**Hydroxychloroquine Prophylaxis for UNM HEALTH SYSTEM healthcare workers at high risk for SARS – COV-2 infection**

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| **UNM HEALTH SYSTEMSC HRRC Study Number:** | 20-206 |
| **Study Product:** | Hydroxychloroquine (HCQ) |

**Initial version:** **0**4.16.2020

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**Statement of Compliance**

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the HRRC, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

**List of Abbreviations**

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| AGP | Aerosol Generating Procedure |
| CFR | Code of Federal Regulations |
| COVID-19 | Coronavirus Disease |
| CQ | Chloroquine |
| CRF | Case Report Form |
| DHHS | Department of Health and Human Services |
| DSMB | Data and Safety Monitoring Board |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HCQ | Hydroxychloroquine |
| HCW | Health Care Worker |
| HCWP | Health Care Worker Prophylaxis |
| HRPO | Human Research Protections Office |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ICU | Intensive Care Unit |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| MOP | Manual of Procedures |
| N | Number (typically refers to participants) |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OHS | Occupational Health Service |
| PCR | Polymerase chain reaction |
| PEP | Post exposure prophylaxis |
| PI | Principal Investigator |
| PI | Principal Investigator |
| PPE | Personal Protective Equipment |
| RA | Rheumatoid Arthritis |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| UNMH | University of New Mexico Hospital |
| UNMHS | University of New Mexico Health System |

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| US | United States |
| WHO | World Health Organization |

**Protocol Summary**

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| Title | Off label study to evaluate the efficacy of hydroxychloroquine as prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among Health Care Workers (HCWs) who are at high risk of occupational exposure to SARS-CoV-2<br>**Short Study Title:** COVID-19 HCWP HCQ Study |
| Brief Summary | The HCW Prophylaxis (HCWP) Study, single, open and off label intervention study. Up to 350 participants will be assigned to group that takes HCQ or group that opts to not take study medication. Participants will be UNM HEALTH SYSTEM HCW at high risk for occupational exposure to SARS-CoV-2. Study timepoints will include Day 1 screening/enrollment, 30 day, 60 day, and 90 day assessments. Questionnaires will be collected in all timepoints. |
| Phase | Off label use of HCQ |
| Primary Objectives | To evaluate the efficacy of hydroxychloroquine (HCQ) for prophylaxis (HCWP) to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among Health Care Workers High Risk of Occupational Exposure to SARS-CoV-2 |
| Methodology | The Health Care Worker Prophylaxis (HCWP) Study, single, open and off label intervention study |
| Primary Endpoint | Number of HCW who test positive for SARS-CoV-2 while in the trial as determined by polymerase chain reaction assays from standard of care swaps. |
| Study Duration | 12 months |
| Participant Duration | Participant Study period: up to 90 days for both groups, inclusive of those who elect to convert from Group B to Group A. |
| Duration of IP administration | Up to 90 days |
| Population | Total number of participants: Up to 350 UNM HEALTH SYSTEM health care workers with high risk of occupational exposure to SARS-CoV-2<br>Group A: up to 275 (HCW choose to be provided HCQ)<br>Group B: up to 75 (HCW choose not to be provided HCQ) |
| Study Sites | UNM HEALTH SYSTEMS |
| Number of participants | Up to 350 |
| Description of Study Agent/Procedure | Hydroxychloroquine- oral administration<br>• Duration: up to 90 days or until meeting study termination criteria<br>• Loading dose: 600 mg once for the first day<br>• Maintenance dose: 200 mg, daily<br><br>Hydroxychloroquine is licensed for the chemoprophylaxis and treatment of malaria and as a disease modifying antirheumatic drug. It has a long history of being safe and well tolerated at typical doses. HCQ has antiviral activity *in vitro* against coronaviruses, and specifically Covid-19. |
| Key Procedures | Questionnaires |

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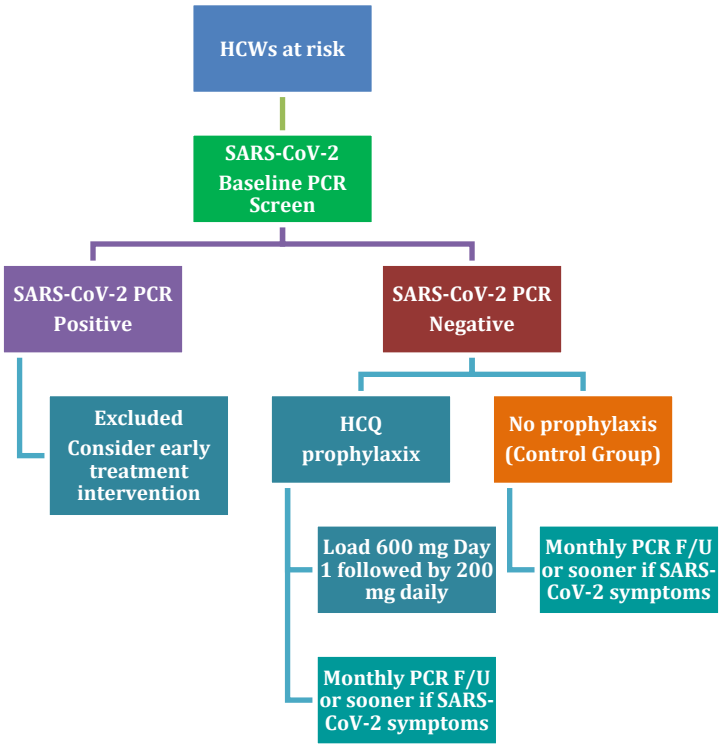
| Statistical Analysis | All data will be summarized using appropriate descriptive statistics, including mean, median, standard deviation, and range for continuous variables and frequency and proportions for categorical variables. Data will also be summarized graphically. Distributional assumptions will be assessed with suitable transformation conducted if indicated. Significance tests will use two-sided Type I error rate of 0.05. The primary analysis will assess the number of HCW who test positive for SARS-CoV2 while on trial. Secondary endpoints include symptoms reported over time via web-based questionnaires, as well as other clinical endpoints such as quarantine, hospital admission, ICU admission, and mortality. |

**Schematic of Study Design**




# 1 Background Information and Scientific Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus novel to the human population discovered in December 2019; it is currently the cause of a global pandemic [1-3]. The World Health Organization (WHO) named the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease caused by SARS-CoV-2 coronavirus disease (COVID-19). As of 7 April 2020, person-to-person transmission has occurred worldwide, approaching 1.5 million cases and over 75,000 deaths. The WHO declared the COVID-19 pandemic a Public Health Emergency of International Concern on 30 January 2020 [4]. Most deaths and severe pneumonitis have occurred in the elderly or in persons with underlying pulmonary, cardiac, and other co-morbidities. SARS-CoV-2 infection can be asymptomatic, mild with self-limited pneumonia and other symptoms, or progress to life threatening respiratory involvement and multi-organ failure. The infection often appears less severe in children and younger adults [5]. Nevertheless, the burden to health and economic systems globally of this pandemic is already substantial and the pandemic has not peaked on a worldwide basis. No acquired immunity to this novel viral infection appears to exist in the human population globally and no effective treatment or preventative agent is licensed at this time.

An early report of 1700 cases of COVID-19 among health care workers (HCWs) caring for COVID-19 patients in China, included 5 deaths, in a published series of over 72,000 cases [6]. The number of HCWs infected with SARS-CoV-2 are increasing every day in USA and other countries.

On 3 March 2020, WHO declared a global shortage of personal protective equipment (PPE) leaving doctors, nurses and other frontline workers dangerously ill-equipped to care for COVID-19 patients [7]. By nature of their work caring for ill patients and evidence that SARS-CoV-2 can be transmitted from human-to-human, HCWs are at increased risk for COVID-19 infection. Many aerosol-generating procedures (AGP) are performed without knowing SARS-CoV-2 infection status. The SARS-CoV-2 epidemic has put tremendous strain on HCW

in all aspects. Scientists at the UNM HEALTH SYSTEMS are interested in studying theSARS-CoV-2 and strategies to protect HCWs in high-risk exposure settings.

As of today, there is no approved treatment or prophylaxis for SARS-CoV-2 by FDA (Food and Drug Administration). The FDA has issued an "emergency use authorization" for HCQ use https://wwwfda.gov/medical/136537/download. HCQ is licensed for the chemoprophylaxis and treatment of malaria and as a disease modifying antirheumatic drug [8-9]. It has a long history of being safe and well tolerated at typical doses. HCQ has antiviral activity in vitro against coronaviruses, and specificallySARS-CoV-2. Pharmacologic modeling based on observed drug levels and in vitro drug testing suggest that prophylaxis at approved doses could prevent SARS-CoV-2 infection and/or ameliorate viral shedding. Based on in vitro data that HCQ inhibits viral replication and limited observations reported from China HCQ has the potential to prevent SARS-CoV-2 infection among HCWs at high risk of occupational exposure to SARS-CoV-2 [10-12].

However, at this time there is no in human data and we are unable to state if the drug will in fact decrease, have no effect or increase the chance of SARS-CoV-2 infection. This study is designed to answer whether prophylaxis with HCQ can mitigate the risk of SARS-CoV-2 infection among HCWs in high-risk settings.

**IND Exemption:**

- HCQ is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50)
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

# 2 Potential Risks & Benefits

## *2.1 Benefits*

It is possible that HCQ will prevent positive SARS-CoV-2 conversion in HCW or reduce subsequent severity of infection. Additionally, medical societies and the general public may benefit from the information collected from this study.

## *2.2 Risks*

### 2.2.1 Risk of study agent

To account for possibilities of drug interactions, we have excluded a small list of anti-arrhythmic because of a theoretic concern of the effects on prolonged QTc interval. Additional drug interactions listed in the monograph are not expected to be clinically relevant at the doses and duration being prescribed. The PI's will monitor subjects who develop side effects. The only anticipated side effect we expect to see in 1-2% of the subject population is mild, self-limited drug reaction presenting as skin rash. More rarely, the drug has been associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, therefore subjects who experience rash will be asked to discontinue HCQ. Additionally, dyspepsia may be encountered with drug administration – not ulcerogenic. This tends to be mild and self-limiting. The drug can be taken with food. Recommendation to subjects is to avoid antacids and cimetidine, as they reduce bioavailability. Alternatives include proton pump

inhibitors and other histamine 2 blockers. As with any experimental treatment for specific diseases, there may be unknown or unforeseeable side effects.

# 3 Objectives

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| To evaluate the efficacy of hydroxychloroquine (HCQ) for prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among HCWs at high risk of occupational exposure to SARS-CoV-2 compared to eligible cohort that declines treatment | Frequency of infection with SARS-CoV-2 as determined by positive PCR for the virus on standard diagnostic tests. |
| | |
| **Secondary Objectives** | **Secondary Endpoints** |
| 1. To characterize whether high-risk HCW who test positive for SARS-CoV-2 have an asymptomatic infection or report symptoms of COVID-19 in the 4 weeks preceding positive SARS-CoV-2 | 1. Symptom questionnaires performed once daily as currently mandated for HCW in high risk settings within UNMHS. |
| 2. Determine role of occupational health exposure risk level on subsequent conversion frequency (mild-moderate-severe) | 2. Online survey required once daily for all at risk HCW (existing document) |
| 3. To assess the severity of any SARS-CoV-2 infection after prophylactic treatment with hydroxychloroquine. | 3. Symptom questionnaires, Hospital admission rate, ICU admission rate, Mortality rate, PSI score of respiratory compromise |
| 4. To assess the tolerability of hydroxychloroquine prophylaxis of SARS-CoV-2 in this population | 4. Incidence of AEs or SAEs related to HCQ at study termination. |
| | |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| 1. To determine whether hydroxychloroquine reduces time lost from work | 1. Days away from work |
| 2. To assess the compliance of hydroxychloroquine prophylaxis | 2. Frequency of missing dose |
| 3. To assess whether HCQ benefits are different for specific AGPs or exposure on certain covid units (MICU v. ED v. covid rule out unit) | 3. Frequency of positive test for SARS-CoV-2 related to AGP's or specific Covid-19 units. |
| 4. To compare seroconversion between HCQ-treated and HCQ-untreated subjects on blood or plasma specimens. | 4. Serological analyses at 4 times points (baseline, 30,60 and 90 days of study enrollment---with a 7-day window after each time point to complete analyses) |

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| 5. Metagenomic next generation sequencing of SARS-CoV-2 isolates detected in subjects | 5. Sequence of viral isolates compared to published genomes and community-circulating SARS-CoV-2 |

# 4 Study Design

### *4.1 Description of Study Design*

This is an open and off label use, interventional, single site study

### *4.2 Study Enrollment and Withdrawal*

#### 4.2.1 Study Population

The HCWP Study eligibility are HCWs at high risk for SARS-CoV-2 exposure (eg MD/DO, NP, RN, and respiratory therapists in ED, Pediatric ED, Urgent Care, Pediatric Urgent Care and on Covid-19 units) at UNM HEALTH SYSTEM meeting all inclusion criteria.

**Total number of participants: 350 (Group A and B)**

- Group A: up to 275 (HCW who choose to be provided HCQ)
- Group B: up to 75 (HCW who choose not to be provided HCQ)

##### 4.2.1.1 Inclusion Criteria

1. Men or women ≥18 years of age who are UNM HEALTH SYSTEM health care workers and are asymptomatic for known presenting symptoms of SARS-CoV-2:
2. UNMHS HCWs include: MD/DO, NP, RN, and respiratory therapists working in ED, Pediatric ED, Urgent Care, Pediatric Urgent Care or on Covid-19 units. Study PI's will consider study enrollment of HCWs from other settings, for example certain outpatient clinics or inpatient units.
3. Are not positive for SARS-CoV-2 testing
4. Willing and able to comply with survey completion, scheduled visits, treatment plan, and other study procedures
5. Willing and able to provide informed consent

##### 4.2.1.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known hypersensitivity to HCQ or other 4-aminoquinoline compounds
2. Currently hospitalized
3. Symptomatic with subjective fever, cough, or sore throat
4. Current medications exclude concomitant use of HCQ, for example anti-arrhythmic agents, digoxin, cyclosporin, cimetidine, or tamoxifen.
5. Concomitant use of other anti-malarial treatment or chemoprophylaxis
6. History of retinopathy of any etiology
7. Psoriasis
8. Porphyria
9. Known bone marrow disorders with significant neutropenia (polymorphonuclear leukocytes <1500) or thrombocytopenia (<100K)
10. Known liver disease
11. Known long QT syndrome
12. Use of any investigational or non-registered drug or vaccine within 30 days preceding the first dose of the study drugs or planned use during the study period. There may be some exceptions to requiring a 30-day washout that will be evaluated by the Co-Investigators on a case by case basis.

#### 4.2.1.3 Vulnerable Subjects

This study will enroll employees of UNM HEALTH SYSTEM. Employees (For example: MD/DO, NP, RN, PA, Respiratory Therapists) recruited as research subjects may be more vulnerable to undue influence or coercion because of the possibility that they may perceive employment or other benefits as dependent upon their participation in research. In addition, UNM HEALTH SYSTEMS employees may experience increased risk of invasion of privacy or loss of confidentiality. To minimize these risks, employees will be allowed to self-identify as interested in being contacted for study participation after recruitment materials are sent to potentially eligible employees. Employees may then reach out to the research team to learn more about the study and if enrolled (if employee elects to participate), informed consent will be performed by a study team member with no direct supervisory or evaluation responsibilities. Additionally, at time of enrollment, the study team member will emphasize that participation is voluntary and refusal to participate will not affect employment or job performance evaluation. All identifying information for employees will be kept strictly confidential following the data security provisions outlined in this protocol.

Pregnant and /or lactating women will not be excluded from this study. HCQ is a standard of care for management of lupus and rheumatic diseases in pregnant women. There is an absence of data that the drug increases the rate of miscarriages or teratogenicity. Additionally, the drug is approved to be used in pregnant women to treat autoimmune disease and there is consensus in the scientific community that the drug does not have adverse effects on the fetus [13-16]. Each participant providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and Individuals engaged in the research will have no part in determining the viability of a neonate. A systematic review determined that HCQ use was not associated with any increased risk of congenital defects, spontaneous abortions, fetal death, pre-maturity or decreased numbers of live births in patients with auto-immune diseases. (Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases, Pediatric Rheumatol Online J. 2009; 7: 9).
Additionally, Arthritis Rheum. 2003 Nov;48(11):3207-11 published. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. Appeared in Expert Opin Drug Saf. 2011 Sep;10(5):705-14.

### 4.3 Strategies for Recruitment

Study participants will be recruited using an HRRC approved email blast that will be sent to the departments that are specific to the desired study population. We will be using UNM HEALTH SYSTEMSC listservs which will be chosen based on their pertinence to the study population. The email blast will direct interested HCW to a study team email address for further study information. Upon email contact from potential participant, study team will reply asking for a time to speak over the phone to discuss pre-screening criteria. In the phone call, pre-screening questions will be asked and documented on paper.

If potential participant is not eligible, participant cannot enroll in the study, and paper pre-screening form will be destroyed. If participant is eligible, paper pre-screening form will be kept in participant's study records and will serve as the screening source document. E-consent will be sent. Participant and study team will go over e-consent, and participant will e-sign. Word of mouth will also be used to recruit participants into the study.

### 4.4 Duration of Study Participation

- Study period: up to 90 days

### 4.5 Total Number of Participants and Sites

We expect to enroll up to 350 participants at UNM HEALTH SYSTEM. Subject visits will be conducted remotely after the Screen and Enrollment visit.

