

If yes, specify allergies:

Vital signs: Temp: BP: HR: RR: SpO2:

Review of systems:

Arthralgia Yes No unknown

Cough Yes No unknown

Conjuctivitis Yes No unknown

Diarrhea Yes No unknown

Fatigue Yes No unknown

Fever Yes No unknown

Chills/Rigors Yes No unknown

Headache Yes No unknown

Malaise Yes No unknown

Myalagia Yes No unknown

Nausea Yes No unknown

Vomiting Yes No unknown

Sore throat Yes No unknown

Shortness of breath Yes No unknown

Other symptoms? Yes No unknown

If yes, specify

Clinical Examination:

COVID19 test result:

EKG:

CBC with differential:

CMP:

IL-6:

CPK:

LA:

LDH:

RPP:

CRP:

d-dimer:

Ferritin:

APPENDIX: C

Follow up Clinical Evaluation Form **Date evaluation form filled:**

*Name:

*Date of birth (mm/dd/yyyy):

Sex:

*Address:

*Phone no:

*Email:

Interpreter used? Yes/No (If Yes, then name of interpreter with spoken language.

Job position (nurse/CTA/Tech./Physician, etc.):

Exposure: a) Numbers of Contact with known COVID19 patients
b) Numbers of Contact with COVID19 suspect patients
c) Estimated Time in minutes or hours of exposure
d) Others (specify)

New medical condition diagnosed since last visit:

No new medical condition	Yes	No	unknown
Cardiac disease (not simple hypertension)	Yes	No	unknown
Chronic lung disease	Yes	No	unknown
Diabetes	Yes	No	unknown
Hemoglobinopathies	Yes	No	unknown
Immunosuppressive condition	Yes	No	unknown
Liver disease	Yes	No	unknown
Renal disease	Yes	No	unknown
Dialysis	Yes	No	unknown

Metabolic disease	Yes	No	unknown
Neurological disorder	Yes	No	unknown
Other medical condition?	Yes	No	unknown

If yes, then specify:

New medications since last visit:	Yes	No	unknown

If yes, specify medications:

New Allergies since last visit:	Yes	No	unknown

If yes, specify allergies:

Vital signs: Temp: BP: HR: RR: SpO2:

Review of systems:

Arthralgia	Yes	No	unknown
Cough	Yes	No	unknown
Conjuctivitis	Yes	No	unknown
Diarrhea	Yes	No	unknown
Fatigue	Yes	No	unknown
Fever	Yes	No	unknown
Chills/Rigors	Yes	No	unknown
Headache	Yes	No	unknown
Malaise	Yes	No	unknown
Myalagia	Yes	No	unknown
Nausea	Yes	No	unknown
Vomiting	Yes	No	unknown
Sore throat	Yes	No	unknown
Shortness of breath	Yes	No	unknown
Other symptoms?	Yes	No	unknown

If yes, specify

Clinical Examination:

Drug Side effects:

Nausea, vomiting	Yes	No	unknown
Headache	Yes	No	unknown
Dizziness	Yes	No	unknown
Irritability	Yes	No	unknown
Muscle weakness	Yes	No	unknown
Alopecia	Yes	No	unknown
Vision changes	Yes	No	unknown
Weight loss	Yes	No	unknown
Vertigo	Yes	No	unknown
Deafness	Yes	No	unknown
Fatigue	Yes	No	unknown
Abdominal pain	Yes	No	unknown
Skin pigmentation	Yes	No	unknown
Arrhythmias	Yes	No	unknown
Others	Yes	No	unknown

If others, specify

APPENDIX: D

Final Clinical Evaluation Form **Date evaluation form filled:**

*Name:

*Date of birth (mm/dd/yyyy):

Sex:

*Address:

*Phone no:

*Email:

Interpreter used? Yes/No (If Yes, then name of interpreter with spoken language.

Job position (nurse/CTA/Tech./Physician, etc.):

Exposure: a) Numbers of Contact with known COVID19 patients (since last visit):
b) Numbers of Contact with COVID19 suspect patients (since last visit):
c) Estimated Time in minutes or hours of exposure:
d) Others (specify):

New medical condition diagnosed since last visit:

No new medical condition	Yes	No	unknown
Cardiac disease (not simple hypertension)	Yes	No	unknown
Chronic lung disease	Yes	No	unknown
Diabetes	Yes	No	unknown
Hemoglobinopathies	Yes	No	unknown
Immunosuppressive condition	Yes	No	unknown
Liver disease	Yes	No	unknown
Renal disease	Yes	No	unknown
Dialysis	Yes	No	unknown

Metabolic disease	Yes	No	unknown
Neurological disorder	Yes	No	unknown
Other medical condition?	Yes	No	unknown

If yes, then specify:

New medications since last visit: Yes No unknown

If yes, specify medications:

New Allergies since last visit: Yes No unknown

If yes, specify allergies:

Vital signs: Temp: BP: HR: RR: SpO2:

Review of systems:

Arthralgia	Yes	No	unknown
Cough	Yes	No	unknown
Conjuctivitis	Yes	No	unknown
Diarrhea	Yes	No	unknown
Fatigue	Yes	No	unknown
Fever	Yes	No	unknown
Chills/Rigors	Yes	No	unknown
Headache	Yes	No	unknown
Malaise	Yes	No	unknown
Myalagia	Yes	No	unknown
Nausea	Yes	No	unknown
Vomiting	Yes	No	unknown
Sore throat	Yes	No	unknown
Shortness of breath	Yes	No	unknown
Other symptoms?	Yes	No	unknown

If yes, specify

Clinical Examination:

Drug Side effects:

Nausea, vomiting	Yes	No	unknown
Headache	Yes	No	unknown
Dizziness	Yes	No	unknown
Irritability	Yes	No	unknown
Muscle weakness	Yes	No	unknown
Alopecia	Yes	No	unknown
Vision changes	Yes	No	unknown
Weight loss	Yes	No	unknown
Vertigo	Yes	No	unknown
Deafness	Yes	No	unknown
Fatigue	Yes	No	unknown
Abdominal pain	Yes	No	unknown
Skin pigmentation	Yes	No	unknown
Arrhythmias	Yes	No	unknown
Others	Yes	No	unknown

If others, specify

COVID19 test result:

EKG:

CBC with differential:

CMP:

IL-6:

CPK:

LA:

LDH:

RPP:

CRP:

d-dimer:

Ferritin: