Study of NYU Langone healthcare workers at high risk for SARS – COV-2 infection

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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 Institutional Review Board (IRB), 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
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease
CQ	Chloroquine
CRF	Case Report Form
DBS	Dried Blood Spot
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
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
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
OHS	Occupational Health Service
OHSR	Office of Human Subjects Research
PCR	Polymerase chain reaction
PEP	Post exposure prophylaxis
PI	Principal Investigator
PI	Principal Investigator
PPE	Personal Protective Equipment
PrEP	Pre Exposure Prophylaxis
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

US	United States
WHO	World Health Organization

Protocol Summary

Title	Off label study to evaluate the efficacy of HCQ for pre-exposure prophylaxis (PrEP) 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 **Short Study Title:** COVID-19 PrEP HCW HCQ Study
Brief Summary	The Pre-exposure Prophylaxis (PrEP) Study, single, open and off label intervention study. 350 participants will be assigned to group that takes HCQ or group that opts to not take study medication. Participants will be NYULH HCW at high risk for occupational exposure to SARS-CoV-2. Study timepoints will include screening/enrollment, 30 day, 60 day, and 90 day visits. Questionnaires, and DBS will be collected in all timepoints.
Phase	Off label use of HCQ
Primary Objectives	To evaluate the efficacy of hydroxychloroquine (HCQ) for pre exposure prophylaxis (PrEP) 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 Pre-exposure Prophylaxis (PrEP) Study, single, open and off label intervention study
Primary Endpoint	Frequency of seroconversion to SARS-CoV-2
Study Duration	12 months
Participant Duration	Participant Study period: up to 90 days for both groups, inclusive of those who convert from Group B to Group A.
Duration of IP administration	Up to 90 days
Population	Total number of participant: 350 NYULH health care workers with high risk of occupational exposure to SARS-CoV-2 Group A: (HCW choose to be provided HCQ) Group B: (HCW choose not to be provided HCQ)
Study Sites	NYU Langone Health
Number of participants	350
Description of Study Agent/Procedure	Hydroxychloroquine- oral administration • Duration: up to 90 days or until meeting study termination criteria • Loading dose: 600 mg once for the first day • Maintenance dose: 200 mg, daily 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, Dried blood spot (DBS) collection

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 assess 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 outcomes of seroconversion to SARS-CoV-2 and influenza infections, comparing these outcomes across groups defined by treatment with different medications. Secondary endpoints include symptoms reported over time via questionnaires, as well as other clinical endpoints such as hospital admission, ICU admission, and mortality.

Schematic of Study Design

Schedules of Activities for COVID-19 PrEP HCW HCQ Study

Task	Screening/ Baseline	30 Day (± 7days)	60 Day (± 7days)	90 Day (± 7days)	Early Termination/ [5]Switch Over Day
Consent	X				
Pre-Screening Questionnaire	X				
Demographic and Employment Questionnaire	X				
Medical History Questionnaire					
[1]Medication Questionnaire	X	X	X	X	X
[2]Symptom Questionnaire	X	X	X	X	X
[3]Dried blood spot (DBS) for serology test	X	X	X	X	X
Data collection from medical chart review	X	X	X	X	X
[4]Hydroxychloroquine dose (HCQ)	X	X	X	X	X
Adverse Events		X	X	X	X

[1]Separate Medication Questionnaires will be used for Group A and Group B. See list of attachments.
[2 and 3] Questionnaires and DBS collection need to be done at the same time.

[4]Group A only - 600 mg for Day 1 (within 4 days from enrollment), 200 mg everyday thereafter for 90 days
[5] Only if previous questionnaires and DBS sample collection is > 7 days.

Key Roles

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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 8 March 2020, person-to-person transmission has occurred in China, across temperate Asia, Europe, and North America, with sporadic cases in Africa and the southern hemisphere. Accurate reporting is limited by availability of diagnostic testing. 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 or cardiac co-morbidities or diabetes. In more healthy adults, including pregnant women, it can cause a febrile, self-limited pneumonia. Infection appears less severe in children and younger adults [5]. Nevertheless, the burden to health and economic systems globally of this pandemic is expected to be substantial. 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.

Over 1700 cases of COVID-19 have been reported among health care workers (HCWs) caring for COVID-19 patients in China, including 5 deaths, representing 3.8% of all COVID-19 patients in a recently published series of over 72,000 cases [6]. The number of HCWs infected with SARS-CoV-2 are increasing every day in Italy 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 are performed without knowing SARS-CoV-2 infection status. The COVID-19 epidemic has put tremendous strain on HCW in all aspects.

Scientists at the NYULH are interested in studying this emerging infections, SARS-CoV-2. This includes studying the immune response to SARS-CoV-2, developing and validating diagnostic assays, vaccines, and therapeutics for SARS-CoV-2, improving our understanding of virus transmission, protecting HCWs, and the understanding of HCQ effect on COVID-19.

As of today there is no approved treatment or prophylaxis for COVID-19 by FDA (Food and Drug Administration). 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 specifically Covid-19. Pharmacologic modelling based on observed drug levels and in vitro drug testing suggest that prophylaxis at approved doses could prevent Covid-19 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 for PrEP to prevent SARS-CoV-2 infection among HCWs who are 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 COVID-19 infection. This study is designed to answer whether pre-exposure prophylaxis (PrEP), HCQ, can mitigate the risk of SARS-CoV-2 infection among HCWs in high-risk setting.

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 pre-exposure HCQ will prevent symptomatic or reduce severity of infection. Additionally, medical society and 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-arrhythmics 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 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 histamine 2 blockers.

Risk of study procedures
Risks of DBS include temporary discomfort, bleeding, bruising, and rarely infection. The risk of infection will be minimized by instructing participants to clean the site with disinfecting agent.

Study Population: The PrEP Study eligibility is high risk HCWs (eg MD/DO, NP, RN, and respiratory therapists in ED and on Covid-19 units) at Tisch/Kimmel, Bklyn and Winthrop meeting all inclusion criteria.

3 Objectives

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of hydroxychloroquine (HCQ) for pre exposure prophylaxis (PrEP) 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 seroconversion to SARS-CoV-2
Secondary Objectives	**Secondary Endpoints**
To characterize whether high-risk HCW who seroconvert to SARS-CoV-2 have asymptomatic infection or report symptoms of COVID-19 in the 4 weeks preceding seroconversion	• Symptom questionnaires
To assess the severity of SARS-CoV-2 infection after treatment with hydroxychloroquine	• Symptom questionnaires • Hospital admission rate • ICU admission rate • Mortality rate
To assess the tolerability of hydroxychloroquine SARS-CoV-2 PrEP in this population	• Incidents of AEs or SAEs related to HCQ upon study termination time
Exploratory Objectives	**Exploratory Endpoints**
To determine whether baseline levels of non-SARS-CoV-2 coronavirus antibodies correlates with COVID-19 disease severity	• Serology test • Symptom questionnaires
To characterize whether pre-existing of non-SARS-CoV-2 coronavirus antibodies are capable of causing antibody dependent enhancement of a pseudotyped SARS-CoV-2	• Serology test • Percentage of cells infected in the laboratory using a standardized dose of pseudotyped SARS-CoV-2 in the presence or absence of blood containing non-SARS-CoV-2 coronaviruses antibodies
To determine whether hydroxychloroquine reduces time lost from work	• Days away from work
To assess the compliance of hydroxychloroquine PrEP	• Frequency of missing dose

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 target population for this study are NYULH health care workers identified as having a high risk of occupational exposure to SARS-CoV-2 (ie., locations where aerosol-generating procedures are frequently performed such as the intensive care units and emergency departments, health care roles (ICU and ER physicians nurses, respiratory therapists, residents, fellows and students,)

Total number of participant: 350 (Group A and B)

- Group A: (HCW choose to be provided HCQ)
- Group B: (HCW choose not to be provided HCQ)

4.2.1.1 Inclusion Criteria for Group A and B

- Men or women ages ≥18 years NYULH health care worker who meets one of the following criteria
    1. Involved in an aerosol generating procedure (nasopharyngeal specimen collection, tracheal intubation, nebulizer treatment, open airway suctioning, collection of sputum, tracheostomy, bronchoscopy, CPR) on a confirmed COVID-19 patient while wearing PPE
    2. Direct bedside care of confirmed COVID-19 patient while wearing PPE for 3 or more shifts in a 7 day period
    3. Direct care of PUIs in the ED or other inpatient unit while wearing PPE for 3 or more shifts in a 7 day period
- Willing and able to provide informed consent

4.2.1.2 Exclusion Criteria

Exclusion Criteria for Group A only :

- Known hypersensitivity to hydroxychloroquine or chloroquine
- Known diagnosis of COVID-19
- Concomitant use of
    1. amiodarone
    2. digoxin
    3. flecainide
    4. procainamide
    5. propafenone
- History of Torsades de pontes
- History of retinal disease
- Known chronic kidney disease ≥ stage 4
- Congenital prolonged QTc interval syndrome (Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome)

4.2.1.3 Vulnerable Subjects

This study will enroll employees of NYULH. Employees (For example: MD/DO, NP, RN, PA, Respiratory Therapists), residents, fellows and students recruited as research subjects are 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, NYULHS 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.