### 4.6 Participant Withdrawal or Termination

Reasons for early Withdrawal or Termination

- Participants become PCR-confirmed SARS-CoV-2 status
- Participant starts disallowed medication (Group A only)
- Advent of an adverse event which necessitates discontinuation of HCQ (Group A only, see section 6)
- Participant decides to withdraw from the study
- PI discontinues participation due to safety concerns
- Participant decides to withdraw consent
- Participant's primary care provider determines the study is not in participant's best interest
- PI decides to withdraw participant due to non-compliance

### 4.7 Study Agent

Name of the medication-Hydroxychloroquine (Off label use)
Hydroxychloroquine- The full prescribing information can be accessed at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b82bbda6-64f2-4426-b4ec-254eeea895ae
Subjects will obtain the study drug in accordance with established SOP from the hospital-based pharmacy.

#### 4.7.1 Disallowed Concomitant Therapy

See attached appendix of exclusionary and potentially exclusionary medications

##### 4.7.1.1 Dose Rationale

Hydroxychloroquine is a long-acting drug (elimination half-life:50 days). Loading dose of HCQ 600 mg has been administered for rheumatoid arthritis or systemic lupus erythematosus, with a usual maintenance dose 200 mg. Since the protocol will be used in HCWs with at high risk of exposure to SARS-CoV-2, the intent is to rapidly achieve an adequate drug level. For this study, we selected a loading dose of 600 mg on day one followed by 200 mg for daily maintenance dose.

##### 4.7.1.2 Administration

- Loading dose: 600 mg, oral, 1 day
- Maintenance dose: 200 mg, oral, daily, for 90 days

The study will follow the study agent's labeling guidelines except the dosing schedule selected as described above.

##### 4.7.1.3 Supplies

HCQ will be dispensed at the time of study enrollment or as soon as practical thereafter, after subjects have completed all Screening procedures and signed informed consent. The drug will be requested from the UNMH Research Pharmacy on the 4$^{th}$ floor or other approved clinical trial pharmacy locations where it may be stored. Drug will be dispensed to subjects by qualified study personnel. There will be no cost to the participants. Currently there is a sufficient amount of HCQ. This study will not deplete HCQ from stores or pharmacies. HCQ supplies for standard of care and patients with preexisting indications will not be compromised by execution of this study.

Dispensing schedules

- 33 pills (200 mg oral tablet) at enrollment
- 30 pills (200 mg oral tablet) at 30 and 60 day visits

# 5 Study Procedures and Schedule

## 5.1 Study Procedures/Evaluations

### 5.1.1 Study Specific Procedures

Employee Exposure Survey and Aerosol Generating Procedures (Appendix A)
Participants from both Group A and B will be asked to complete the Employee Exposure Survey. This online instrument asks health care providers currently working in at risk units to report symptoms or exposures (eg. AGPs) related to their encounters with patients who have or are suspected of Covid-19. These HCWs are reminded to complete the Survey once per day. The link to this REDCap survey is currently being emailed to UNMHSC HCWs and they can access it through widely distributed QR codes. Given its active use, this survey will not add additional stress or workload to study participants. Additional study specific questions will be added to this survey and the data is linked to REDcap a database.

Confirmation of Pregnancy in Women of Childbearing Potential: We will document in subject's research record whether they are pregnant based on self-report and date of last menses (at Screening and follow-up visits). Pregnancy is not a contraindication for receiving HCQ.

A list of potential Aerosol Generating Procedures (AGP) is also provided in Appendix A.

Subjects will only be asked to complete SARS-CoV-2 testing at study enrollment and the 30, 60 and 90 day follow up points, with a 7-day window after each time point to complete the testing.

## 5.2 Study Schedule

### 5.2.1 Schematic of Study Design

**Schematic of Study Design**

**Schedules of Activities for COVID-19 HCWP HCW HCQ Study**

| Task | Screening/ Baseline | Daily (existing required survey) | 30 Day (± 7days) | 60 Day (± 7days) | 90 Day (± 7days) | Early Termination or Clinically Suspected SARS-CoV-2 |
|---|---|---|---|---|---|---|
| Consent | X | | | | | |
| Health history | X | | | | | |
| Exposure Survey (online) | X | X | | | | X |
| Swab* for SARS-CoV-2 and plasma/serum sample | X | | X | X | X | X |
| Hydroxychloroquine dosing initiation | X | | | | | |
| Adverse Events | | X | X | X | X | X |

*Lab has confirmed ability to test samples from week over next weekend. Estimate up to 50 total per week (25 Sat, 25 Sun). Lab has also agreed to bank plasma and serum samples for delayed analysis.

### 5.2.2 Screening and Enrollment Visit

Both Screening and Enrollment visits can occur on the same day. Participants will be assessed for study eligibility through a pre-screening visit which may be conducted via telephone and include completion of the Employee Exposure Survey. Those who decide to take HCQ will be the experimental group (Group A), and participants who choose not to take HCQ will be part of the control group (Group B).

