PATCH 2 & 3: (Prevention and Treatment of COVID-19 with Hydroxychloroquine)

A double-blind placebo controlled randomized trial of hydroxychloroquine in the prevention and treatment of COVID-19

NCT04353037

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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STUDY TITLE:	PATCH 2 & 3: (Prevention and Treatment of COVID-19 with Hydroxychloroquine) *A double-blind placebo controlled randomized trial of hydroxychloroquine in the prevention and treatment of COVID-19*
STUDY ID	IRB # 2020-003
PROTOCOL VERSION	05/12/2020

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

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Principal Investigator Name	Signature
_____	_____
Principal Investigator Name	Signature
_____	_____
Institution	Date

Abbreviations:

Ab: antibody
AE: adverse event
ALT: alanine aminotransferase
ANC: absolute neutrophil count
AST: aspartate aminotransferases
BID: twice daily
BP: blood pressure
BSA: body surface area
CNS: central nervous system
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
DSMC: Data Safety and Monitoring Committee
eCRF: electronic case report form
EKG: electrocardiogram
FDA: Food and Drug Administration
FFPE: formalin fixed-paraffin embedded
HBV: hepatitis B virus
HCQ: hydroxychloroquine
HCV: hepatitis C virus
HUP: Hospital of the University of Pennsylvania
IHC: immunohistochemistry
IND: investigational new drug
INR: international normalization ratio
IRB: institutional review board
IV: intravenous
LLN: lower limit of normal
LVEF: left ventricular ejection fraction
PPT1: palmitoyl-protein thioesterase 1
PR: partial response
PT: prothrombin time
PTT: partial thromboplastin time
SAE: serious adverse event
SUSAR: Suspected, Unexpected Serious Adverse Reaction
ULN: upper limit of normal
WBC: white blood cell

STUDY SUMMARY

Title	PATCH 2 & 3: (Prevention and Treatment of COVID-19 with Hydroxychloroquine) A double-blind placebo controlled randomized trial of hydroxychloroquine in the prevention and treatment of COVID-19
Protocol Number	2020-0003
Phase	Phase II
Methodology	Double-blind placebo controlled randomized prevention and treatment trial
Study Duration	1 year
Study Center(s)	Virtual trial based out of a clinical research institution – ProHealth NY
Objectives	**PRIMARY OBJECTIVES:** **PATCH 2 (Sub-Study 1***, Patients tested for COVID-19 who meet symptomology and age requirements for eligibility)***:** Rate of hospitalization **PATCH 3 (Sub-Study 2***, Health Care Workers)***:** Rate of COVID-19 infection (confirmed by accepted testing methods) over two months (60 days) **SECONDARY OBJECTIVES** **PATCH 2 (Sub-Study 1):** Rate of secondary infection of co-inhabitants, adverse events, and negative for COVID-19 (confirmed by accepted testing methods) at 14 days **PATCH 3 (Sub-Study 2):** Number of shifts missed, rate of adverse events, and hospitalization
Number of Subjects	**PATCH 2 (Sub-Study 1):** 500 with interim analysis at time points corresponding to 34% and 68% of the desired sample size ***PATCH 3 (Sub-Study 2):** 350 with interim analysis at time points corresponding 25% and 50% of the desired total sample size **Total: 850** ***Eventual expectation for needing 100% crossover**
Diagnosis and Main Inclusion/Exclusion Criteria	**PATCH 2 and PATCH 3 Inclusion Criteria** • Willing and able to provide informed electronic consent via DocuSign

	• Willing to report compliance with HCQ or Placebo ("tablets") in the form of an on-line journal and participate in other forms of self-reporting (e.g., symptom tracker and experience log) • Willing and able to go to designated areas for testing (COVID-19/SARS-CoV-2 and/or serologic) and/or administer at home testing kits for study data collection purposes. • Must be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels • Must have adequate baseline organ function • Subjects meeting the following criteria by Sub-Study: **PATCH 2 Inclusion (Sub-Study 1):** 50-75 years of age; self-reporting as having a fever within four days prior to time of enrollment; and not requiring hospitalization. Enrolled individuals will undergo testing for COVID-19 and return home for self-quarantine. Patient must be willing and able to provide informed consent, agree to testing for COVID-19 at time of enrollment to confirm diagnosis, at the end of treatment (Day 15, 16 or 17) and two weeks after the end of treatment (Day 29, 30 or 31) where Day 1 is defined as the first day blinded study drug is taken by the patient. (See Appendix- PATCH2 process flows) **PATCH 3 Inclusion (Sub-Study 2):** Currently employed as a health care worker (Medical Doctor, MD; Doctor of Osteopathic Medicine, DO; Nurse Practitioner, NP; Physician's Assistant, PA; and Registered Nurse, RN or other members of the medical care team with significant COVID-19 exposure); asymptomatic and presumed negative for COVID-19 (no confirmatory testing conducted); scheduled for an average of $\geq$20 hours per week of clinical care over the next two months (or equivalent indicating at least part-time employment). Participant will be asked to comply with their employer's potential or confirmed COVID-19 incident protocol and must agree to undergo COVID-19 testing per standard of care using an FDA approved method upon the presentation of symptoms indicative of an influenza like illness; if a confirmatory COVID-19 diagnosis is given, participant will be offered to cross-over to HCQ 600 mg qd for 14 days. At the end of the 60-day medication period, participants remaining undiagnosed for COVID-19 will undergo virus and serology testing. (See Appendix- PATCH3 process flows)

	PATCH 2 & PATCH 3 Combined **Exclusion Criteria** *(See Study Exclusions and Content Job Aid)* • Allergy to hydroxychloroquine, 4 aminoquinolines, or quinine • Known G6PD deficiency • Pregnant or lactating or intention of becoming pregnant during the study as self-reported during enrollment screening • Receiving any trial treatment drug for 2019-nCoV within 14 days prior to screening evaluation (off label, compassionate use or trial related) • Known retinal disease including but not limited to macular degeneration, retinal vein occlusion, visual field defect, diabetic retinopathy • History of interstitial lung disease severe emphysema or asthma, or chronic pneumonitis Current diagnosis of porphyria or psoriasis • Serious intercurrent illness that requires active intravenous therapy, intense monitoring, or frequent dose adjustments for medication including but not limited to infectious disease, cancer, autoimmune disease, cardiovascular disease • Have undergone major abdominal, thoracic, spine or CNS surgery in the last two months, or plan to undergo surgery during study participation • Is receiving cytochrome P450 enzyme-inducing anticonvulsant drugs (i.e. phenytoin, carbamazepine, Phenobarbital, primidone or oxcarbazepine) within four weeks of the start of the study treatment • Currently taking digoxin • History or evidence of increased cardiovascular risk including any of the following: o Left ventricular ejection fraction (LVEF) < institutional lower limit of normal. Baseline echocardiogram is not required o Current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation o History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment o Current ≥ Class II congestive heart failure as defined by New York Heart Association

	• Deemed unable to participate for medical reasons identified by Co-PI and study staff
Study Product, Dose, Route, Regimen	Hydroxychloroquine, various doses, oral Matching placebo, oral
Duration of administration	**PATCH 2 (Sub-Study 1):** COVID-19 patients in self-quarantine. *Arm 1:* HCQ 400 mg bid (two 200 mg tablets taken twice a day; totaling 800 mg per day) for 14 days *Arm 2:* Placebo 2 pills bid for 14 days **PATCH 3 (Sub-Study 2):** Asymptomatic health care worker prophylaxis. *Arm 1:* HCQ 600 mg qd (three 200 mg tablets taken once a day) for up to 60 days *Arm 2:* Placebo 3 pills qd for up to 60 days; cross-over from placebo to HCQ 600 mg qd for 14 days is allowed upon confirmatory diagnosis for COVID-19
Study design	1:1 randomization in each cohort between the arms
Duration of trial	Approximately 1 year

1.0 OBJECTIVES

1.1 Primary Objectives

PATCH 2 (Sub-Study 1): Rate of hospitalization
PATCH 3 (Sub-Study 2): Rate of COVID-19 infection (confirmed by accepted testing methods) over two months

1.2 Secondary Objectives

PATCH 2 (Sub-Study 1): Rate of secondary infections for co-inhabitants, rate of adverse events (AEs), and rate of COVID-19 negativity (confirmed by accepted testing methods) after 14 days of treatment
PATCH 3 (Sub-Study 2): Number of shifts missed, rate of hospitalization, and rate of adverse events (AEs)

2.0 BACKGROUND AND RATIONALE

2.1 Overview of SARS-CoV-2 and Chloroquine Derivatives

Chloroquine derivatives show preclinical efficacy against coronavirus but very little clinical data is available. Emerging viral diseases (EVDs) encompass a growing list of zoonotic viruses that have a major impact on global health and economics. These include Ebola, SARS, MERs, Marburg, and the recently identified virus that causes COVID-19 disease (Wuhan Coronavirus: SARS-CoV-2) (1). In each of these cases there is currently no effective drug treatments or prophylaxis agents that can be quickly applied to large populations at risk for the virus. As of March 2020, The SARS-CoV-2 virus has infected more than 180,000 people causing more than 5000 deaths. This has led to a lockdown of entire megacities in China, international travel bans, and disruptions in global supply chains. More alarming is the recent evidence that health care workers are getting infected and dying of the virus, wreaking havoc on the chain of care. In addition, while prior epidemics such as Ebola seemed to be contained in Africa, the current COVID-19 global crisis demonstrates how with the extent of globalization and international travel, no country is safe from these EVDs.

Coronaviruses are a large family of viruses that commonly infect many animals, including camels, cattle, cats, and are often found in bats as their zoonotic reservoir. While it is rare, animal coronaviruses can infect people and then spread between people, as had occurred with Middle East respiratory coronavirus (MERS-CoV) and severe acute respiratory coronavirus (SARS-CoV), and now the newly emerged coronavirus SARS-CoV-2 (also known as COVID-19). The SARS-CoV-2 virus is a betacoronavirus, like MERS-CoV and SARS-CoV. All three of these viruses have their origins in bats. While SARS-CoV and MERS-CoV exhibit significantly higher mortality than SARS-CoV-2, the ability to spread between humans is less than SARS-CoV-2. There is emerging evidence from Asia that patients can be highly contagious with one patient spreading viral particles to 87% of 15 sites within the patient's room. Virus can be shed in urine and feces as well as respiratory secretions increasing the likelihood that sick contacts and hospital staff will become infected (2). An epidemiological survey of 72,000 cases in China found and overall 3.8% infection rate in hospital workers, but a 68% infection rate of hospital workers in Wuhan at the epicenter of disease. This suggests that if low rates of infection are in a community, the likelihood of hospital workers contracting disease is low, but if there are a large number of cases then the likelihood of hospital workers contracting the disease is high (3). Patients above the age of 50 are more likely to die of this disease and the time from diagnosis to death can occur within one month despite access to high-level intensive care units (4). A high rate of intra-family transmission and rapid community transmission has been documented in Shenzen China (5). Meanwhile a screen of compounds found that chloroquine prevented and eradicated established infection of SARS-CoV-2 virus in vitro. I was contacted by researchers in China who indicated that 8/10 coronavirus infected patients treated with chloroquine 500 mg daily cleared their virus. The hospital ran out of chloroquine, and they have had to turn to other means of treating the virus. We believe hydroxychloroquine is a safer drug than chloroquine and affords the ability to dose escalate to concentrations that we know are effective at blocking the lysosome in patients.

Our ***hypothesis*** is that high doses of hydroxychloroquine for at least 2 weeks can be effective antiviral medication both as a treatment in ambulatory patients and prophylaxis/treatment in health care workers because it impairs lysosomal function and reorganizes lipid raft (cholesterol and sphingolipid rich microdomains in the plasma membrane) content in cells, which are both critical determinants of EVD infection. This hypothesis is based on a growing literature linking chloroquine to antiviral activity. We believe there is enough information to launch a clinical trial of hydroxychloroquine for COVID-19.

2.2 Mechanistic rationale for antiviral properties of chloroquine derivatives

2.2a Coronaviruses. Coronaviruses (CoV) infect mammals and birds causing respiratory, gastrointestinal, and central nervous system diseases. Coronavirus virions contain an envelope, a helical capsid, and a single-stranded RNA genome, the largest among all RNA viruses. The name "coronaviruses" derives from the spike proteins on their envelope that give the virions a crown-like shape. CoVs include the following: 1) α-genus: human coronavirus NL63 (HCoV-NL63), porcine transmissible gastroenteritis coronavirus (TGEV), and porcine respiratory coronavirus (PRCV) 2) β-genus: SARS-CoV-2/COVID-19, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), mouse hepatitis coronavirus (MHV), and bovine coronavirus (BCoV). 3) CoVs of the γ-genus include avian infectious bronchitis virus (IBV) and do not infect humans so are valuable laboratory agents (6). Coronaviruses impose health threats to humans and animals. SARS-CoV caused the SARS epidemic in 2002 to 2003, with over 8,000 infections and a fatality rate of ~10%. MERS-CoV emerged from the Middle East in 2012 causing 877 infections with a fatality rate of ~36%. HCoV-NL63 from the α-genus is a widespread pathogen that produces the common cold in healthy adults and acute respiratory illness in young children. CoVs are also major animal pathogens. TGEV and MHV cause close to 100% fatality in young pigs and young mice, respectively; BCoV and IBV also cause significant healthcare burden for domesticated cattle and chickens, respectively. Therefore, research on coronaviruses has strong health and economic implications (6).

2.2b CoV infection requires functional lysosomes. Receptor recognition by viruses is the first and essential step of viral infections of host cells. An envelope-anchored spike protein mediates coronavirus entry into host cells by first binding to a receptor on the host cell surface and then fusing viral and host membranes. CoVs recognize a number of different host receptors. Once the receptor is bound, there is viral and cell membrane fusion, followed by endocytosis and lysosomal processing. CoVs like SARS enter the cell through lipid raft enriched endocytosis (7). The details of the interaction between the virus spike protein, virus membrane and the lipid rafts are not worked out. In the lipid raft literature, it is often the case that lipid rafts (semisolid phase membrane filled with cholesterol and sphingolipids) are only physiologically functional if there is a non-lipid raft membrane region next to it. After membrane fusion, endosomal pH acidification is a fusion trigger for CoVs and other viruses including influenza virus and vesicular stomatitis virus (VSV). For instance the use of lysosomal inhibitor blocked the entry of the model coronavirus IBV (8). The authors directly assessed the pH dependence of IBV fusion and found that fusion only occurs at acidic pH. For some CoVs that harbor a non-cleaved spike protein on their surface, such as MHV-2 and SARS-CoV, it has been shown that they rely on lysosomal proteases for productive entry. In fact one study found that bat cells have more efficient lysosomal proteolysis than human cells providing an explanation for why bats are preferred zoonotic hosts for CoVs (9).

2.2c Evidence that chloroquine prevents coronavirus infection. It has been reported that chloroquine has strong antiviral effects on SARS-CoV infection and spread in vitro (10-12). In to increasing endosomal/lysosomal pH, these studies demonstrated that CQ abrogates glycosylation of ACE2, the cellular receptor of SARS-CoV, which may contribute further to infection suppression. The IC50 of chloroquine for inhibition of SARS-CoV in vitro is 8.8 micromolar which would require higher concentrations than typically delivered in malaria. Importantly, the suppressive effects are observed when the cells are treated with chloroquine either before or after exposure to the virus, suggesting both prophylactic and therapeutic treatment paradigms could be employed (10, 11). The work by Kayaerts looked at human coronavirus OC43 which causes neonatal death in mice. Treatment with chloroquine of pregnant mothers provided a 98.6% protection against death in newborn mice. This is in the only in vivo demonstration of chloroquine efficacy against a CoV. DeWilde et al. screened a library of 348 FDA-approved drugs for anti- MERS-CoV activity in cell culture and only four compounds (chloroquine, chlorpromazine, loperamide, and lopinavir) were found to inhibit the viral replication (50% effective concentrations, EC50 3–8 lmol/L) (12). The protective activity of chloroquine against CoVs such as SARS, MERS and COVID-19 has not yet been established in animal models.

2.2d Chloroquine is active against COVID-19/ SARS-CoV-2: A recent paper from Wuhan China isolated SARS-CoV-2 (the virus that causes COVID-19 disease) and tested 6 modern antiviral drugs and chloroquine and found that the best suppressors of viral infection were remdesivir (IC50 0.77 μmol) and chloroquine (IC50 1 μmol) (13). Only chloroquine given at 10 μM was able to suppress infection either with pretreatment, at the time

of infection, or after infection occurred. This has led to clinical trials and off label use of chloroquine in China (Dr. Amaravadi personal communication with scientists in China). There are Chinese guidelines for the use of chloroquine 500 mg bid for the treatment of COVID-19 (Ref). In addition, an update provided by Chinese physicians suggests initial experience with chloroquine and/or hydroxychloroquine have been positive (ref). Hospitals have run out of chloroquine, and doctors are not confident on proper dosing of hydroxychloroquine. Careful clinical trials with optimized chloroquine derivatives would be well received in a hot zone.

2.3 Clinical experience with high dose hydroxychloroquine in cancer patients

In contrast to CQ, which can produce blindness at high cumulative doses, our recent body of work has demonstrated that high dose HCQ can be administered safely to humans for months. Our work on autophagy as a resistance mechanism to cancer therapy had identified CQ derivatives as potential anti-cancer agents (14). Since HCQ has had a longer track record of dose escalation and chronic dosing in rheumatoid arthritis and lupus, we chose HCQ as our lysosomal autophagy inhibitor to test in combination regimens in cancer patients. We reported the first 6 phase I dose escalation clinical trials involving HCQ in combination with FDA approved anti-cancer drugs in refractory stage IV cancer patients (15-20). In most patients on these trials we were able to escalate the dose of HCQ to 1200 mg per day and dose patients in some cases safely for more than one year. In over 220 patients treated across multiple studies the rate of grade 3-4 non-hematological toxicities was < 10%. Most of these had more to do with the severity of the cancer and would likely not be seen in a healthy population. Specifically, no retinal, cardiac, neurological, hepatic or renal toxicity was observed. Hematological toxicities could be attributed to the other cancer drug (chemotherapy) that HCQ was paired with, and the most common side effects included manageable gastrointestinal symptoms such as bloating, diarrhea, constipation and mild non-bloody diarrhea.

2.4 Low dose versus high dose HCQ

In HCQ studies in cancer patients we conducted population pharmacokinetic studies and pharmacodynamic studies and determined that 800-1200 mg daily was required to effectively and consistently impair the lysosome in peripheral blood mononuclear cells. Our PK studies determined that it took roughly 2 weeks to achieve steady state in cancer patients. For these reasons there is rationale to propose a high dose (600 mg po bid) prolonged schedule treatment (2 weeks). In contrast an in vitro study recently published which included PK-PD modeling extrapolated from published PK studies indicated that HCQ was very active against COVID-19 but only 400 mg po bid X1 followed by 200 mg po bid for 5-10 days was enough for treatment. A recent non-randomized open label French trial Geuret et al Int J Antimicrobial Agents 2020) showed that 600 mg qd of HCQ cleared virus in 70 % of mildly ill hospitalized patients compared to 12.5% at 6 days of control patients. This generates a major question in how to use this agent in different populations that can best be answered in this two-part placebo controlled randomized trial.

3.0 PARTICIPANT SELECTION

The inclusion and exclusion criteria apply to both patient (PATCH 2) and health care worker (PATCH 3) populations unless indicated otherwise.

3.1 **PATCH 2 and PATCH 3 Inclusion Criteria** (See Study Process Flows)

- Willing and able to provide informed electronic consent via DocuSign
- Willing to report compliance with HCQ or Placebo (“tablets”) in the form of an on-line journal and participate in other forms of self-reporting (e.g., symptom tracker and experience log)

- Willing and able to go to designated areas for testing (COVID-19/SARS-CoV-2 and/or serologic) and/or administer at home testing kits for study data collection purposes.
- Must be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels
- Must have adequate baseline organ function
- Subjects meeting the following criteria by Sub-Study:

  PATCH 2 Inclusion (Sub-Study 1): 50-75 years of age; self-reporting as having a fever within four days prior to time of enrollment; and not requiring hospitalization. Enrolled individuals will undergo testing for COVID-19 and sent home for self-quarantine. Patient must be willing and able to provide informed consent, agree to testing for COVID-19 at time of enrollment to confirm diagnosis, at the end of treatment (Day 15, 16 or 17) and two weeks after the end treatment (Day 29, 30 or 31) where Day 1 is defined as the first day blinded study drug is taken by the patient. (See Appendix- PATCH2 process flows)

  PATCH 3 Inclusion (Sub-Study 2): Currently employed as a health care worker (Medical Doctor, MD; Doctor of Osteopathic Medicine, DO; Nurse Practitioner, NP; Physician's Assistant, PA; and Registered Nurse, RN or other members of the medical care team with significant COVID-19 exposure); asymptomatic and presumed negative for COVID-19 (no confirmatory testing conducted); scheduled for an average of $\geq$20 hours per week of clinical care over the next two months (or equivalent indicating at least part-time employment). Participant will be asked to comply with their employer's potential or confirmed COVID-19 incident protocol and must agree to undergo COVID-19 testing per standard of care using an FDA approved method upon the presentation of symptoms indicative of an influenza like illness; if a confirmatory COVID-19 diagnosis is given, participant will be offered to cross-over to HCQ 600 mg qd for 14 days. At the end of the 60-day medication period, participants remaining undiagnosed for COVID-19 will undergo virus and serology testing. (See Appendix- PATCH3 process flows)

PATCH 2 & PATCH 3 Combined Exclusion Criteria
(See Study Exclusions and Content Job Aid)

- Allergy to hydroxychloroquine, 4 aminoquinolines, or quinine
- Known G6PD deficiency
- Pregnant or lactating or intention of becoming pregnant during the study as self-reported during enrollment screening
- Receiving any trial treatment drug for 2019-nCoV within 14 days prior to screening evaluation (off label, compassionate use or trial related)
- Known retinal disease including but not limited to macular degeneration, retinal vein occlusion, visual field defect, diabetic retinopathy
- History of interstitial lung disease severe emphysema or asthma, or chronic pneumonitis Current diagnosis of porphyria or psoriasis
- Serious intercurrent illness that requires active intravenous therapy, intense monitoring, or frequent dose adjustments for medication including but not limited to infectious disease, cancer, autoimmune disease, cardiovascular disease

- Have undergone major abdominal, thoracic, spine or CNS surgery in the last two months, or plan to undergo surgery during study participation
- Is receiving cytochrome P450 enzyme-inducing anticonvulsant drugs (i.e. phenytoin, carbamazepine, Phenobarbital, primidone or oxcarbazepine) within four weeks of the start of the study treatment
- Currently taking digoxin
- History or evidence of increased cardiovascular risk including any of the following:
    - Left ventricular ejection fraction (LVEF) < institutional lower limit of normal. Baseline echocardiogram is not required
    - Current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment
    - Current ≥ Class II congestive heart failure as defined by New York Heart Association
- Deemed unable to participate for medical reasons identified by Co-PI and study staff

4.0 PARTICIPANT REGISTRATION/PROCEDURES

The following information is to be provided at the time of registration to the trial:

<u>Participant Identification</u> Information for PATCH 2 & PATCH 3:

- Participant initials (first and last)
- Participant's chronic medical problems
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- State of residence
- County of residence
- Cell phone number and alternate numbers
- Email address

<u>Participant Identification</u> Information for PATCH 2 Only (Sub-study 1): Identify the number of fulltime inhabitants at the residence where the participant will stay during the 14-day self-quarantine as well as ages and sex of each co-inhabitant and relationship to the study participant.

Participant Procedure for PATCH 2 (Sub-Study 1) *(See study process flows)*

1. Interested participants self-refer for study by completing online eligibility checklist on study portal (www.patchstudy.com)
2. Review inclusion and exclusion criteria: participant is 50-75 years of age and self-reported as having a fever within the last four days will undergo swab testing for COVID-19 per clinical care guidelines and approach, and then sent home for a self-imposed quarantine
3. Reviews the study and the Informed Consent Form with the subject and obtains informed consent via DocuSign
4. Participant study ID is assigned, and subsequently, randomized into a study arm (HCQ or placebo).
5. Package containing blinded study drug, study journals (medicine log, symptom tracker and experience log) and study documents (details on aims, design, consent forms, and any additional instructions) delivered to address provided by participant as place of residence during period of self-quarantine. Day 1 is defined as the first day the blinded study drug is taken by the participant
6. Lab provides participant's COVID-19 test results to designated Co-PI with designee
7. PI or designee calls participant informing them of result, discussing how to proceed on the trial (if positive, continue taking medication; otherwise, stop) and documenting discussion.
8. Each day, participants will record 1) temperature (to be reported twice daily, either via thermometer or self-report); 2) time medication taken; 3) any symptoms and AEs; and 4) if any co-inhabitants develop symptoms and/or become positive for COVID-19 (confirmed by accepted testing methods)
9. Three times a week, participants will be called by clinical research coordinators to assess AEs and symptoms with all discussions well-documented. Clinical research coordinators may clinically escalate any medical determinations to Co-PI
10. After Day 14, which marks the end of the treatment period, participants will no longer be expected to continue self-reporting information into the study portal. Participant will undergo follow-up testing for COVID-19 at two additional time points. The first will be either day 15, 16 or 17, with the second on either on day 29, 30 or 31
11. If during active participation, the participant reports worsening of symptoms related to COVID-19 from baseline, this is reported to the PI for further clinical evaluation

Participant Procedure PATCH 3 (Sub-Study 2) *(See study process flows)*

1. Interested participants self-refer for study by completing online eligibility checklist on study portal (www.patchstudy.com)
2. Review inclusion and exclusion criteria:
    - Currently employed as a health care worker (Medical Doctor, MD; Doctor of Osteopathic Medicine, DO; Nurse Practitioner, NP; Physician's Assistant, PA; and Registered Nurse, RN or other members of the medical care team with significant COVID-19 exposure);
    - Asymptomatic and presumed negative for COVID-19 (no confirmatory testing conducted);
    - Scheduled for an average of >20 hours per week of clinical care over the next two months (or equivalent indicating at least part-time employment).
    - Willing to comply with their employer's potential or confirmed COVID-19 incident protocol
    - Agrees to undergo COVID-19 testing per standard of care using an FDA approved method upon the presentation of symptoms indicative of an influenza like illness (if a confirmatory COVID-19 diagnosis is given, participant will be offered to cross-over to HCQ 600 mg qd for 14 days.)
3. Reviews the study and the Informed Consent Form with the subject and obtains informed consent via DocuSign
4. Participant study ID is assigned, and subsequently, randomized into a study arm (HCQ or placebo).

5. Package containing blinded study drug supply, study journals (medicine log, symptom tracker and experience log) and study documents (details on aims, design, consent forms, and any additional instructions) are delivered to the address provided by participant as place of residence during study. Delivery of blind study drug supply will occur in two shipments, each containing a 30-day supply. Day 1 is defined as the first day the blinded study drug is taken by the participant.
6. Each day active medication is taken (HCQ or placebo), participants will record 1) temperature (to be reported twice daily, either via thermometer or self-report); 2) time medication taken; and 3) any symptoms and AEs.
7. Every week, clinical research coordinators will review the study portal to assess for AEs and indication of reported symptoms indicative of influenza like illness. The research coordinator will also review self-reported fever and/or temperature. If COVID-19 symptoms are evident, the research coordinator will outreach to the HCW (at clinic or by phone). Clinical research coordinators may clinically escalate any medical determinations to Co-PI following study portal review.
8. The HCW also has access to the study coordinators via the study phone number. If the HCW feels symptomatic, then he/she should call the clinical research coordinator team, and document symptoms in the study portal. Clinical research coordinators may clinically escalate any medical determinations to Co-PI.
9. If during the study symptoms indicative of an influenza like illness present, participant will be asked to comply with their employer's potential or confirmed COVID-19 incident protocol and be tested for COVID-19 by an accepted method. Participants negative for COVID-19 continue with the assigned blinded study drug regimen.
10. If confirmed COVID-19 diagnosis, participant will be unblinded. Participants assigned to HCQ can continue with medication schedule. Individuals assigned to the placebo arm will be offered the opportunity to cross-over to HCQ 600 mg daily for 14 days. Individuals will be expected to continue self-reporting temperature, time medication taken and any symptoms/AEs into the study portal while taking active HCQ medication.
11. Participants who remain undiagnosed for COVID-19 by the end of the medication period (Day 60) will be asked to undergo COVID-19 and serology testing for IgM/IgG on either Day 61, 62, or 63.

5.0 RANDOMIZATION

Randomization will be done using computer generated randomization numbers. Randomization will be stratified by age. Treatment **will start upon receipt of the product by the patient after enrolling in the study, notifying the pharmacy and having the product/placebo sent.**

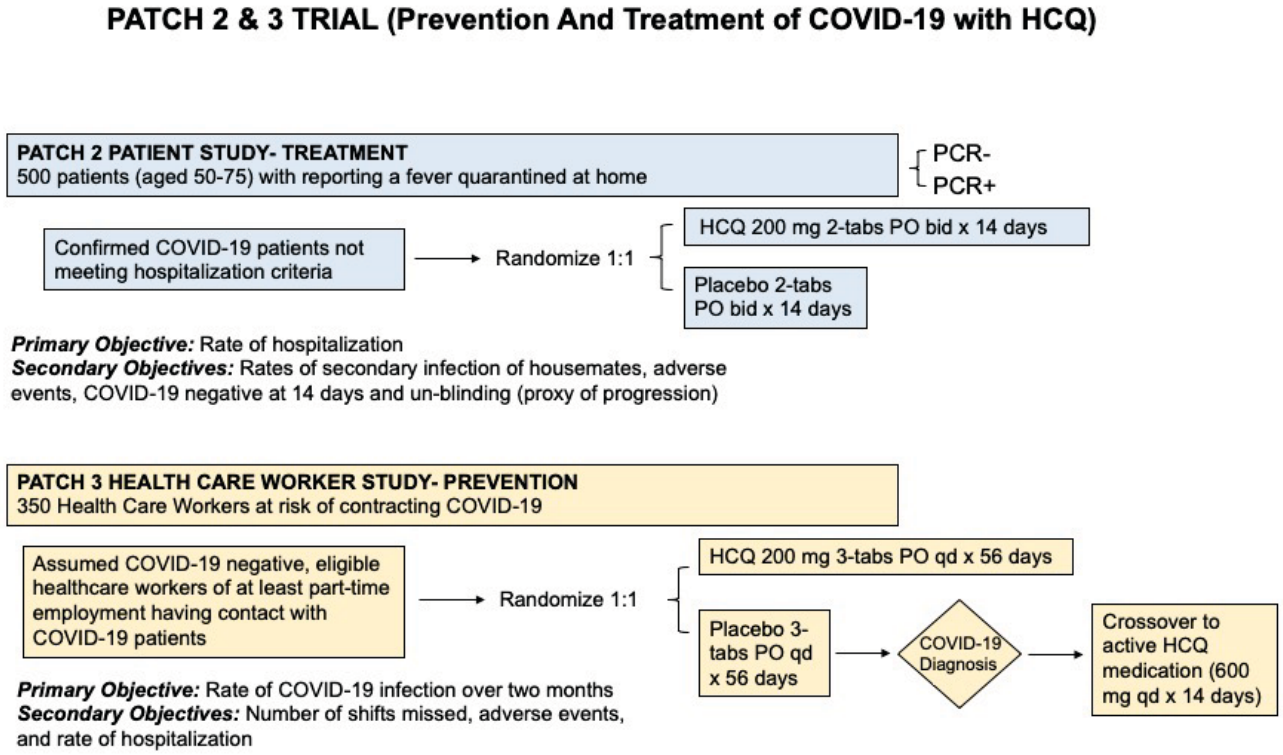
Blinding: Both sub-studies will have a double-blind placebo-controlled design.

Unblinding: (*See study process flows*)

- For PATCH 2 (Sub-study 1), If patient in PATCH 2 experiences worsening of symptoms, a Co-PI will be notified to take appropriate clinical action. Co-PI can choose to unblind for clinical determinations.

- For PATCH 3 (Sub-Study 2), confirmation of a COVID-19 diagnosis would trigger the unblinding pathway for a participant (for details see *Section 4.0, Participant Registration, PATCH 3 (Sub-Study 2) Participant Procedure*).

Figure 1. Schematic of PATCH 2 and PATCH 3 Study Designs



6.0 TREATMENT PLAN

PATCH 2 (Sub-Study 1) 500 patients with 2 interim analyses

- *Arm 1 (HCQ):* Hydroxychloroquine 400 mg bid (two 200 mg tablets taken twice a day; totaling 800 mg per day) for 14 days
- *Arm 2 (Placebo):* Two pills taken twice daily (totaling four pills each day) for 14 days

PATCH 3 (Sub-Study 2) 350 participants with 2 interim analyses

- *Arm 1 (HCQ):* Hydroxychloroquine 600 mg qd (three 200 mg tablets taken once day) for 60 days
- *Arm 2 (Placebo):* Three pills once a day for 60 days with optional crossover to HCQ 600 mg qd for 14 days upon presentation of symptoms indicative of an influenza like illness and subsequent confirmatory diagnosis for COVID-19

7.0 DETAILS OF STUDY TREATMENT

7.1a Hydroxychloroquine

Mechanism of Action: The mechanism of action is not fully understood. Previously it was thought that HCQ and other chloroquine derivatives are weak bases that deacidify lysosomes through purely chemical basis. Recently our group has identified the missing molecular target of HCQ as palmitoyl protein thioesterase 1 (PPT1).

Storage and formulation: HCQ tablets are manufactured by a number of generic drug companies as well as Novartis. Each tablet contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base). It is dispensed in a tight, light-resistant container as defined in the USP/NF.HCQ should be stored at room temperature up to 30° C (86° F).

Pharmacokinetics: The PK of HCQ is characterized by a large volume of distribution, binding to red blood cells, and long time to peak concentration and steady state. Population PK studies in cancer patients have demonstrated dose proportional change in exposure.

Administration: Hydroxychloroquine is an oral medication available in 200 mg tablets. HCQ will be supplied by the study team via Avella Pharmacy. Tablets of HCQ are available in 200 mg strength. In PATCH 2 (**Sub-Study 1)**, HCQ will be administered in divided doses (every 12 hours) with each dose consisting of two 200 mg tablets (or 400 mg bid), totaling 800 mg daily. **The two daily doses of HCQ should be taken 12 hours apart, for example, 9 am and 9 pm.** In PATCH 3 (**Sub-Study 2)**, HCQ will be administered as three 200 mg tablets taken once a day (600 mg qd) at the same time. Hydroxychloroquine sulfate tablets should be taken with a meal or a glass of milk. Participants will be required to keep a study journal and document the time HCQ doses are taken; journal completion will be reviewed by study staff. The HCQ schedule may be adjusted if necessary, to minimize gastrointestinal side effects.

For complete information please refer to the package inserts at http://dailymed.nlm.nih.gov/dailymed/

7.1b Placebo

There will be no active medication in the placebo tablets, which will be supplied by the study team via Avella Pharmacy and mailed to the participant's provided address. In PATCH 2 (Sub-Study 1), placebo will be administered in two divided doses (every 12 hours) with each dose consisting of two tablets, totaling four tablets daily. The two daily doses of placebo should be taken 12 hours apart, for example, 9 am and 9 pm. In PATCH 3 (Sub-Study 2), placebo will be administered as three tablets taken once a day at the same time. Tablets should be taken with a meal or a glass of milk. Participants will be required to keep a study journal and document the time placebo doses are taken. The dosing schedule may be adjusted if necessary, to minimize, gastrointestinal side effects. Journal completion will be reviewed by study staff.

7.2 Concomitant Medication, Drug-Drug interactions and Procedures

Participants will be instructed not to take any medications, including over the counter products, without first consulting with the study team. The study phone number and additional contact information will be provided with the welcome packet, allowing for the study team to be contacted if the participant is seen by a health care provider or medications are changed.

Drug Interactions

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

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

Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with HCQ.

Cyclosporin: An increased plasma cyclosporin level was reported when cyclosporin and HCQ were co-administered.

Because HCQ has known effects on P450 enzymes, participants requiring anti-convulsants may be treated with any of the non-enzyme inducing anti-convulsants which include: felbamate, valproic acid, gabapentin, lamotrigine, tiagibine, topiramate, or levetiracetam. Due to the fact that both zonisamide and HCQ accumulate in red blood cells, zonisamide should be avoided if possible. Other concomitant medications may be permitted.

The following medications and treatments are not allowed during the study. The sponsor must be notified if the participant receives any of these during the study:

1. PATCH 2 and 3 (**Sub-Studies 1 and 2):** Any investigational or off-label antiviral therapy

2. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, except as noted in the exclusion criteria. Concurrent use of hormones for noncancer-related conditions (e.g. insulin for diabetes, hormone replacement therapy) is acceptable.

3. Immunosuppressive medications, including, corticosteroids at doses exceeding 10mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-alpha blockers. Use of immunosuppressive medication for the management of study treatment-related AEs or in subjects with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted

4. Live attenuated vaccines during the study through 180 days after the last dose of both drugs

7.3 Duration of Protocol Treatment and Follow-up.

PATCH 2 (Sub-Study 1) duration of treatment is 14 days (two weeks) with follow-up with COVID-19 testing on Day 15, 16 or 17, and Day 29, 30 or 31 where Day 1 marks the first day blinded study drug is taken by the participant.

PATCH 3 (Sub-Study 2) duration of treatment is up to 60 days with an option to cross-over for participants taking placebo upon presentation of symptoms indicative of an influenza like illness and testing positive for COVID-19 (or a COVID-19 diagnosis is made by a health care provider). Participants remaining undiagnosed for COVID-19 by Day 60 will undergo testing for SARS-CoV-2 and IgM/IgG antibodies on either Day 61, 62, or 63. The maximum study medication duration and follow-up testing is 63 days.

7.4 Crossover from Control to HCQ arm.

PATCH 2 (Sub-Study 1): There is no cross-over.

PATCH 3 (Sub-Study 2): Participants that develop symptoms indicative of an influenza like illness and diagnosed with COVID-19 will be unblinded. If they were assigned to the placebo arm and deemed appropriate, they will be offered the option crossover to HCQ 600 mg qd for 14 days.

8.0 TOXICITY CRITERIA, MONITORING, DOSE DELAYS AND MODIFICATIONS

8.1 Toxicity Criteria

This study will utilize the DAIDS table for grading adult adverse events (AEs). A copy of the DAIDS grading system is available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. All appropriate treatment areas should have access to a copy of the DAIDs grading table.

8.2 Dose Delays

Major Events are Grade 3 and 4 hematologic and non-hematologic toxicities that are not treatment related. Treatment should be delayed for major events if HCQ may further complicate the non-treatment related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ Grade 2 or ≤ Baseline). For treatment-related toxicities and major events, if toxicity is not resolved in ≤ 7 days, participant will be taken off treatment unless there is an exception granted by the medical monitor.

8.3 Ocular toxicity

The only toxicity that requires discontinuation of HCQ is retinopathy. Published literature indicates HCQ retinopathy is idiosyncratic and is uncommon in patients receiving HCQ for less than a few years. Our ongoing study of dabrafenib, trametinib, and HCQ (BAMM; NCTNCT02257424) found no clinically meaningful ocular toxicity in 10 patients studied extensively with serial ocular exams (21). Therefore, we have not included mandatory ocular exams in this protocol. However, if there is a visual field deficit, retinal vein occlusion, serous retinopathy, bullseye retinopathy, or retinal detachment, HCQ should be permanently discontinued.

8.4 Participant Safety Monitoring and Data Collection

Adverse events will be captured via self-report by participants within the study portal. Participants are instructed to contact the study team at the phone number provided in the Welcome Packet to report all adverse events. The study team will reach out to the participant to gather additional information surrounding the adverse event in order to complete DAIDS grading if necessary. Additional information pertaining to the adverse event will be captured within the study portal by the study team and reviewed by the PI's for causality to study drug. Adverse events meeting seriousness criteria will be reported to the IRB as noted below.

PATCH 2 (Sub-Study 1):

Clinical Symptom Monitoring: Participants will be contacted three times per week to assess AEs and COVID-19 symptoms and collect/review self-reported AE's. Worsening COVID symptoms and/or new or worsening AE's will be reviewed by the PI's for causality to study drug.

Temperature Measurements: Home quarantined participants will be asked to report twice daily either presence of fever or temperature and record the measurements.

COVID-19/SARS-CoV-2 Testing: On Days 15-17 and 29-31, participants will undergo follow-up testing for COVID-19.

Pill Count and Journal: Participants will be contacted three times per week and following the end of treatment to compare data entry on the portal and collect any missed entries over the phone.

Monitoring Co-Inhabitants: Participants will be contacted three times per week to identify if any co-inhabitants have developed symptoms and/or tested positive for COVID-19. Participants will also be asked to provide a description of co-inhabitants' symptomology, and time of positive testing for COVID-19 via self-reporting.

PATCH 3 (Sub-Study 2):

Adverse events will be captured solely based on participant self-reporting via the study portal and/or by calling the study team at the number provided in the Welcome Packet. The study team will review the portal for self-reported AE's not previously reported to the study team. New AEs not previously reviewed which cannot be

graded based upon self-reported data within the portal will require follow-up from the study team to gather additional information from the participant. New or worsening AE's will be reviewed by the PI"s for causality to study drug.
COVID-19/SARS-CoV-2 testing: Upon the presentation of symptoms indicative of an influenza like illness, participants will be asked to undergo testing for SARS-CoV-2 virus. Participants undiagnosed for COVID-19 at Day 60 will also be tested for SARS-CoV-2 and IgM/IgG antibodies (via serology testing) on either Day 61, 62, or 63.
Clinical Symptom monitoring: The study team will assess AEs, symptoms, and record temperature (either reported temperature or self-report of fever) for any participants taking active medication (placebo or HCQ). Worsening COVID symptoms and/or new or worsening AE's will be reviewed by the PI's for causality to study drug. The rate of conversion to receiving a positive COVID-19 test result in each arm at the 2-month mark will be used to assess the primary endpoint.
Pill count and Journal: Participants will be contacted to compare data entry on the portal and collect any missed entries over the phone.

Participants will be instructed to call 911 upon immediate presentation of the following symptoms as identified by the CDC as requiring emergency action: bluish lips or face; new confusion/dizziness or inability to arouse; persistent pain or pressure in the chest (not caused by coughing); and difficulty breathing (including severe shortness of breath and single word speech).

Participant confidentiality is strictly held in trust by all personnel granted access to the trial data. Therefore, the study data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to unauthorized parties.

The study investigators and study team, the research sponsor and its designees, personnel from ProHealth with authorized access to study data, government agencies, reviewing Institutional Review Board (IRB), regulatory agencies and/or company supplying study product may inspect all documents and records required to be maintained by the sponsor, including but not limited to, clinical, pharmacy and lab records for participants enrolled in the study. All applicable parties will permit access to such records.

The participant's study contact information will be securely stored within the online study portal 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 as dictated by the reviewing IRB and institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at UHG R&D in a de-identified manner. This will not include participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured, and password protected. At the end of the study, study data will be de-identified and may be made public.

UHG R&D follows the standards of HITRUST for data management and data governance. Our data always remains encrypted in transit and at rest. Our data has managed access with expiration dates, and we follow minimum use guidelines with regard to dataset usage. UHG R&D uses Google Cloud Platform (GCP) for the storage of all encrypted data. UHG R&D has a dedicated Data Integration team for data management and data governance objectives and this team serves as the "Gate Keeper" of identifiable data. UHG R&D utilizes a "Clean Room" for data acquisition and isolation of identifiable data. The Clean Room is an environment that requires elevated access permission by a separate set of credentials. Access is limited to a small scope of approved "white

listed" locations and to specific individuals filling a specific list of objectives associated with the Data Services department at UHG R&D.

8.5 Hydroxychloroquine Dose Reduction

Any Adverse Event Grade 3 or higher requires HCQ to be withheld. Treatment may be resumed once toxicity is ≤ Grade 2 according to the below Dose Reduction Schema (Table 1). If toxicity does not resolve or improve to ≤ Grade 2 within 7 days, participant will be withdrawn from active treatment unless granted an exception by the Medical Monitor. Medical Monitor should be notified of all toxicities requiring dose withholding or dose adjustments via email or phone.

Any AE = Grade 2 and **attributed as possibly, probably or definitely related to HCQ** will result in a dose reduction of HCQ as described in Table 1.

If AE remains = Grade 2 following the first dose reduction **and attributed as possibly, probably or definitely related to HCQ** following the second dose reduction, then the participant should discontinue treatment.

No more than 2 dose reductions are allowed. It is recommended that dose reductions occur at a minimum of 48 hours apart.

Table 1: Dose Reduction Schema

Sub-Study	Dose mg/day	First dose reduction	Second Dose reduction
1 (PATCH 2)	400 mg (two tablets) twice daily	400mg (two tablets) once daily	200 mg (one tablet) once daily
2 (PATCH 3)	600 (three tablets) mg daily	400 mg (two tablets) once daily	200 mg (one tablet) once daily

Reported non-serious toxicities attributable to HCQ include nausea, anorexia, vomiting, constipation, diarrhea and rash. For any of these AEs occurring at Grade < 2, HCQ may be continued and the AE managed with supportive care. For **Any AE** with a Grade ≥ 3, HCQ will be held until the toxicity improves to ≤ Grade 2, after which HCQ may be restarted at a reduced dose as described in Table 1.

Example: Management of diarrhea in randomized subjects

Grade 1: (an increase in stool up to 3 per day) results in no change to HCQ

Grade 2: (an increase in stool up to 4-6 per day) results in a Dose Reduction according to Table 1

Grade 3+: (an increase in stool up to 7 or more per day) results in Withholding of HCQ until AE at Grade level 2 or less, followed by a reduction in dose per Table 1.

9.0 ADVERSE EVENTS AND REPORTING

The timely reporting of adverse events (including toxic deaths) is required by the Food and Drug Administration. The reporting of toxicities is part of the data reporting for this study. The investigator is responsible for ensuring that all adverse events (AEs) and serious adverse events (SAEs) as self-reported during the study are collected and reported to the FDA, appropriate IRB(s), in accordance with CFR 312.32 (IND Safety Reports).

9.1 Adverse Events Definition

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the study that does not necessarily have a causal relationship with this treatment. 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 or considered by the investigator to be of clinical significance

9.2 Adverse Events Reporting Period

The study period during which adverse events must be reported is defined as the period from the initiation of the first study treatment to the last administration of study treatment.

9.3 Adverse Events Post Study

All unresolved adverse events at the conclusion of the dosing period should be followed by the investigator until the event is resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled contact, the study staff should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study.

9.4 Adverse Events Assessment and Recording

At each contact with the participant, the investigator or study staff will assess for information on adverse events and review all self-reported AE's via the study portal. Information surrounding adverse events should be recorded in the study portal. Related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the study portal and grouped under one diagnosis as applicable.

Adverse events can be spontaneously reported or elicited during open-ended questioning. Adverse events will be measured and graded in accordance with the document entitled *Division of AIDS (DAIDs) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017* issued by the US Department of Health and Human Services. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

9.4.1 Relationship to Study Drug

The causal relationship can be one of the following:

- Related: There is a possible, probable or definite causal relationship between study drug administration and the AE
- Not related: There is evidence suggesting a causal relationship to something other than the study drug.

9.5 Abnormal Laboratory Values

This trial does not require any safety laboratory assessments. However, in the event a participant has a standard of care labs completed which are self-reported and meet the DAIDS criteria for Grade 2 or greater, and cannot be attributed to another cause, study drug should be held and or reduced in accordance with section 8 above.

9.6 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.7 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.0 SERIOUS ADVERSE EVENTS

A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- a suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug
- an important medical event

- All Serious Adverse Events (SAEs) that occur following the participant’s written consent to participate in the study must be reported, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure.
- Following the participant’s written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs should be followed to resolution or stabilization. Serious adverse events that are ongoing at the end of the study period must be followed to determine the outcome. Any serious adverse event that occurs after the study period and is at least possibly related to the study treatment or study participation should be recorded and reported immediately to the Medical Monitor and the IRB per the IRB reporting guidelines.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

10.1 Important Medical Event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

10.2 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

10.3 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 12.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

10.4 Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 120 days after the last dose of study drug, the investigator must immediately notify the Sponsor in accordance with SAE reporting guidelines. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, details of the birth, and the presence or absence of any congenital anomaly/birth defect or maternal and/or newborn complications in a child born to a female subject exposed to the study drug should be reported as an SAE. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported. In order for Sponsor or designee to

collect any pregnancy surveillance information from the female partner must sign an informed consent form for disclosure of this information. Any pregnancy that occurs in a female partner of a male study participant should be reported. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

11.0 IRB NOTIFICATION

The UHG IRB requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Deaths occurring for participants on-study and within 30 days of study drug administration that are considered unforeseen and indicates participants or others are at increased risk of harm (i.e. unexpected and probably/definitely related), must be reported to the IRB within 24 hours of notification.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

For clinical drug trials, the following events are also reportable to the IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human participants.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - -- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - -- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.

-- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.

- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of participants.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant. Reports requiring IRB consideration or consultation are to be emailed to Tracy Ziolek, Vice President, Human Research Affairs at UnitedHealth Group at tracy_ziolek@uhg.com.

11.1 Reporting Process to IRB.

Principal Investigators are encouraged to submit reports of unanticipated problems posing risks to participants or others via a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation) within 7 working days to the UnitedHealth Group Office of Human Research Affairs (OHRA). Participating sites should follow local, institutional guidelines on Event Reporting. For reportable deaths, the initial submission to the IRB may be made by contacting Tracy Ziolek at tracy_ziolek@uhg.com.

This study is IND exempt and reporting to the FDA is voluntary using a MedWatch 3500 or via the FDA's website for voluntary reporting.

12.0 PARTICIPANT WITHDRAWAL

Each participant has the right to withdraw from the study at any time without prejudice. The investigators may discontinue any participant's participation for any reason, including adverse event or failure to comply with the protocol. Should a participant withdraw from the study, the reason(s) must be recorded within the study portal. Reasons for withdrawal include the following:

- Progression of Disease: Remove participant from study at the time progressive disease is documented.
- Extraordinary Medical Circumstance: If at any time the treating physician feels constraints of this protocol are detrimental to the participant's health the participant should be withdrawn.
- Participant's refusal to continue treatment: In this event, document the reason(s) for treatment refusal.
- Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).
- Delay in treatment > 7 days due to toxicity or ongoing toxicity ≥ Grade 2 following two (2) dose reductions.