Residents, Fellows and Students

Residents, fellows and students recruited as research subjects are more vulnerable to undue influence or coercion because they may perceive their employment or grades as dependent upon their participation in research. Study team members will emphasize that participation in the study is voluntary and refusal to participate will not affect employment, job evaluations or grades. To minimize the risk of invasion of privacy or loss of confidentiality residents, fellows and students will self-identify as being interested in study participation, as per the strategies for recruitment stated below.

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Pregnant 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. Each individual 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. This conclusion: HCQ is not associated with any increased risk of congenital defects, spontaneous abortions, fetal death, pre-maturity and decreased numbers of live births in patients with auto-immune diseases appears as conclusion in peer reviewed article entitled Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases published in 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 IRB approved email blast that will be sent the departments that are specific to the desired study population. We will be using NYU Langone Health listservs which will be chosen based on their pertinence to the study population we are looking at, described in Section 4.2.1 of this protocol. The email blast will direct interested HCW to send an email to a study team email address with their phone number and best times to call. Upon email contact study team will call participant 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 350 participants across NYULH. Subject visits will be conducted remotely.

4.6 Participant Withdrawal or Termination

- Reasons for Withdrawal or Termination
  1. Participants become PCR-confirmed SARS-CoV-2 status
  2. Participant starts disallowed medication (Group A only)

3. Advent of an adverse event which necessitates discontinuation of HCQ (Group A only)
4. Participant decides to withdraw from the study
5. PI discontinues participation due to safety concerns
6. Participant decides to withdraw consent
7. Participant's primary care provider determines the study is not under participant's best interest
8. 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 pharmacies (Tisch/Kimmel, NYULangone Brooklyn, and NYU Langone Winthrop).

4.7.1 Disallowed Concomitant Therapy

- amiodarone
- digoxin
- flecainide
- procainamide
- propafenone

4.7.2 Dosing and Administration (applies only to Group A)

4.7.2.1 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 maintenance dose

4.7.2.2 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.

If participants are already taking HCQ prior to enrolling into the study, patients will continuing their dosing schedule as prescribed (200mg per day). We will screen these subjects to document their reason for taking HCQ (i.e clinically indicated for lupus, persons who elected to take HCQ off-label). These subjects will be included into Group A, but their data will not be incorporated into the analysis for primary endpoint.

4.7.2.3 Supplies

HCQ will be dispensed at outpatient or inpatient pharmacies of NYULH at no cost to the participants.
Dispense schedules

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

5 Study Procedures and Schedule

5.1 Study Procedures/Evaluations

5.1.1 Study Specific Procedures

Questionnaires (Attachment A, B,C,D,E, F)

Participants from both Group A and B will be asked to complete the following questionnaires.

- Attachment A- Pre - Screening questionnaire (paper format)
- Attachment B- Demographic/Employment Questionnaire (paper format)
- Attachment C - Medication Questionnaire for Group A
- Attachment D – Medication Questionnaire for Group B
- Attachment E - Symptoms Questionnaire
- Attachment F - Medical History Questionnaire (paper format)

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)

Dried Blood Spots

Kits will either be mailed to participants or be distributed in specific locations within Tisch/Kimmel, Brooklyn and Winthrop locations. Collection kit will include supplies to collect a DBS, instructions to collect, and store the sample until ready for drop off. DBS collection and storage supplies will include alcohol pads, lancets, gauze, collection cards, desiccant packets, and sealable foil bags for storage. Participants will be instructed to use a lancet to prick their fingertip, apply blood spot to the collection card, air dry the card, and store it in a foil bag containing desiccant packets. Samples will be returned via designated drop off locations at each of the participating NYULH facilities. Participants will be instructed to collect DBS sample on the same time of questionnaires.

Chart review

Chart review will be done after participant sign e-consent form. Data will be collected from participant's EPIC medical chart review, including Occupational Health encounters associated with COVID-19. Data collection will be include information related to the diagnosis of SARS-CoV-2 infection and COVID-19 disease. This may include data relating to demographics or other medical conditions that are suspected or known to be risk factors for SARS-CoV-2 infection and/or modulate COVID-19 disease severity (including but not limited to diagnosis of respiratory illness, inclusive of COVID-19, pneumonia, etc).