The Employee Exposure Survey can be accessed online via the following URL: https://is.gd/reportexposure. It can also be accessed by this QR code placed strategically in relevant patient care areas:

A hard copy of the survey is also attached as an appendix at the end of this protocol document. Questions relevant to this study will be added to the survey if the respondent indicates they are a study participant. We will use the REDcap database to track adherence to the protocol required surveys and send email or phone reminders if more than 2 days are missed.

#### 5.2.3 Visit for Switching from Group B to Group A

This study will allow participants to switch from Group B to Group A. If the previous visit is more than 7 days, survey collection will be done at the time of switch over. Switched participants will follow the study agent administration described in 4.7.1.2. Participants will be rescreened using screening form at the time of switch.

- Group A: approximately up to 275 (HCW choose to be provided HCQ)
- Group B: approximately up to 75 (HCW choose not to be provided HCQ)

Subjects who switch from Group B to Group A will not be replaced.

#### 5.2.4 Early Termination Visit

Early termination visit will consist of questionnaire and nasal swab.

### 5.3 Laboratory Procedures/Evaluations

Standard diagnostic swabs will be collected from the participants at baseline and at 30, 60, and 90 day follow up points (with a 7-day window after each time point to complete the testing). A portion of any participant sample testing positive for SARS-CoV-2 will also be evaluated with metagenomic next-generation sequencing. Only viral RNA will be sequenced, not human DNA/RNA.

The Executive Director of Research at the UNM Health Sciences Center Office of Research will be working with institutional officials to ensure the use of viral transport media and swabs during the study do not interfere with adequate supplies available for clinical use. A modification will be submitted to clarify who will supply the swabs and the transport media (i.e. TriCore, UNMH).

## 6 Assessment of Safety

Participants will be asked about any potential side effects experienced during study period at the 30, 60, and 90 day visits. In addition, subjects will report any potential AE's as part of the modified, daily Employee Exposure Survey to be completed daily. All subjects are HCW's and a space will be included for them to enter any new symptoms they may have experienced. If none they will indicate none. In their busy, at-risk environment, enrolled HCW's will not be presented with a lengthy list of uncommon and rarely serious AE's reported with HCQ. Given concerns of cardiac toxicity (dysrhythmias) with the use of the study drug, particularly when combined with azithromycin, the following verbiage will be inserted into the informed consent form: "In addition, taking macrolide antibiotics (azithromycin, clarithromycin, erythromycin, spiramycin, telithromoycin) while receiving hydroxychloroquine may increase the risk of serious heart rhythm problems (e.g. torsades de pointes). You may wish to consult with your physician before participating in the trial because you may be predisposed to these problems." The FDA warning about the use of hydroxychloroquine for treatment of COVID-19 (released April, 2020) will also be discussed in the consent form.

## 6.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

All AEs will be recorded on eCRFs. All recorded AE's will have a severity grade as well as causality (related or not related to Hydroxychloroquine) as determined by an investigator.

## 6.2 Definition of Serious Adverse Events (SAE)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above)

## 6.3 Classification of an Adverse Event (AE)

### 6.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

### 6.3.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

## 6.4 Time Period and Frequency for Event Assessment and Follow-Up

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE and all AEs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, designated study personnel will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

### 6.4.1 AEs and SAEs Reporting

All AEs and SAEs must be reported to the local IRB per their guidelines.

Data Safety Monitoring Plan: The Data Safety Monitoring Board (DSMB) will be monitoring the subjects in real time for adverse events. Accumulated data and adverse events will be reviewed at 30-day intervals. Additionally, data will be reviewed for safety after the first 20 subjects are enrolled, then after the next 50 and then in increments of 50 thereafter. If there is an unanticipated safety signal, stopping the study will be considered. A summary of the outcomes of these reviews will be submitted to the IRB.

The DSMB will consist of the following members:

- Dr. Greg Mertz, MD, DOIM-Infectious Disease, will chair the DSMB for this study.
- CTSC biostatistician as assigned based on demand from other clinical trials.
- Medical ethics or legal – Jonathan Bolton or Scott Sauder
- Critical care – Dr. Michelle Harkins or designee. Cannot be participating in the clinical trial.

# 7 Statistical Considerations

## 7.1 Statistical and Analytical Plans (SAP)

All data will be summarized using appropriate descriptive statistics, including mean, median, standard deviation, and range for continuous variables and frequency and proportions for categorical variables. Data will also be summarized graphically.