13.0 MEDICAL MONITORING

It is the responsibility of the investigators to oversee the safety of the study at their site. This safety monitoring will include careful assessment and appropriate reporting of adverse events, as noted above, as well as the construction and implementation of a site data and safety monitoring plan. Medical monitoring by an independent clinician, will include a regular assessment of the number and type of serious adverse events on a periodic basis.

13.1 Study Monitoring Plan

This study will be monitored by the investigators and sub-investigators, as appropriate. Such monitoring will include at least weekly meetings of the study team to review accrual, toxicity, SAEs. Dose escalations and study finding. In addition, the PI will ensure that data are completed in a timely manner and their designee will review the data for accuracy, completeness and integrity.

13.2 Auditing and Inspecting

The investigator will permit the Office of Human Research Affairs, UnitedHealth Group to review records, data and facilities at mutually agreeable times. This study will be audited on an as needed basis with a complete review occurring at completion of enrollment. If enrollment numbers are not met, audit will occur in alignment with being notified of closure of the trial.

14.0 SCHEDULE OF EVENTS

See appropriate *Process Flows* for **PATCH 2 (Sub-Study 1)** and **PATCH 3 (Sub-Study 2)**

15.0 MEASUREMENT OF EFFECT

15.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with HCQ or placebo through final assessment.

Evaluable for primary outcome: Participants who received at least one continuous week of HCQ will be evaluable for the primary outcome.

15.2 Response Criteria

PATCH 2 (Sub-Study 1): Measurement of SARS-CoV-2 positivity confirmed by an accepted testing method. Rate of hospitalization will be defined by a hospitalization occurring within 30 days of the date of participant enrollment.

PATCH 3 (Sub-Study 2): Rate of COVID-19 infection will be defined by measurement of SARS-CoV-2 identified by accepted testing methods.

16.0 STATISTICAL CONSIDERATIONS

16.1 Sample size calculation

Because we are uncertain about the outcome values for both control (placebo) and treatment (HCQ) arms of the study, we will use group-sequential methods, allowing us to stop early for both efficacy and futility. We conduct two interim analyses and a final analysis, after approximately 1/3, 2/3, and 100% of participants have completed.

PATCH 2 & 3 TRIAL

We will use the Hwang-Shih-DeCani alpha spending rules. Boundaries for efficacy and futility decisions are shown below. Futility boundaries are non-binding.

z-value ——— Boundaries ———			Information
Stage	**Efficacy**	**Futility**	**Proportion**
1	2.7819	-0.8235	0.3400
2	2.2653	0.4262	0.6800
3	1.6813	1.6813	1.0000

p-value ——— Boundaries ———			Information
Stage	**Efficacy**	**Futility**	**Proportion**
1	0.00270	0.79490	0.3400
2	0.01175	0.33497	0.6800
3	0.04636	0.04636	1.0000

PATCH 2 (Sub-Study 1), Home quarantined patients with COVID-19: We will assume the null hypothesis that in the placebo arm 70% will recover without requiring hospitalization. For the low dose HCQ cohort 95% of home quarantined patients recover without requiring hospitalization. We will continue to enroll and randomize patients at the time of testing 1:1 HCQ to control until we reach at least 100 patients with at least 50 in the low dose HCQ arm and at least 50 in the placebo arm who have tested positive COVID19. The one-sided z- test (alpha=.05) will have an at least 90% power to detect a significant difference between the groups of greater than 25% between the population rates. We estimate we will need to enroll 500 patients at the time of testing to reach the 100 patients who test positive for COVID19.

The *hypothesis* will be tested with only patients who tested positive for COVID19 using a one-sided test, with a z-score corresponds to the log of the odds-ratio for recovery between the two groups. We will obtain the estimate of the odds ratio, and 95% CI, from logistic regression. As a secondary analysis, we will stratify the analysis, and obtain separate estimates of the odds-ratio by group. However, we are not powered to test the interaction for significance, and we do not expect significance within group.

Interim analysis: We will perform two interim analyses at 34% and 68% completion, testing for early efficacy or futility, using z-score boundaries that follow Hwang-Shih-DeCani alpha spending rules. Following those rules, we have 90% power using 100% of the sample, if scenario is true.

PATCH 3 (Sub-Study 2), Prophylaxis in Health Care Workers: The transmission of SARS-COV-2 from patient to hospital worker depends on many factors including specifics of standard care to prevent transmission, but especially on the number of patients seen at a given hospital or outpatient practice. Across China the reported hospital worker infection rate is 3.8%, but in Wuhan it is reported as 58% at the height of the epidemic. We will use a 10% transmission rate as the null hypothesis (low dose group). In order for HCQ to be considered effective our alternative hypothesis will be a 1% transmission rate. With a 1:1 randomization for the HCQ to control arms we would require a total of 350 health care workers across all participating ProHealth NY and AHN sites. With the placebo group of 175 participants and the high dose HCQ arm of 175 participants, a one-sided z-test (alpha=0.05) comparing the rates in the two groups would have an at least 80% power to detect a significant difference when the difference in the population rates is at least 9%.

The *hypothesis* will be tested using a one-sided test, with a z-score corresponds to the log of the odds-ratio for the rate of transmission between the two groups. We will obtain the estimate of the odds ratio, and 95% CI, from logistic regression.

Interim analysis: We will perform two interim analyses at 25% and 50% completion, testing for early efficacy or futility, using z-score boundaries that follow Hwang-Shih-DeCani alpha spending rules. Following those rules, we have 80% power using 100% of the sample, if our 10% versus 1% scenario is true.

Z-Value Boundaries

	Boundaries		Information
Stage	**Efficacy**	**Futility**	**Proportion**
1	2.9473	-1.2318	0.2500
2	2.5825	-0.2676	0.5000
3	1.6664	1.6664	1.0000

P-Value Boundaries

	Boundaries		Information
Stage	**Efficacy**	**Futility**	**Proportion**
1	0.00160	0.89099	0.2500
2	0.00491	0.60550	0.5000
3	0.04782	0.04782	1.0000

16.2 Analysis of Secondary Endpoints.

Secondary outcomes will be analyzed as summary statistics, with group means, odds-ratios, and 95% CIs. We may conduct exploratory analyses using regression methods appropriate for each type of measure. Tests for significance of estimated parameters will not be reported as we will not be controlling for multiple testing.

PATCH 2 (Sub-Study 1): Rate of secondary infection of housemates is a binomial count by household. We will summarize the proportion or rate by group, with 95% CI. With sufficient data, we will explore subgroups, patient, and secondary patient characteristics using logistic regression. Rate of hospitalization is a binary measure. We will summarize rates by group and estimate the odds-ratio for treatment. Adverse event rates will be summarized as a count by participant, and mean count by group, and we will estimate a rate-ratio for treatment. We will summarize rates by group and estimate the odds-ratio for treatment.

PATCH 3 (Sub-Study 2): Rate of hospitalization is a binary measure. We will summarize rates by group and estimate the odds-ratio for treatment. Adverse event rates will be summarized as a count by participant, and mean count by group, and we will estimate a rate-ratio for treatment. We will summarize the count of shifts missed by group and estimate the rate ratio for treatment.

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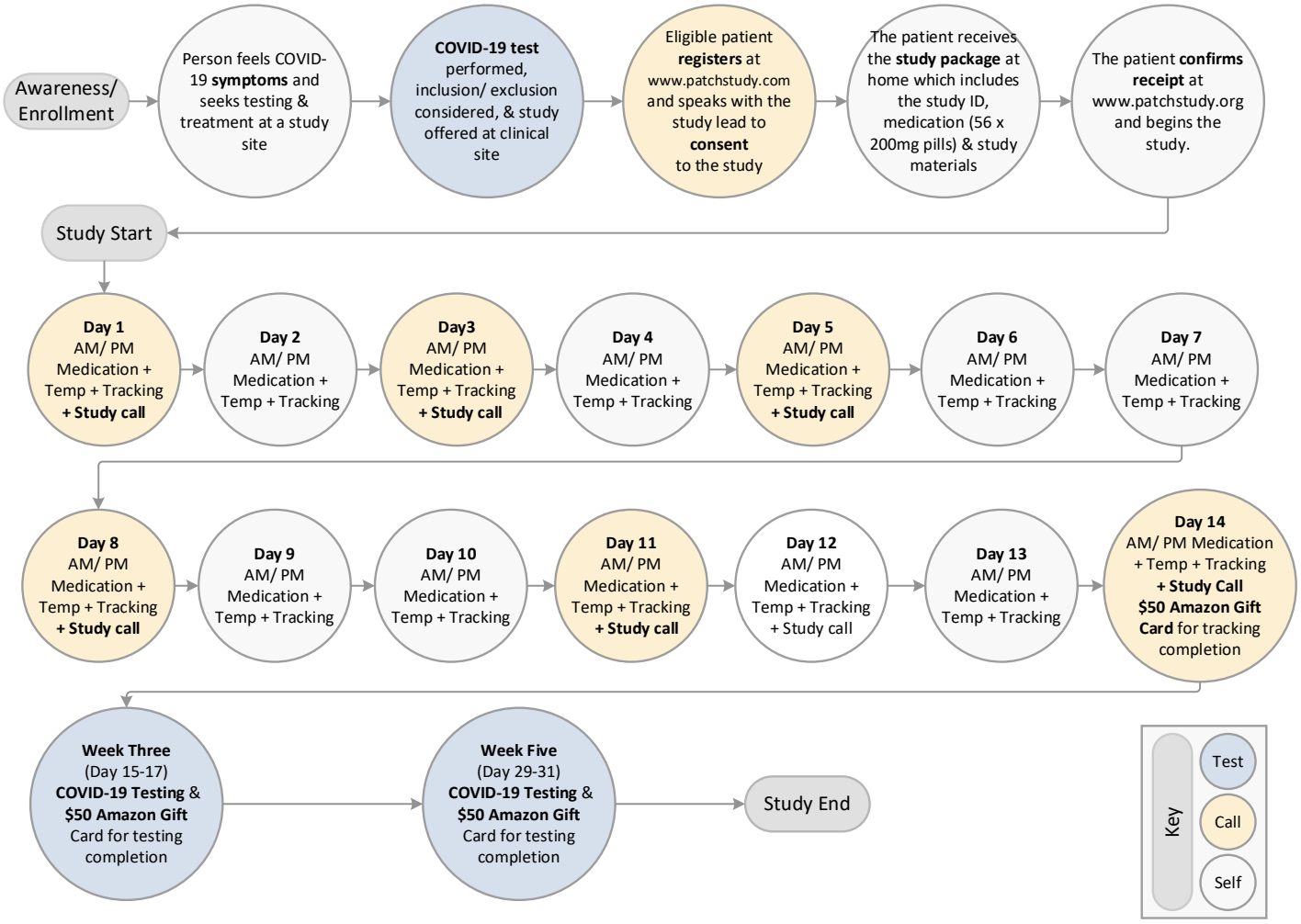
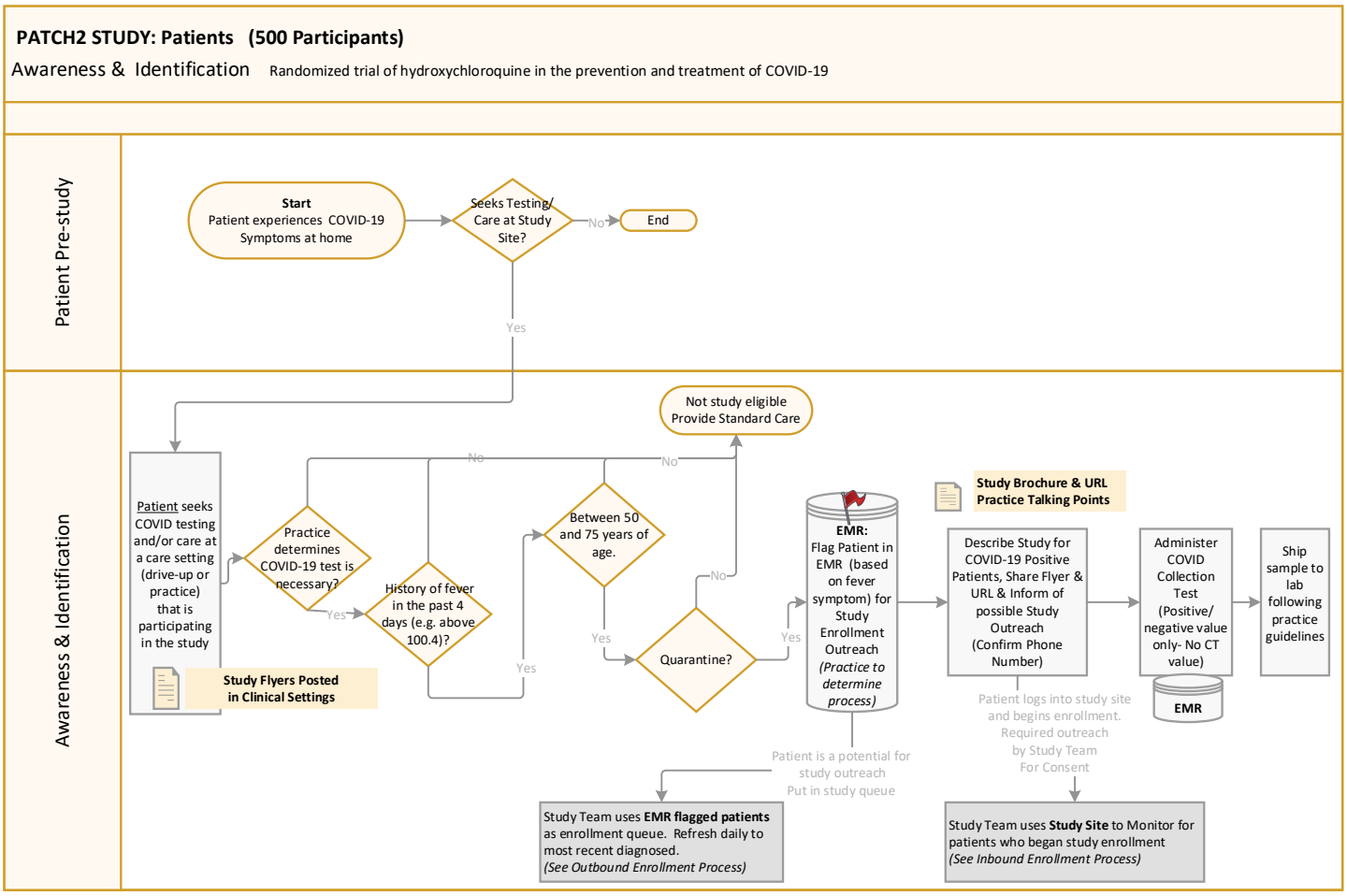
Appendix 1: PATCH 2 Process Flows

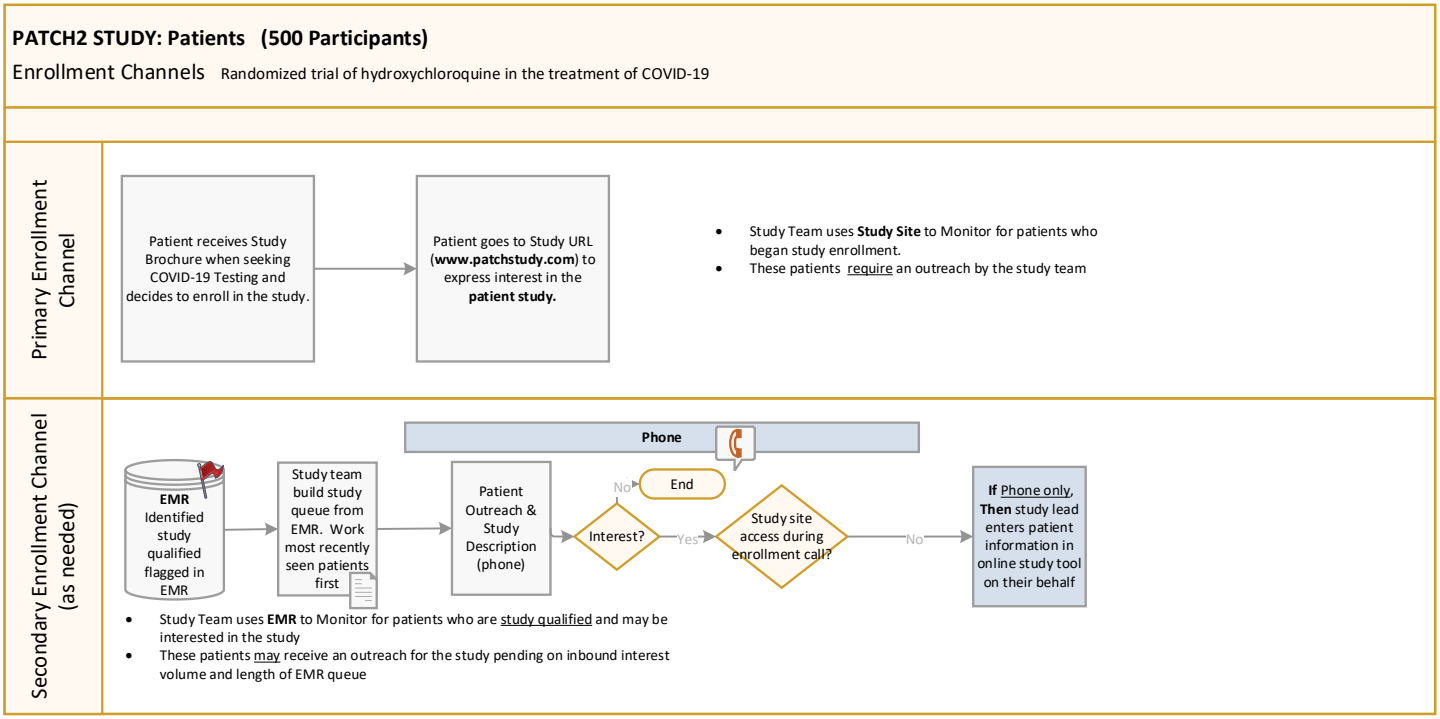
PATCH2 STUDY: Patients (500 Participants)