5.1.2 Specimen Preparation, Handling, and Storage

DBS samples will be initially sent to the CTSI. Upon receipt, the CTSI will check the Symptom Questionnaire to label each sample as from a symptomatic or symptomatic participant. All samples will be routed to laboratories that are under biosafety level 2 conditions (BSL-2) for initial processing.

Both samples from participants with and without symptoms will undergoing an initial, brief processing check under BSL-2 conditions using a class II biosafety hood. This entails opening the sealed specimen bag, check whether the dried blood spot card is appropriately labeled and completed, and re-seal the specimen in an individual container labeled with the symptom status of the participant containing desiccant packs. The re-sealed specimen container will then be frozen for storage until elution for the intended experiments is ready to occur at BSL-2 conditions in a laboratory secured by badge access and/or passcode access provided samples from symptomatic and asymptomatic participants are appropriately labeled and stored in separate containers. This may occur at either the NYULVC processing lab located on the 4th floor of the Medical Science Building, 540 1st Avenue, New York, NY, 10016 or the NYULVC research lab located on the 3rd floor of the Alexandria Center for Life Sciences, 430 E 29th Street, New York, NY, 10016. Elution of dried blood spots for the intended experiments collected from asymptomatic and symptomatic

participants must follow NYU Langone biosafety regulations pertaining to use of samples from COVID 19 positive research participants in place at the time the elution and/or experiments are performed.

Due to the virulent nature of SARS-CoV-2 and other potential pathogens, all personnel handling specimens related to this protocol will follow CDC and NIH guidelines. As it is unknown whether specimens will contain infectious materials, all dried blood spots will be transported in compliance with regulations for Category B Biological substances and CDC shipping guidelines for dried-blood spot specimens.

5.2 Study Schedule

5.2.1 Schematic of Study Design

Schematic of Study Design

Schedules of Activities for COVID-19 PrEP HCW HCQ Study

Task	Screening/ Baseline	30 Day (± 7days)	60 Day (± 7days)	90 Day (± 7days)	Early Termination/ [5]Switch Over Day
Consent	X				
Pre-Screening Questionnaire	X				
Demographic and Employment Questionnaire	X				
Medical History Questionnaire					
[1]Medication Questionnaire	X	X	X	X	X
[2]Symptom Questionnaire	X	X	X	X	X
[3]Dried blood spot (DBS) for serology test	X	X	X	X	X
Data collection from medical chart review	X	X	X	X	X
[4]Hydroxychloroquine dose (HCQ)	X	X	X	X	X
Adverse Events		X	X	X	X

[1]Separate Medication Questionnaires will be used for Group A and Group B. See list of attachments.
[2 and 3] Questionnaires and DBS collection need to be done at the same time.

[4]Group A only - 600 mg for Day 1 (within 4 days from enrollment), 200 mg everyday thereafter for 90 days

[5] Only if previous questionnaires and DBS sample collection is > 7 days.

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 conducted via telephone with a member of the study team and will document consent via e-consenting through an email link via REDCap. Demographic and Employment questionnaire, Medical History questionnaire will be documented through paper format. Medication questionnaire and Symptom questionnaire will be administered via REDCap. Once eligibility is determined, participants will be asked if they opt to take study medication. Those who decide to take HCQ will be the experimental group (Group A), and participants who do not take HCQ will be part of the control group (Group B).

Specimen collection kit for enrollment visit and all subsequent visits will be either mailed to the participant or distributed in specific areas within the Tisch/Kimmel, Bklyn and Winthrop institutions. Kit will include instructions for collection. In addition, the link for study questionnaires will be emailed to the participant upon enrollment.

5.2.3 30, 60, 90 Day Visits

Follow-up remote study visits will be conducted in 30 day intervals. Each follow-up visit will entail questionnaires, DBS sample collection. Group A will continue study medication as per dosing schedule.

5.2.4 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, questionnaires and DBS collection will be done at the time of switch over. Switched participants will follow the study agent administration described in 4.7.2.2. Participants will be rescreened using screening form at the time of switch.
Subjects in Group B can switch to Group A up to Day 65. They will continue the study until day 90.

5.2.5 Visit for Switching from Group A to Group B

In the event where a Group A participant decides to stop HCQ dosing prematurely, but still wishes to participate in DBS collection and questionnaire administration, they will be assigned to Group B. These patients will continue their original study timeline.

5.2.6 Early Termination Visit

Early termination visit will consist of questionnaires, DBS sample collection.