## 7.2 Statistical Hypotheses

We will test the null hypothesis that the positive SARS-CoV-2 rate is the same among participants who opt to take HCQ as among participants who opt not to take HCQ. The alternative hypothesis is that the positive SARS-CoV-2 rate differs between the groups.

## 7.3 Analysis Datasets

The primary analysis data set will consist of positive SARS-CoV-2 outcomes for all enrolled participants. Sensitivity analyses will be conducted using the subset of HCQ participants who complete their entire course of treatment.

### 7.4 Description of Statistical Methods

#### 7.4.1 General Approach

All data will be summarized using appropriate descriptive statistics, including mean, median, standard deviation, and range for continuous variables and frequency and proportions for categorical variables. Data will also be summarized graphically. Distributional assumptions will be assessed with suitable transformation conducted if indicated. Significance tests will use two-sided Type I error rate of 0.05.

#### 7.4.2 Analysis of the Primary Efficacy Endpoint(s)

Detection of SARS-CoV-2 RNA by PCR will be the primary endpoint and will be compared between treatment groups (prophylaxis vs. no prophylaxis). Positive SARS-CoV-2 will be defined as a binomial variable (i.e., positive SARS-CoV-2 or no positive SARS-CoV-2) and analyzed using Wilcoxon rank analysis. Potential confounders of the primary endpoint will be addressed by using standard statistical matching techniques, such as propensity score matching, and logistical regression to assess for confounding by exposure risk, demographic factors and comorbidities that are known or suspected to affect the likelihood of developing SARS-CoV-2 infection.

#### 7.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints include symptoms reported over time via questionnaires, as well as other clinical endpoints such as hospital admission, ICU admission, and mortality. These binary clinical outcomes will be analyzed in a manner similar to that described above for the primary endpoint. Symptoms will be included as predictor variables. Antibody titers for SARS-CoV-2, measured as an exploratory endpoint in serum or plasma samples, will also be analyzed as binomial values. Positive values will be defined as a four-fold or greater increase in IgG antibody titers compared to baseline. Other descriptive analyses will be provided of the antibody titer results, including geometric mean, median, standard deviation, and titer range.

### *7.5 Sample Size*

The total sample size will be approximately 350 participants. We do not know in advance how many will opt to take or not take HCQ. The table below provides the detectable difference in positive SARS-CoV-2 rate for different proportions of participants in the treated and control groups. For example, if two-thirds of the sample opt to take HCQ, we will have 80% power to detect a difference in positive SARS-CoV-2 rate of approximately 15 percentage points (e.g., a 35% PCR positivity rate in the control group and a 20% PCR positivity rate in the HCQ group). These calculations assume a two-sided Type I error rate of 0.05. The exploratory endpoints remain independent of enrollment in Group A vs. Group B.

| Treatment Group | Control Group | Detectable difference |
|---|---|---|
| 175 | 175 | 0.14 |
| 230 | 120 | 0.15 |
| 260 | 90 | 0.17 |

# 8 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Information from clinical parameters will be obtained from the Symptoms Questionnaire. A separate electronic dataset (using REDcap) will be constructed to capture the most important clinical information on the patients including the following: demographic information (gender, age, DOB, place of residence, ethnicity and race), presenting and daily symptoms and signs (including fever, cough, SOB, sputum production, anosmia, hyposmia, fatigue, sore throat, nasal congestion, diarrhea, headache, vital signs, pulmonary auscultatory findings)

Each person participating in this Study will be assigned a randomly generated study ID that will be linked to identifiers (MRN, DOB) in a linking table to be kept separate from the research data. Data and specimens will

be labelled with the study ID only. Only HRRC-approved members of the study team who have the appropriate training will have access to the data and identifiers. All data that we collect in this study will be entered into REDCap, a secure data-base, on a password-protected computer using a secure network. Any hard copy records/data will be kept in a locked file cabinet in the locked office of a designated member of the Study team. The specimens will be kept and stored in the Clinical and Translational Science Center at the UNM HSC and can only be accessed by the members of the study team. Investigators will transport the specimens to TriCore Reference Laboratories for lab analysis through standard transport hospital procedures. Once data collection is complete, data will be de-identified by destruction of the linking table.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

# 9 Ethics/Protection of Human Subjects

## 9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 9.2 Institutional Review Board (UNM HEALTH SYSTEMSC HRRC)

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

## 9.3 Informed Consent

An approved member of the study team will conduct the consent process with the participant in a private area of the hospital or by phone if needed. .