Randomized trial of hydroxychloroquine in the treatment of COVID-19

High-Level Patient Journey Map



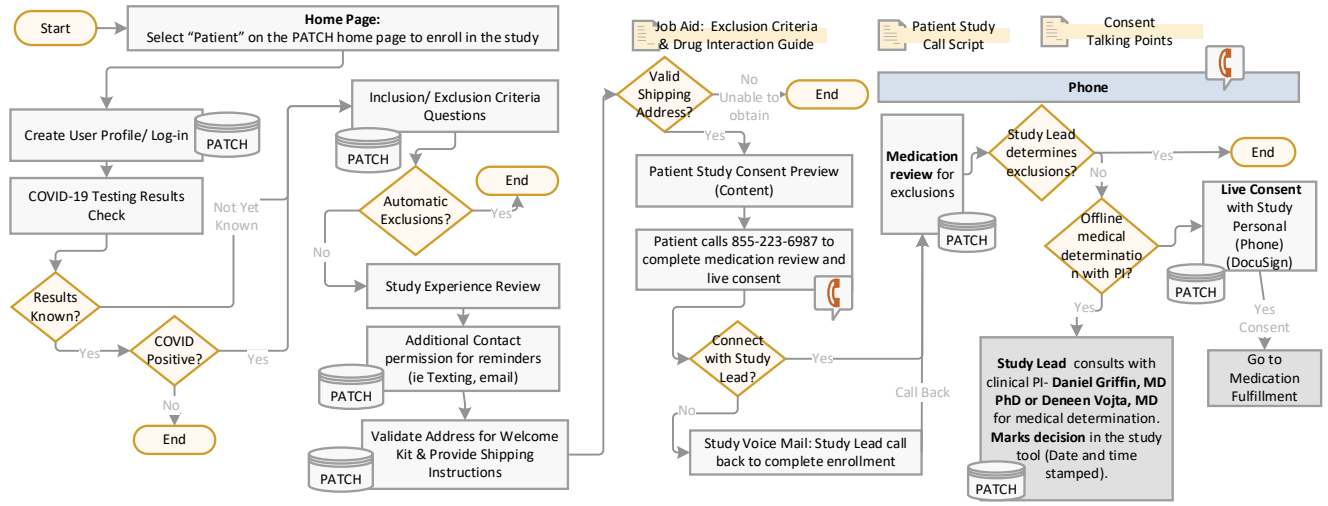

PATCH2 STUDY: Patients (500 Participants)
Awareness & Identification
Randomized trial of hydroxychloroquine in the prevention and treatment of COVID-19
Patient Pre-study
Awareness & Identification
Start
Patient experiences COVID-19 Symptoms at home
Seeks Testing/ Care at Study Site?
No
End
Yes
Patient seeks COVID testing and/or care at a care setting (drive-up or practice) that is participating in the study
Study Flyers Posted in Clinical Settings
Practice determines COVID-19 test is necessary?
Yes
No
History of fever in the past 4 days (e.g. above 100.4)?
Yes
No
Between 50 and 75 years of age.
Yes
No
Quarantine?
Yes
No
Not study eligible
Provide Standard Care
EMR:
Flag Patient in EMR (based on fever symptom) for Study Enrollment Outreach
(Practice to determine process)
Study Brochure & URL
Practice Talking Points
Describe Study for COVID-19 Positive Patients, Share Flyer & URL & Inform of possible Study Outreach (Confirm Phone Number)
Administer COVID Collection Test (Positive/ negative value only- No CT value)
EMR
Ship sample to lab following practice guidelines
Patient is a potential for study outreach
Put in study queue
Patient logs into study site and begins enrollment.
Required outreach by Study Team
For Consent
Study Team uses EMR flagged patients as enrollment queue. Refresh daily to most recent diagnosed.
(See Outbound Enrollment Process)
Study Team uses Study Site to Monitor for patients who began study enrollment
(See Inbound Enrollment Process)


PATCH2 STUDY: Patients (500 Participants)
Enrollment Channels
Randomized trial of hydroxychloroquine in the treatment of COVID-19
Primary Enrollment Channel
Patient receives Study Brochure when seeking COVID-19 Testing and decides to enroll in the study.
Patient goes to Study URL (www.patchstudy.com) to express interest in the patient study.
Study Team uses Study Site to Monitor for patients who began study enrollment.
These patients require an outreach by the study team
Secondary Enrollment Channel (as needed)
Phone
EMR
Identified study qualified flagged in EMR
Study team build study queue from EMR. Work most recently seen patients first
Patient Outreach & Study Description (phone)
No
End
Interest?
Yes
Study site access during enrollment call?
No
If Phone only, Then study lead enters patient information in online study tool on their behalf
Study Team uses EMR to Monitor for patients who are study qualified and may be interested in the study
These patients may receive an outreach for the study pending on inbound interest volume and length of EMR queue

PATCH2 STUDY: Patients (500 Participants)

Enrollment Randomized trial of hydroxychloroquine in the treatment of COVID-19

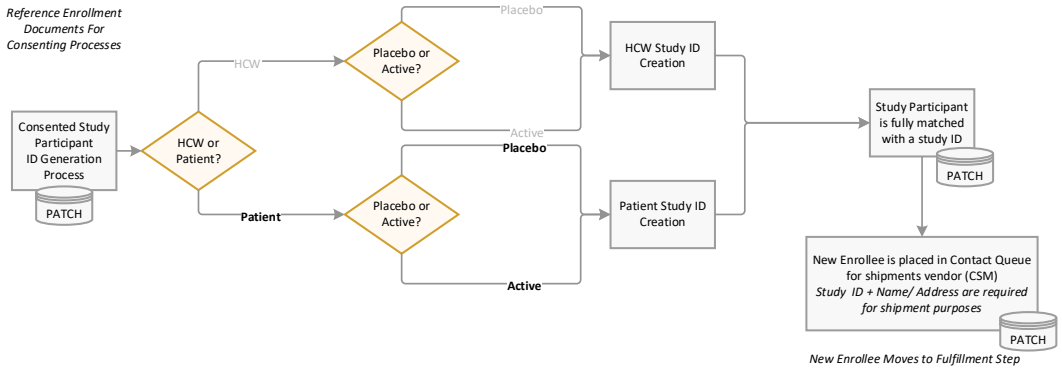
Patient Enrollment (Study Portal + phone)



PATCH2 STUDY: Patients (500 Participants)

Randomization & Study ID Process

UHG R&D



PATCH2 STUDY: Patients (500 Participants)

Medication & study kit determinations

PATCH2 STUDY: PATIENT POPULATION 500 Participants

56 count Active blinded 200 mg

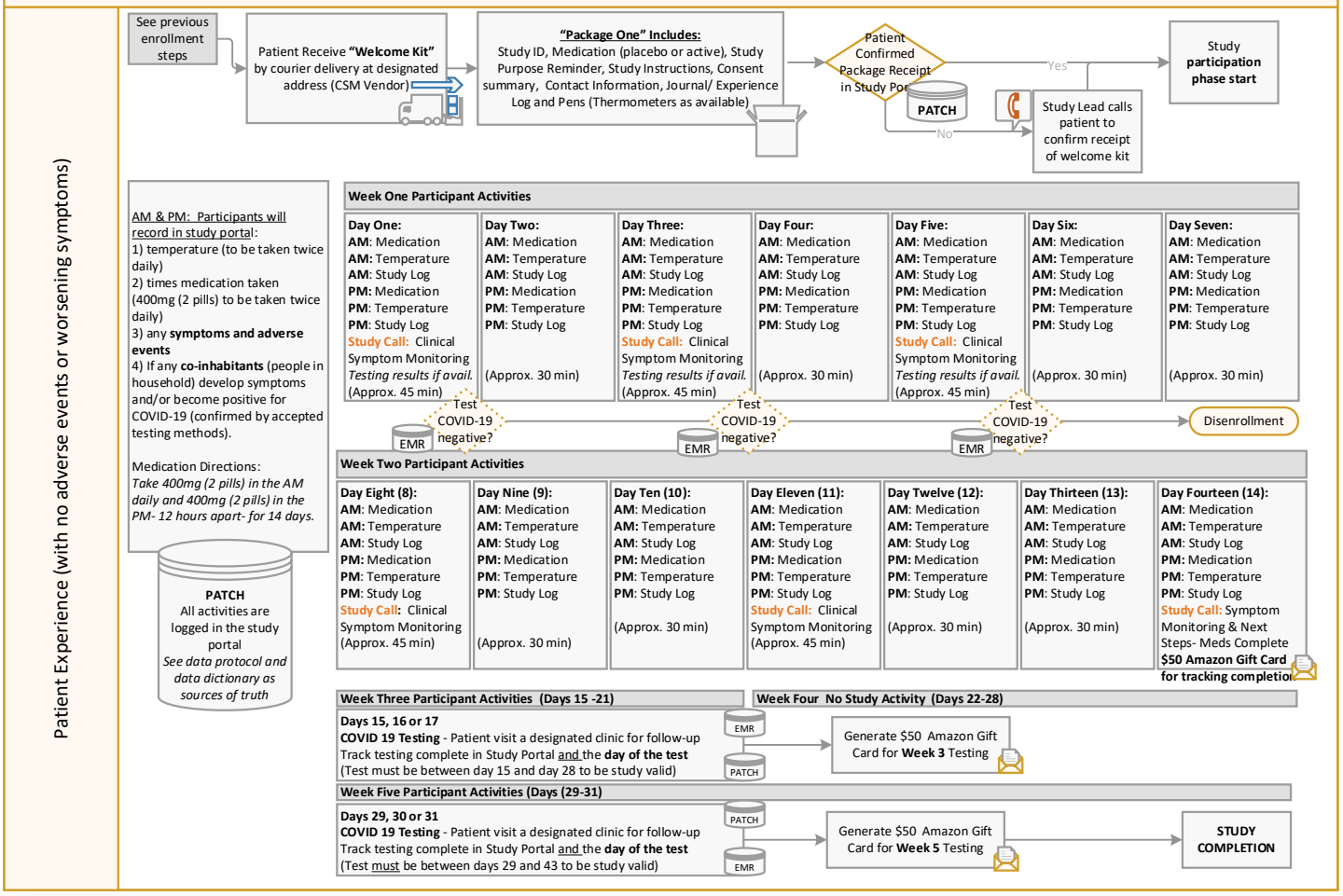
PARTICIPANT PACKAGE 1: Blinded Label
PATIENT + ACTIVE MEDICATION
(A total of 250 shipments)
- Pill Bottle containing 200mg pills **(56 count)**
- Instructions: (Take 400mg (2 pills) in the AM daily and 400mg (2 pills) in the PM- 12 hours apart- for 14 days. no refill)
- Patient Thermometer (as available)
- Study ID Card
- Study Journal/ Instructions/ FAQ/ Side effect & Contact information

56 count Placebo blinded 200 mg

PARTICIPANT PACKAGE 1: Blinded Label
PATIENT + PLACEBO
(A total of 250 shipments)
- Pill Bottle containing 200mg placebo pills **(56 count)**
- Instructions: (Take 400mg (2 pills) in the AM daily and 400mg (2 pills) in the PM- 12 hours apart- for 14 days. no refill)
- Patient Thermometer (as available)
- Study ID Card
- Study Journal/ Instructions/ FAQ/ Side effect & Contact information

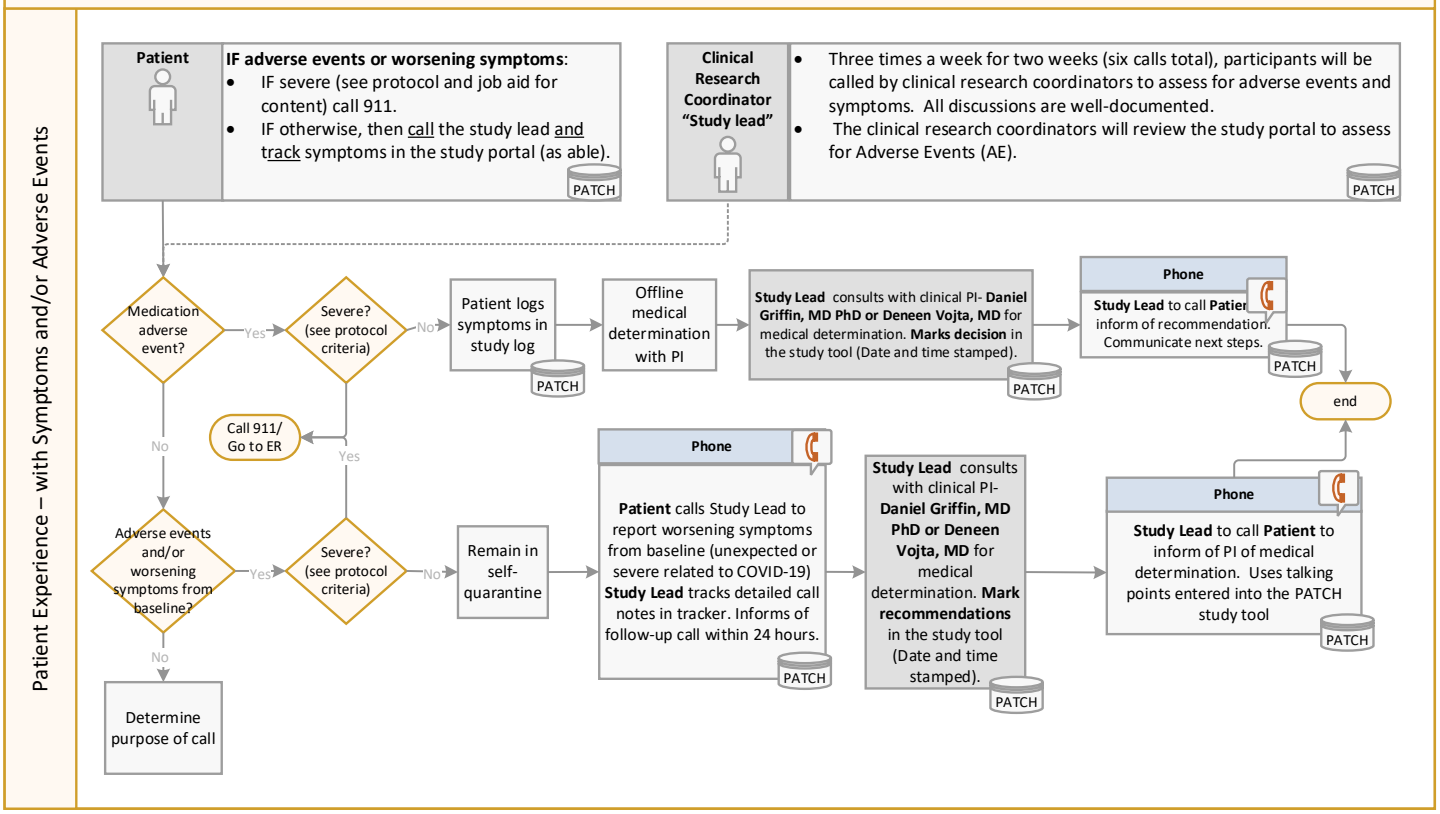
PATCH2 STUDY: Patients (500 Participants)

Participation Randomized trial of hydroxychloroquine in the treatment of COVID-19