5.3 Laboratory Procedures/Evaluations

Dried blood spot samples collected in this study will be used for serological testing. If sufficient sample remains after the primary and secondary objectives are completed, dried blood spot samples may be used to evaluate for the ability of non-SARS-CoV-2 coronavirus antibodies to cause antibody dependent enhancement of a pseudotyped virus expressing SARS-CoV-2 spike protein in laboratory cell lines.

6 Assessment of Safety

Participants will be asked about any potential side effects experiencing during study period.

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 the 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 PI's H. Michael Belmont and Vanessa Raabe 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.

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 seroconversion 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 seroconversion rate differs between the groups.

7.3 Analysis Datasets

The primary analysis data set will consist of seroconversion outcomes for all enrolled participants. Subjects that were initially considered dropouts are permitted to submit DBS samples at a later date and will be used as part of the analysis. 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 assess 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)

The primary analysis will assess the outcomes of seroconversion to SARS-CoV-2 as a marker of SARS-CoV-2 infection, comparing this outcome across groups defined by treatment with different medications. Antibody titers will be measured to determine seroconversion, a binomial endpoint defined by a four-fold increase in antibody titers compared to baseline. Seroconversion will be defined as a binomial variable (i.e., seroconversion or no seroconversion) and analyzed using Wilcoxon rank analysis. Additionally, descriptive analysis will be provided of the antibodies titer results, including geometric mean, median, standard deviation, and titer range. 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 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 outcome will be analyzed in a manner similar to that described above for the primary endpoint. Symptoms will be included as predictor variables.

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 seroconversion 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 seroconversion rate of approximately 15 percentage points (e.g., a 35% serocoversion rate in the control group and a 20% sercoversion 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. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use case report forms (CRFs) as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

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

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

REDCap will be utilized to capture patient consent to participate in study. This will be an electronic format which will reflect language approved by the IRB, referred to as the e-consent.

When patient expresses interest in participating in the study, they are to provide an email address in which the study team member will use to email a direct link to the e-consent, as well as phone number. The study team member will be on the phone and reviewing the e-consent with the participant. The study team member will remain on the phone with the participant to answer any questions and address any concerns.

The e-consent will describe in detail the study agent, study procedures, and risks are given to the participant and documentation of informed consent is required prior to starting intervention/administering study product. The subject will document their consent by approving the e-consent in REDCap.

Language in the e-consent will be submitted to the IRB for review and approval. IRB approval will be obtained prior to enrolling any study participants.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. Designated study personnel will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form via REDCap and ask questions prior to e-signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will e-sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the e-signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Since this study will enroll NYULH employees, the study personnel will emphasize that participation in this research study is voluntary and that the participant's employment status, job performance evaluation, and the quality of any medical care the participant receives will not be adversely effected if he/she declines to participate in the study.

A copy of the e-signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process and the justification for such alteration will likewise be documented.

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.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

10 Data Handling and Record Keeping

10.1 Data Collection and Management Responsibilities

Data will be collected on electronic CRFs in REDCap and printed versions of each document will be placed in the paper research chart and will be stored at Clinical Research Center. Both electronic (REDCap) and paper research charts will be maintained as source documents and for recording data for each participant enrolled in the study. Access to REDCap will be restricted to authorized study team members, who must log on to the REDCap system through NYU using their Kerberos ID and password to access study documents. Any discrepancies between electronic and paper documents will be explained and captured in a note and maintained in the participant's official electronic and paper study records. Data and study charts will be maintained for the duration of the study and afterwards per NYULH requirements.
The study CRFs is the primary data collection instrument for the study. All key elements required to be completed during consent, screening, and questionnaires will be listed as required elements in REDCap, therefore not allowing submission of the form until all required information has been completed.

If a space on the CRF is left blank because the procedure was not done or the question was not asked, study team personnel will write/enter “N/D”. If the item is not applicable to the individual case, study team personnel will write/enter “N/A”. All paper chart entries will be printed legibly in blue or black ink. If an entry error has been made, study team personnel will draw a single straight line through the incorrect entry and enter the correct data above it. All such changes will be initialed and dated.
Documents considered study records include: regulatory documents, protocols, e-consent forms, e-screening forms, laboratory inventory forms, and electronic case report forms.

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. NYULH 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

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan. All NYULMC investigators will follow the applicable conflict of interest policies.

13 References

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14 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

Attachment A – Pre-Screening questionnaire
Attachment B - Demographic/Employment Questionnaire
Attachment C - Medication Questionnaire for Group A
Attachment D – Medication Questionnaire for Group B
Attachment E - Symptoms Questionnaire
Attachment F - Medical History Questionnaire