It may not be possible to have an in-person discussion of the study with participants. Investigators may need to conduct a phone consent via conference phone call because the investigator and participant may not be in the same location. Documenting written informed consent in these instances must involve a process as follows: the participant receives a copy of the informed consent document in advance of a telephone discussion. The investigator obtains consent over the telephone with the participant. A Legal Authorized Representative will not be required. Only English-speaking participants will be enrolled.

The informed consent form may be mailed, emailed or faxed to the participant. The consent discussion may then be conducted by phone, conference phone call or in person so that the participant can read the consent form during the discussion.

Investigators will explain the study to the potential participant by reading the informed consent document to the participant and provide all pertinent information (purpose, procedures, risks, benefits, alternatives to participation), and allowing the potential participant ample opportunity to ask questions. This can be done by phone, conference phone call or in person.

Investigators will ensure a thorough verbal discussion was conducted by phone, conference phone call or in person of the consent form. Investigators will allow the potential participant time to read the consent form and allow the participant sufficient time to consider whether or not to participate in the research.

Investigators will ensure the potential participant additional questions have been addressed.

Participants will be asked to explain the purpose of the study, procedures involved, and/or conditions for participation to confirm understanding.

If the participant agrees to participation, s/he signs the consent form and returns it to the investigator for signature and date. If informed consent took place via the phone or via conference phone call, the signed and dated consent form can be returned to investigators by mail, fax, or by scanning the consent form and returning it through a secure e-mail account by the participant. It is possible that multiple consent forms will be obtained for a single participant because the investigator obtaining consent and the participant were not in the same location but together via conference phone call. In this instance, each separate consent will be signed and dated by each individual appropriately. All dates on the multiple consent forms will be congruent for the day the consent took place. In these instances, a note-to-file will explain that separate consent forms exist for a single participant because all individuals could not be in the same room and that the consent took place over a conference phone call in an effort to decrease the contact and exposure to the novel coronavirus.

### *9.4 Participant and Data Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the investigators and their staff. This confidentiality is extended to cover testing of biological samples and the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All study data will be stored in REDCap database. Participant electronic material are only labeled with study ID and the link to identifiable info is stored separately.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

# 10 Data Handling and Record Keeping

## 10.1 Data Collection and Management Responsibilities

- Participants will be assigned a randomly generated study ID that will be linked to identifiers (MRN, DOB) in a linking table to be kept separate from the research data. Data and specimens will be labelled with the study ID only.
- Only HRRC-approved members of the study team who have the appropriate training will have access to the data and identifiers.
- Data will be entered into REDCap on a password-protected computer using a secure network.
- Any hard copy records/data will be kept in a locked file cabinet in the locked office of a designated member of the study team
- The specimens will be kept and stored in the Clinical and Translational Science Center at the UNM HSC and can only be accessed by the members of the study team. Then specimens will be transported to TriCore Laboratory and can only be accessed by laboratory personnel for the purpose specified in the protocol.
- Once data collection is complete, data will be de-identified by destruction of the linking table. Study records will be kept for 6 years past study closure.
- Biological samples collected for the study (e.g. blood) will not be stored in a repository, but will be destroyed after analysis and after completion of the study.

## 10.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

## 10.3 Publication

This study will adhere to the NIH Public Access Policy. UNM HEALTH SYSTEM will have the publication right of the papers as outcomes of this study.

# 11 Study Finances

## 11.1 Costs to the Participant

There will be no cost to the participant.

## 11.2 Participant Reimbursements or Payments

There are no participant reimbursements or payment for this study.

# 12 Conflict of Interest Policy

All investigators and study personnel must have up to date financial declarations reviewed and approved by the UNMHSC Conflict of Interest Committee.

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**Appendix A : Questionnaires or Survey**

Employee Exposure Survey

Employee Exposure Survey.pdf

List of Potential Aerosol Generating Procedures and Risks:

BiPAP, CPAP, high flow oxygen (>10L/minute)
Bronchoscopy
Cardiopulmonary resuscitation (CPR)
Cardioversion
Clinical (bedside) swallow evaluations
Conscious sedation
Electroconvulsive shock therapy (ECT)
Excessive coughing
Extubation
Fiberoptic endoscopic evaluation of swallowing
GI Endoscopy
Intubation
Laryngoscopy
Manual ventilation before intubation
Nasogastric, orogastric, or nasoenteric feeding tube placement
Nasopharyngeal swabbing
Nebulizer treatments
Oral care
Patient actively coughing in room)
Patient use of Incentive Spirometry
Planned regional anesthetic with high likelihood of requiring conversion GA (mask or intubation)
Prone positioning
Speech valve trials with tracheostomies
Sputum induction
TEE
Tracheostomy
Videofluoroscopic swallow studies