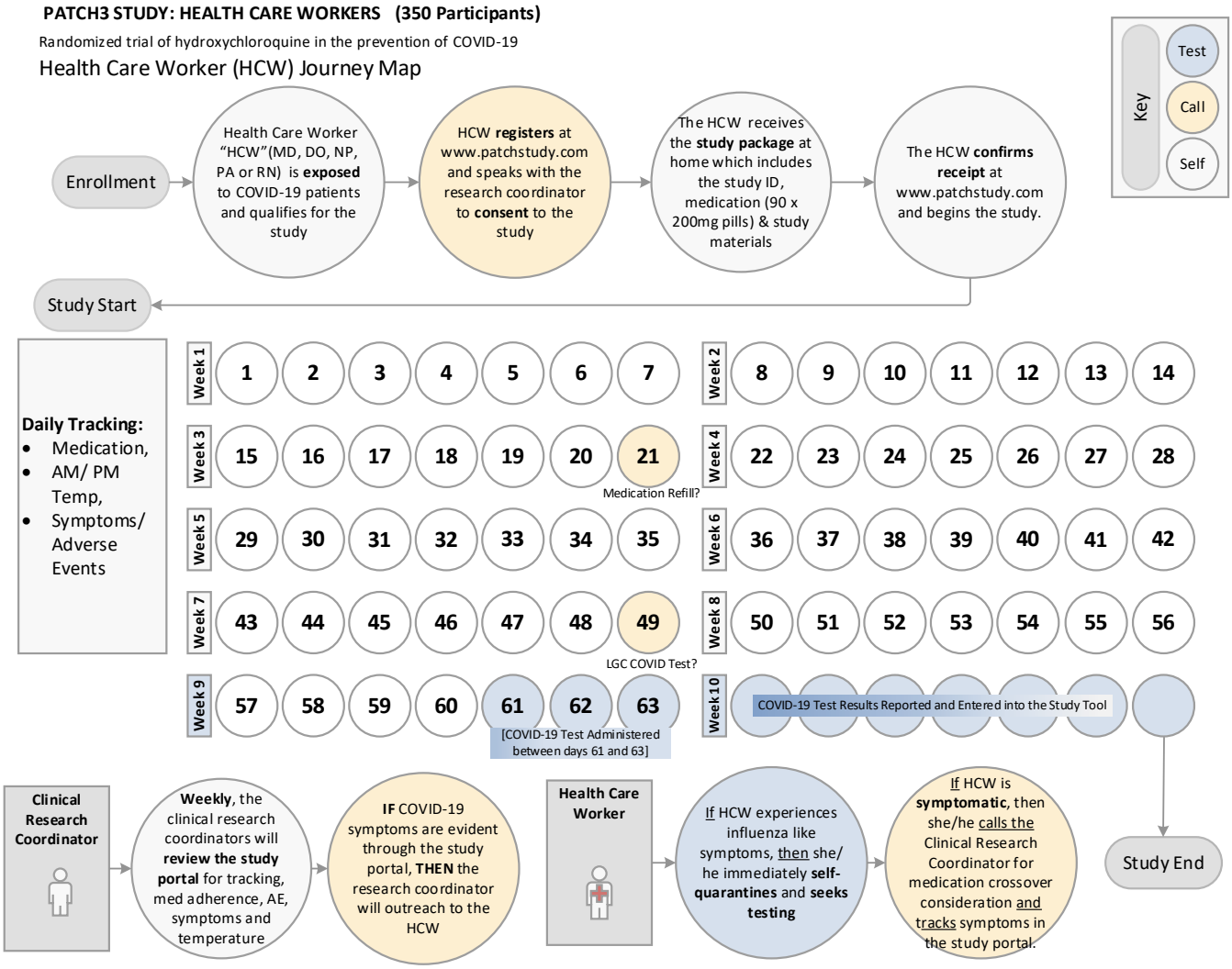


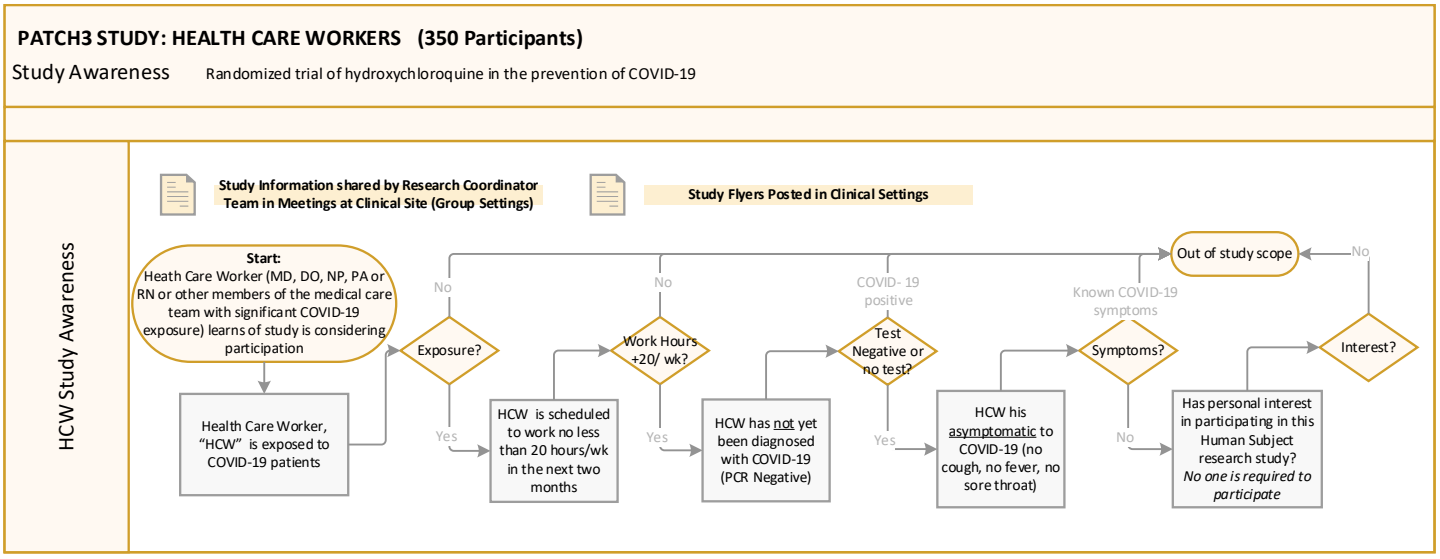
PATCH2 STUDY: Patients (500 Participants)

Symptoms/ Adverse Events Randomized trial of hydroxychloroquine in the treatment of COVID-19



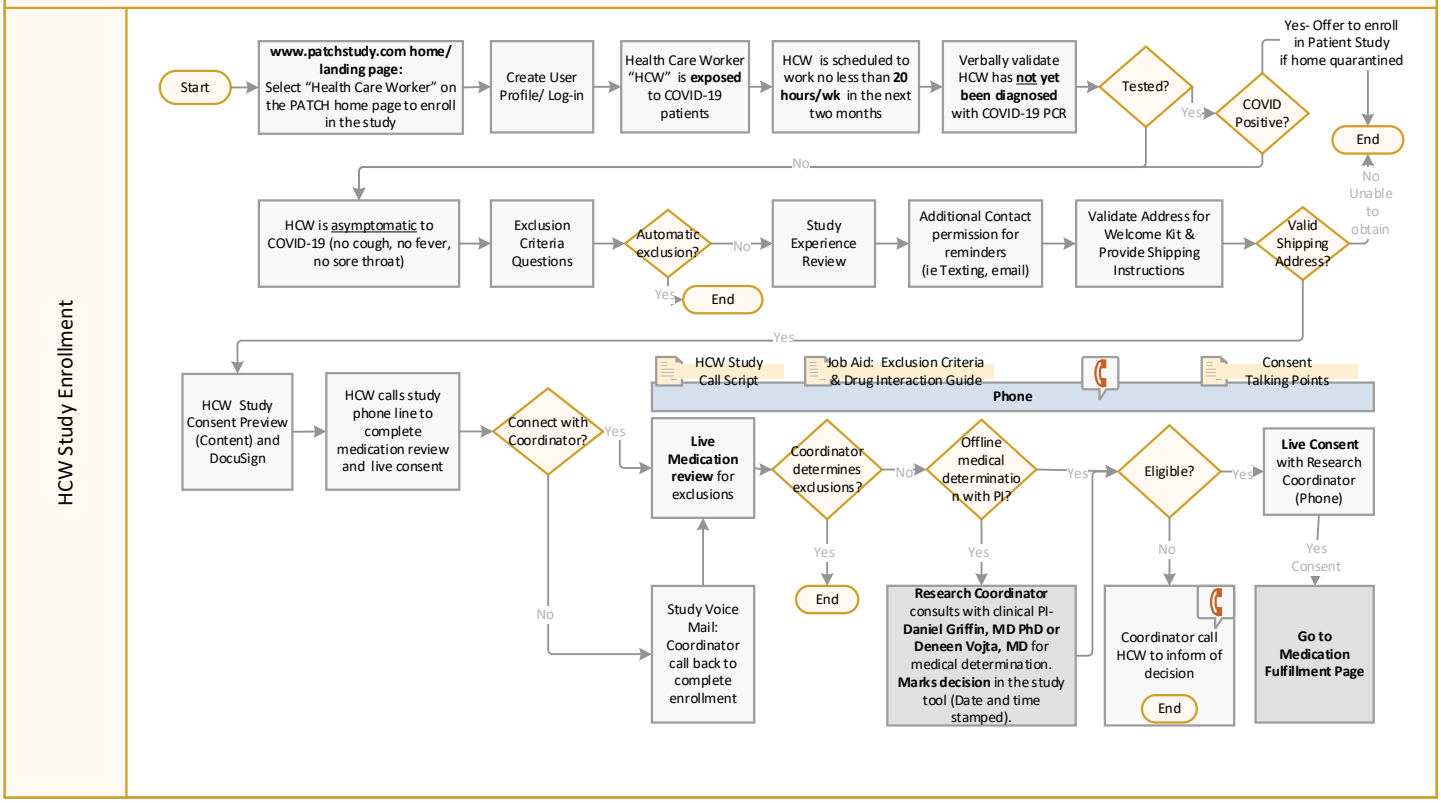
Appendix 2: PATCH 3 Process Flow





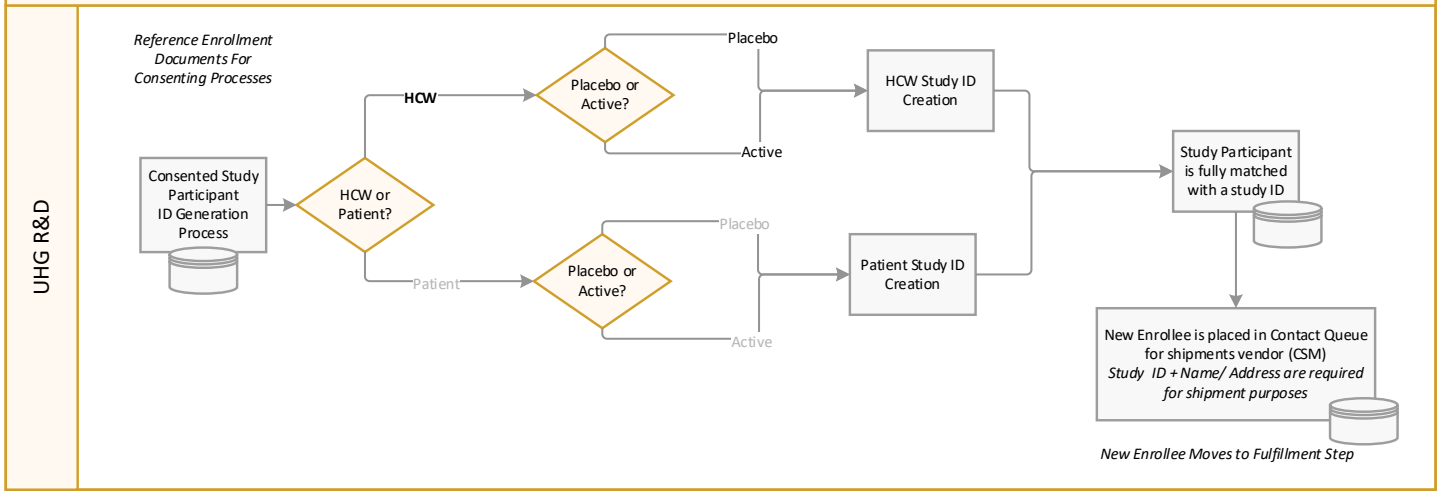
PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)

Enrollment Randomized trial of hydroxychloroquine in the prevention of COVID-19

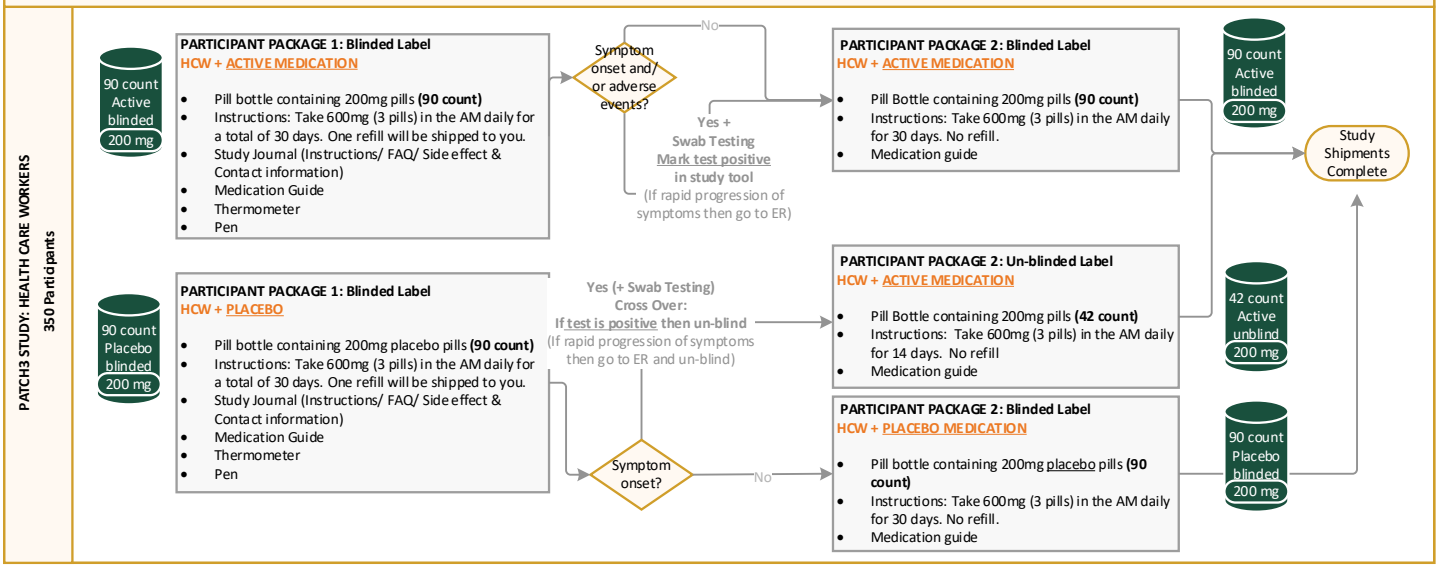


PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)

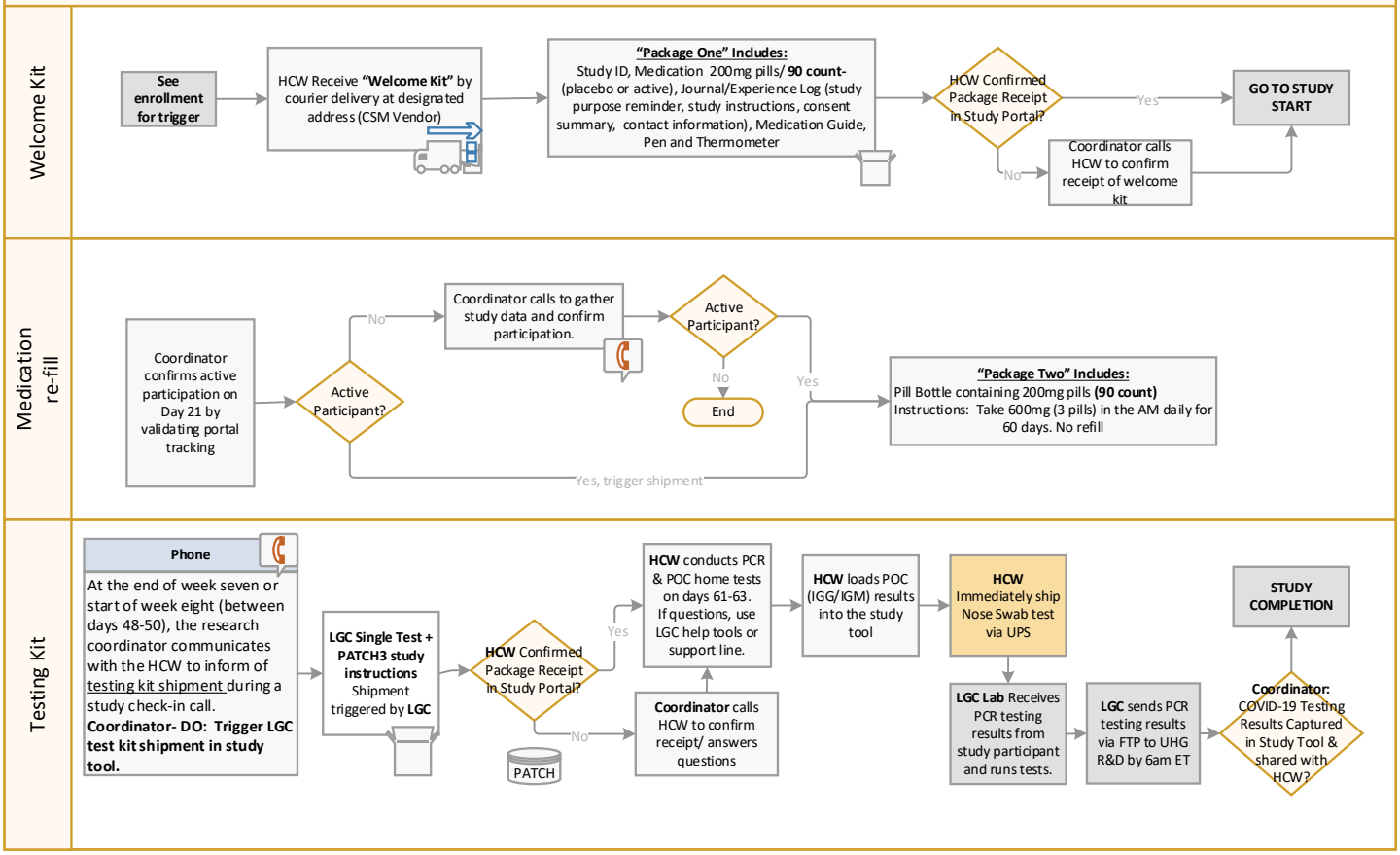
Randomization & Study ID Process (Offline- not consumer facing)



PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)
Medication & study kit determinations Randomized trial of hydroxychloroquine in the prevention of COVID-19

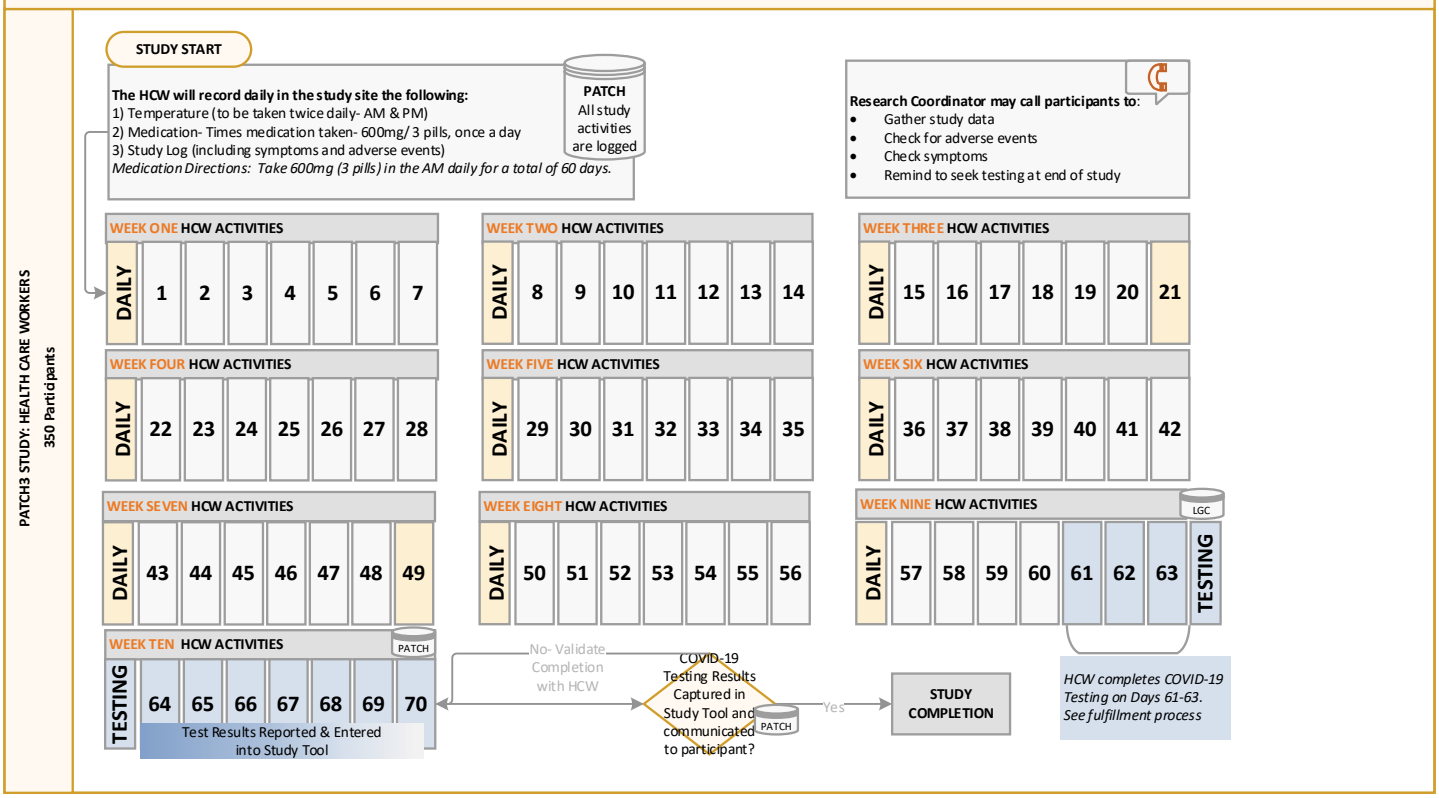


PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)
Participation Randomized trial of hydroxychloroquine in the prevention of COVID-19



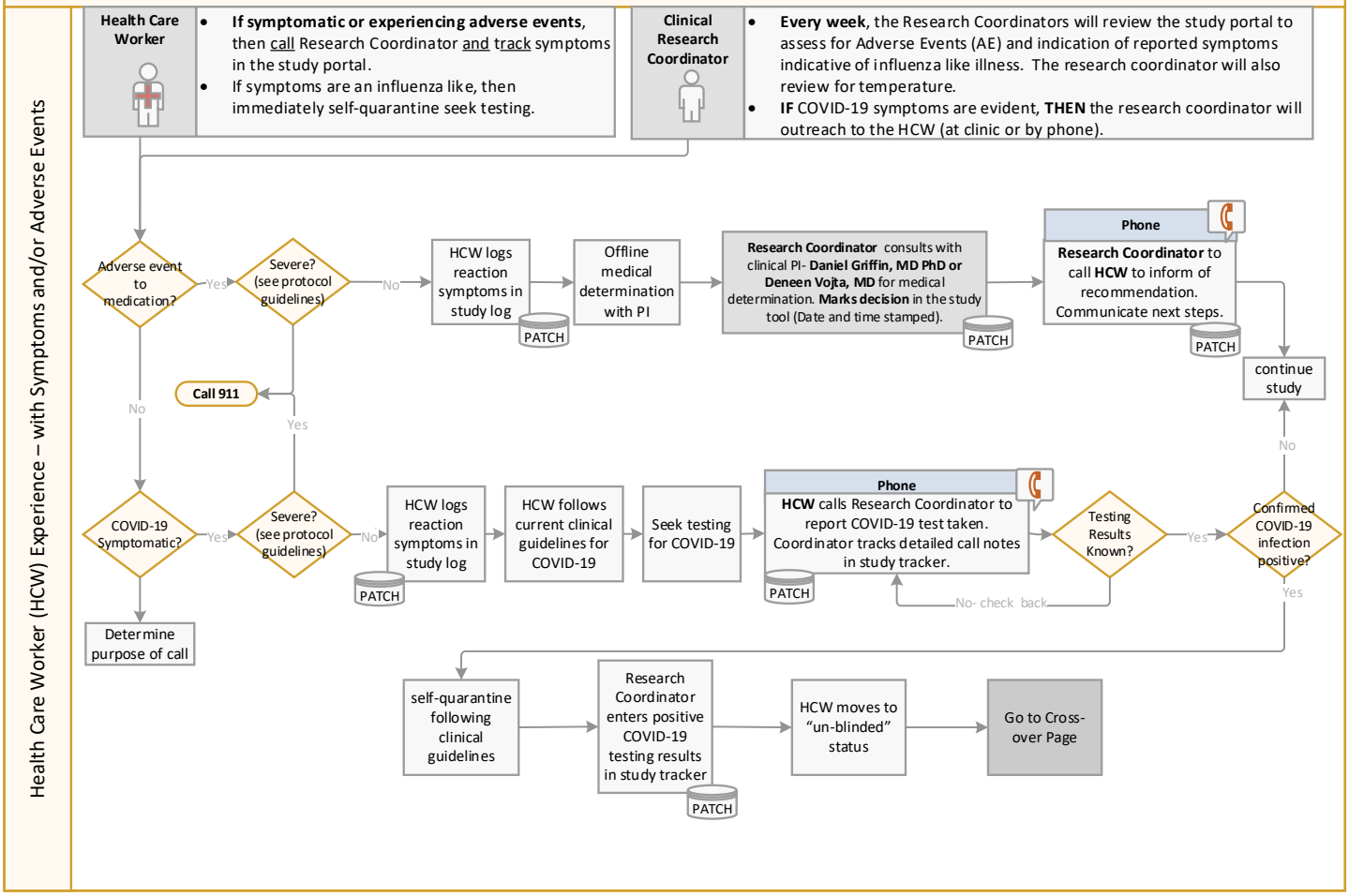
PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)

Participation Randomized trial of hydroxychloroquine in the prevention of COVID-19



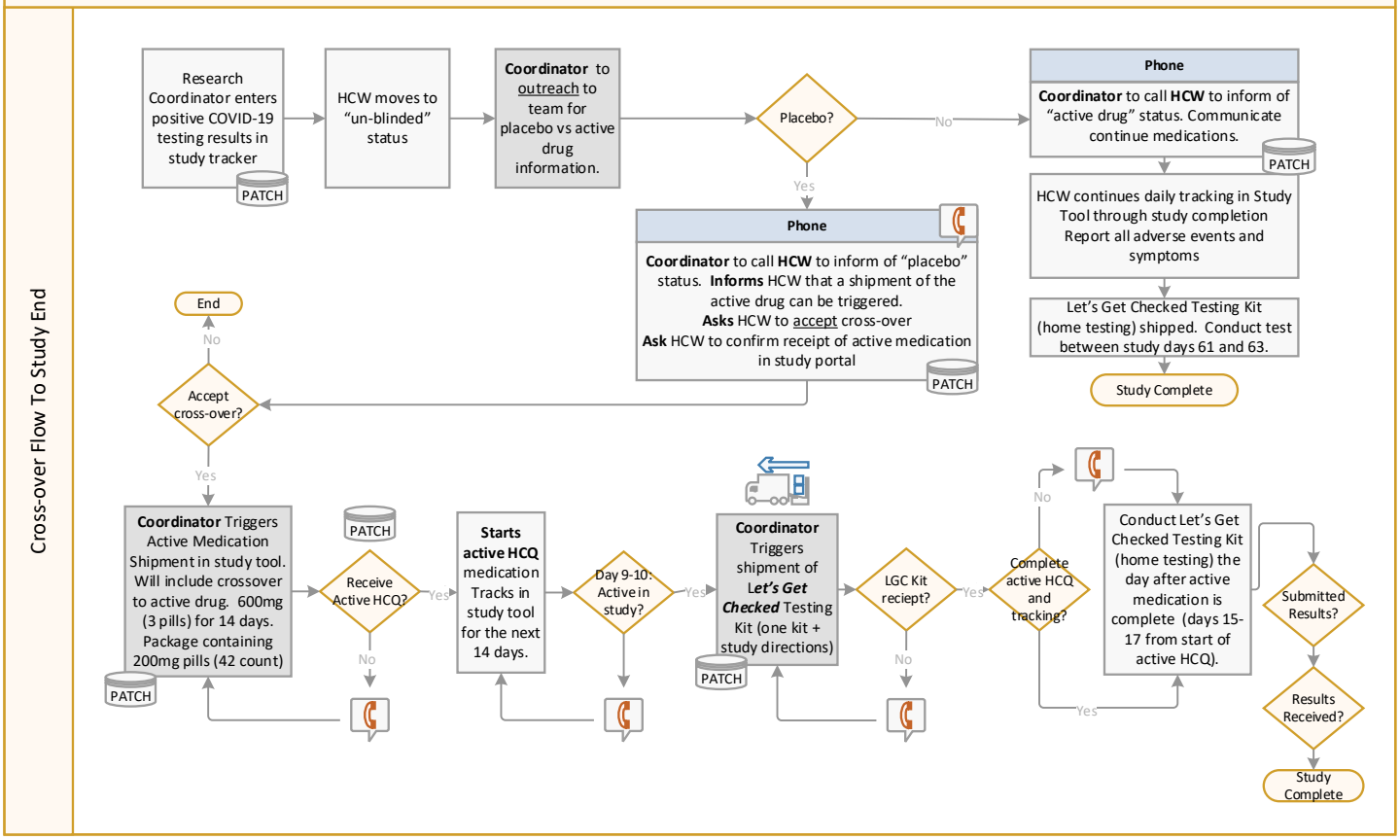
PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)

Symptoms and/or Adverse Events Randomized trial of hydroxychloroquine in the prevention of COVID-19



PATCH3 STUDY: HEALTH CARE WORKERS (350 Participants)

Cross-over Flow Randomized trial of hydroxychloroquine in the prevention of COVID-19



Appendix 3: PATCH 2 Job Aid

PATCH2 STUDY LEAD JOB AID

A PATCH2 AUTOMATIC STUDY EXCLUSIONS

Consumer Language for Enrollment Exclusions • These exclusions are automatic during the online enrollment experience in the enrollment portal • If indicated exclusion response is selected, it is an automatic exclusion from the study	**Automatic Portal Exclusion**
Are you between the ages of 50-75? [yes/ no]	**If NO**
Have you had a fever within the last four days? [yes/ no]	**If NO**
Do you require hospitalization? [yes/ no]	**If YES**
Are you able to self-quarantine at home for 14 days? [yes/ no]	**If NO**
Have you been tested for COVID-19? [yes/ no]	**If NO**

B AUTOMATIC CLINICAL EXCLUSIONS

Consumer Language for Enrollment Exclusions • These exclusions are automatic during the online enrollment experience in the enrollment portal • If "yes" to any, it is an automatic exclusion from the study.		**Automatic Portal Exclusion**
Protocol Language: Allergy to hydroxychloroquine, 4 aminoquinolines, or quinine	**Do you have an allergy to hydroxychloroquine (HCQ), aminoquinolines, or quinine?** [yes/ no]	**X**
Protocol Language: Patients with G6PD deficiency	**Do you have a G6PD deficiency?** [yes/ no]	**X**
Protocol Language: Pregnant or lactating or positive pregnancy test during pre-medication examination	**Are you pregnant?** [yes/ no]	**X**
	Are you breast feeding? [yes/ no]	**X**
Protocol Language: Receiving any trial treatment drug for 2019-ncov within 14 days prior to screening evaluation (off label, compassionate use or trial related)	**Have you been in any other drug trial for COVID-19?** [yes/ no]	**X**
Protocol Language: Patients with serious intercurrent illness that requires active infusional therapy, intense monitoring, or frequent dose adjustments for medication including but not limited to infectious disease, cancer, autoimmune disease, cardiovascular disease.	**Are you on any IV or other serious medications, such as chemotherapy?** [yes/ no]	**X**
Protocol Language: Patients who have undergone major abdominal, thoracic, spine or CNS surgery in the last 2 months, or plan to undergo surgery during study participation.	**Have you had any surgery in the last two months?** [yes/ no]	**X**
Protocol Language: Patients currently taking digoxin	**Do you take the medication, digoxin or lanoxin?** [yes/ no]	**X**
(From Medication Section)	**Have you ever had a seizures?** [yes/ no]	**X**
(From Medication Section)	**Have you ever had a transplant?** [yes/ no]	**X**

Protocol Language: History or evidence of increased cardiovascular risk including any of the following: • Left ventricular ejection fraction (LVEF) < institutional lower limit of normal. Baseline echocardiogram is not required; • Current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation; • History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment; • Current ≥ Class II congestive heart failure as defined by New York Heart Association.	**Do you have any heart disease such as congestive heart failure, history of heart attack, angina, arrhythmias or atrial fibrillation (also called AFib)?** [yes/ no]	**X**

C STUDY LEAD DECIDED EXCLUSIONS

Consumer Language for Enrollment Exclusions

- These exclusions will be asked prior to the consent call through the study enrollment portal. "Yes" response do not trigger an automatic exclusion.
- "Yes" responses require a live conversation between the prospective participant and the study lead during live consent.
- If a medical consult is needed, then the study lead will conduct a medical consult with study PIs. Track all medical consult language in the study portal.
- Call the prospective study participant back with the final decision (yes or no) on enrollment. If he/she is eligible, then finish study consenting, and trigger tablet + journal shipment

DISEASE EXCLUSIONS

Protocol Language	Study Portal Language		
Eye Disease: Known retinal disease including but not limited to macular degeneration, retinal vein occlusion, visual field defect, diabetic retinopathy	**Do you have eye disease?** [yes/ no]		
	(if yes) **Please describe.** [open text]		
	INCLUDED IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**
	Wears eye glasses		Any eye disease

Protocol Language	Study Portal Language		
Lung Disease: History of interstitial lung disease, severe emphysema or asthma, or chronic pneumonitis unrelated COVID-19.	**Do you have lung disease, such as asthma or emphysema?** [yes/ no]		
	(if yes) **Please describe.** [open text]		
	INCLUSION IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**
	If moderate or controlled	If in question, then medical consult	If severe, then exclude

Protocol Language	Study Portal Language		
Porphyria and Psoriasis: Due to risk of disease exacerbation patients with porphyria or psoriasis are ineligible unless the disease is well-controlled, and they are under the care of a specialist for the disorder who agrees to monitor the patient for exacerbations.	**Do you have porphyria?** [yes/ no]		
	Do you have psoriasis? [yes/ no]		
	INCLUSION IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**
	If moderate or controlled	If in question, then medical consult	If severe, then exclude

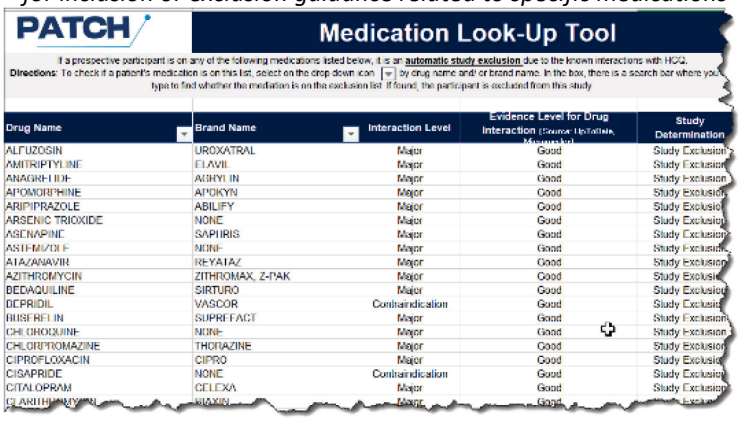
MEDICATION EXCLUSIONS

Study Portal Language	**Please list all medications that you are currently taking** [text fields- one per medication]
• The following medications are not allowed during the study. • The sponsor must be notified if the participant receives any of these during the study. • Participants must be instructed not to take any medications, including over the counter products, without first consulting with the investigator. • IF a study participant sees another provider, they are instructed to bring their study journal to this provider visit. • IN ADDITION, the participant should contact the study lead any time they seek medical treatment.	

Drug Classes	Protocol Language
Anticonvulsant	• **(Exclude)** Patients receiving cytochrome P450 enzyme-inducing anticonvulsant drugs (i.e. phenytoin, carbamazepine, Phenobarbital, primidone or oxcarbazepine) within 4 weeks of the start of the study treatment • **Acceptable drug alternatives include:** Because HCQ has known effects on P450 enzymes, patients requiring anti-convulsants may be treated with any of the non-enzyme inducing anti-convulsants which include: felbamate, valproic acid, gabapentin, lamotrigine, tiagibine, topiramate, or levetiracetam. Due to the fact that both zonisamide and HCQ accumulate in red blood cells, zonisamide should be avoided if possible. All other concomitant medications are permitted.
Antiviral	• **(Exclude)** Any investigational or off-label antiviral therapy • **(Include)** Patients with HIV may participate • **(Include)** Patients with herpes may participate
Cancer Treatments	• **(Exclude)** Anyone receiving active cancer treatments. • **(Exclude)** Any concurrent chemotherapy, radiotherapy (except radiotherapy as designated in this study or radiotherapy indicated for CNS metastasis) • **(Exclude)** Immunotherapy, • **(Exclude)** Biologic or hormonal therapy for cancer treatment, except as noted in the exclusion criteria. • **(Include)** A Cancer survivor receiving no treatments may participate • **(Include)** Concurrent use of hormones for non-cancer-related conditions (e.g. insulin for diabetes, hormone replacement therapy).
Immunosuppressive	• **(Exclude)** Immunosuppressive medications, including, corticosteroids at doses exceeding 10mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-alpha blockers. • **(Include)** Use of immunosuppressive medication for the management of study treatment related AEs or in subjects with contrast allergies is acceptable. • **(Include)** In addition, use of topical, inhaled and intranasal corticosteroids is permitted.
Live attenuated vaccines	• **(Exclude)** If using live attenuated vaccines during the study through 180 days after the last dose of both drugs. Examples include: MMR, Zostavax, Polio, Varicella • **(Include)** If using non-living vaccines. Examples include: Flu vaccine, Pneumonia vaccine
Insulin or antidiabetic drugs	• **Reduce dosage consideration.** As HCQ may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.
Arrhythmogenic	• **Drugs that prolong QT intervals.** • HCQ can prolong the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. • Also, there may be an increased risk of inducing ventricular arrhythmias if HCQ is used concomitantly with other arrhythmogenic drugs
Antiepileptics	• **Side effect.** The activity of antiepileptic drugs might be impaired if co-administered with HCQ.

Cyclosporin	• **Side effect.** An increased plasma cyclosporin level was reported when cyclosporin and HCQ were co-administered

*See **medication look up tool***
for inclusion or exclusion guidance related to specific medications



PATCH

Medication Look-Up Tool

If a prospective participant is on any of the following medications listed below, it is an **automatic study exclusion** due to the known interactions with HCQ.
Directions: To check if a patient's medication is on this list, select on the drop down icon by drug name and/ or brand name. In the box, there is a search bar where you type to find whether the medication is on the exclusion list. If found, the participant is excluded from this study

Drug Name	Brand Name	Interaction Level	Evidence Level for Drug Interaction (Source: UpToDate, Micromedex)	Study Determination
ALFUZOSIN	UROXATRAL	Major	Good	Study Exclusion
AMITRIPTYLINE	ELAVIL	Major	Good	Study Exclusion
ANAGRELIDE	AGRYLIN	Major	Good	Study Exclusion
APOMORPHINE	APOKYN	Major	Good	Study Exclusion
ARIPIPRAZOLE	ABILIFY	Major	Good	Study Exclusion
ARSENIC TRIOXIDE	NONE	Major	Good	Study Exclusion
ASENAPINE	SAPHRIS	Major	Good	Study Exclusion
ASTEMIZOLE	NONE	Major	Good	Study Exclusion
ATAZANAVIR	REYATAZ	Major	Good	Study Exclusion
AZITHROMYCIN	ZITHROMAX, Z-PAK	Major	Good	Study Exclusion
BEDAQUILINE	SIRTURO	Major	Good	Study Exclusion
BEPRIDIL	VASCOR	Contraindication	Good	Study Exclusion
BUSERELIN	SUPRFFACT	Major	Good	Study Exclusion
CHLOROQUINE	NONE	Major	Good	Study Exclusion
CHLORPROMAZINE	THORAZINE	Major	Good	Study Exclusion
CIPROFLOXACIN	CIPRO	Major	Good	Study Exclusion
CISAPRIDE	NONE	Contraindication	Good	Study Exclusion
CITALOPRAM	CELEXA	Major	Good	Study Exclusion
CLARITHROMYCIN	BIAXIN	Major	Good	Study Exclusion

D EMERGENCY INDICATIONS

EMERGENCY SYMPTOMS (911)	Protocol Language
	Participants will be instructed to **call 911** upon immediate presentation of the following symptoms as identified by the CDC as requiring emergency action: • Bluish lips or face • New confusion/dizziness or inability to arouse • Persistent pain or pressure in the chest (not caused by coughing) • Difficulty breathing (including severe shortness of breath and single word speech)

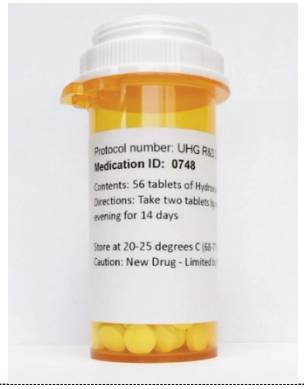
E SIDE EFFECT GUIDE

Directions

- Ask the study doctor if you have questions about the **signs or symptoms of any side effects**.
- Please tell the study doctor or study staff right away if you have any **side effects**.
- Please tell them if you have any other **problems with your health** or the way you feel during the study, whether or not you think these problems are related to the study drugs.

Serious	Protocol Language
Side effects occurring at a frequency which cannot be estimated from available data	• **Convulsions** • **Heart problems** (e.g. breathlessness with exercise or even at rest, swelling of the legs, ankles and feet, irregular heartbeats that feel rapid or pounding, chest pain, sudden fainting) • **Hypoglycemia** (low blood sugar) (e.g. sweating, shakiness, weakness, dizziness, fast heartbeat, nausea, irritability, blurred vision, confusion, loss of consciousness) • **Increased sensitivity to sunlight**. Skin rash due to sunlight can be reduced by appropriate use of sunscreen creams • **Liver problems** with symptoms such as: unusual tiredness, nausea, vomiting, abdominal pain, or jaundice (yellow discoloration of the eyes or skin) • Long-lasting **involuntary muscle contraction**; impairment of voluntary movements, tremor • **Lowered blood cell counts** (e.g. fatigue, weakness, increase susceptibility to infections or bleeding) • **Muscle weakness** • **Psychosis** (e.g. hallucinations, loss of contact with reality) • Severe **breathing problem** (bronchospasm, angioedema) • Severe **skin problem** • **Suicidal thoughts**
Rare	**Protocol Language**
These occurring in 0.1 to 1% of participants receiving this drug	• **Dizziness** • **Hair loss** or bleaching of hair • Loss of **skin pigment** or increase in skin pigment (bluish-black color) • **Nerve and muscle disorders** (e.g. tingling, numbness, burning pain, weakness, cramps, and spasms • Ringing in the **ears**, decreased hearing
Common	**Protocol Language**
These occur in 1 to 10% of participants receiving this drug	• **Diarrhea** • **Vomiting** • Loss or **lack of appetite** (anorexia) • **Headache** • Nervousness, **emotional changes** • Rash, **itchy rash** • **Visual problem:** blurred vision, difficulty focusing, seeing halos around lights, especially at night, seeing light flashes and streaks, night blindness, visual field loss, change in eye color (eye pigmentation), difficulty focusing eye, difficulty reading (skipped words). • **Notes on Vision:** HCQ may rarely cause problems with your vision. A review of over 1000 patients taking HCQ found that this side effect occurred in only 1 patient and only after they had taken the drug for 7 years. Vision problems include visual disturbances such as flickering or flashing lights, dimming of your vision (things appear darker) and decreased vision that could progress to blindness.
Very Common	**Protocol Language**
These occur in 10% or more of participants receiving this drug	• Nausea • Stomach pain • Stomach cramps

F. PATCH2 PATIENTS WELCOME BOX

Content	Description
	**THE MEDICATION BOTTLE** **Blinded - 56 tabs** Protocol number: UHG R&D 2020-0003 Medication ID: [bottle serial number] Contents: 56 tablets Directions: Take two tablets by mouth every morning and every evening for 14 days Store at [insert storage instructions from the manufacturer] Caution: New Drug - Limited by Federal (or United States) law to investigational use
	**THE HYDOXYCHLOROQUINE MEDICATION GUIDE** • The HCQ Medication Guide opens with: "*You have received your medication tablets in this box. These tablets may be a placebo or they may be the active hydroxychloroquine (HCQ) medication. Below is a list of possible side effects from taking active HCQ.*" • This guide will be shipped in the welcome kit that comes via courier in the overnight package from CSM.
	**THE STUDY JOURNAL** • 15 page Study Journal • Includes a variety of study information, contact information, FAQ, reminders and study tracking examples • Will be shipped in the welcome kit that comes via courier in the overnight package from CSM
	**A THERMOMETER** • A thermometer will be sent to all patient participants. • It will be all white
	**PEN** • This ink pen will be shipped in the welcome kit that comes via courier in the overnight package from CSM

E FREQUENTLY ASKED QUESTIONS (FAQ)

Type of Question	Question	Response
Study Info	What will be expected of me if I decide to participate in this study?	A package will be sent to you with either HCQ active or placebo pills. We ask that you take your medication according to the package direction, check your temperature twice daily, record and report any adverse events, and upload this information daily through the study portal at patchstudy.com for the full duration of this study. You'll also be asked to get your swab samples taken at the end of the study.
Study Info	How can I enroll and participate in this study?	If you are interested in learning more and want to enroll in this research study, go to our study portal at patchstudy.com. You will then be asked to create a user profile and answer a few eligibility questions. If eligible, you will sign a consent form via the study portal and provide a valid shipping address to receive your pills and study materials. Once completed, call us at 1-855-223-6987 to confirm your enrollment and consent to our study.
Study Info	What happens to my data, who sees it, and how is it used?	To ensure your privacy, a study ID will be used in place of your name whenever researchers outside of the clinic access your information. Your information may be shared with individuals and organizations that conduct or watch over this research. Sharing your health data will be in accordance with the consent form and applicable data privacy laws. The data collected will be used in analysis to determine the efficacy of HCQ as an antiviral medication for COVID-19.
PATCH2	What is the PATCH2 Study?	PATCH, also known as Prevention and Treatment of COVID-19 with Hydroxychloroquine (HCQ), is a research study that is being conducted by ProHEALTH NY, University of Pennsylvania, and UnitedHealth Group Research & Development to determine if HCQ can be an effective antiviral medication for treating COVID-19.
PATCH2	How long will I be required to participate?	We expect that your taking part in this research will last for 5 weeks including follow-up visits.
	What happens if I sign-up and change my mind later?	You can stop taking part in this research at any time. If you choose to drop out, there will be no penalty and you won't lose any benefits. You'll still get all the same medical care and benefits that you're entitled to. If you decide to leave this research, contact the research team at 1-855-223-6987.
Medication Info	What is hydroxychloroquine standardly used for?	Hydroxychloroquine is a quinoline medicine used to treat or prevent malaria. Hydroxychloroquine is also an antirheumatic medicine and is used to treat symptoms of rheumatoid arthritis and systemic lupus erythematosus.
Medication Info	What happens if I miss a dose?	Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.
Medication Info	What is Hydroxychloroquine?	Hydroxychloroquine, also known as HCQ, is an antiviral medication that has been used for many years for the treatment of other illnesses such as malaria, lupus, and rheumatoid arthritis. Chloroquine derivatives have shown preclinical efficacy against COVID-19, but little clinical data is available.

Adverse Event	What happens if I overdose?	Seek emergency medical attention or call the Poison Help line at 1-800-222-1222. An overdose of hydroxychloroquine can be fatal, especially in children. Hydroxychloroquine overdose must be treated quickly. You may be told to induce vomiting right away (at home, before transport to an emergency room). Ask the poison control center how to induce vomiting in the case of an overdose. Overdose symptoms may include drowsiness, vision changes, slow heart rate, chest pain, severe dizziness, seizure (convulsions), or shallow breathing.
Adverse Event	What should I do if I experience side effects?	If **severe,** such as bluish lips or face; new confusion/dizziness or inability to arouse; persistent pain or pressure in the chest (not caused by coughing); and difficulty breathing (including severe shortness of breath and single word speech), call 911 immediately. If not severe, track side effects at patchstudy.com and discuss symptoms during your next study call.
Adverse Event	What is an adverse event?	An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens during the course of the study. An adverse event does not need to be directly related to the study treatments. The following examples are considered adverse events: • If you experience an illness during the study • If you have a diagnostic procedure and the results are abnormal • If you seek an additional treatment during the study based on a diagnostic test
Adverse Event	What if my partner or I becomes pregnant?	Under FDA guidelines, that is considered an adverse event. Please call the study team at 1-855-223-6987 between 8am and 5pm.
Adverse Event	What should I do if I experience and adverse event?	If you are experiencing a health emergency, call 911 Please do share any adverse event with your study team. • Please track all adverse events in the study portal at patchstudy.com • You can also call the study team to discuss your adverse event at 1-855-223-6987 between 8am and 5pm.
Adverse Event	What will happen if I report an adverse event during the study?	We care about your health and safety. • A study lead will follow up with you to gather more information and determine if any changes need to be made to the medicine you are taking. • Additionally, the information will be analyzed as part of the study results."
Adverse Event	What should I do if I have an adverse event, but it is the end of the study?	During your last call with the study team, please make a plan for follow-up. Our study team will continue to follow up with you until your adverse event is resolved. We also encourage you to share events with your personal physician.
HCQ vs CQ	What is the difference between the recently published study in Brazil and	There are several key but crucial differences between the recently published study in Brazil and the PATCH studies: 1. The Brazil study involved chloroquine, not hydroxychloroquine. Chloroquine is chemically similar to hydroxychloroquine but the

	the PATCH studies being conducted at ProHEALTH?	two have very different safety records at high doses with hydroxychloroquine being the safer of the two. 2. Participants in the Brazil study were taking two additional antibiotics (Ceftriaxone and Azithromycin) which are known to exacerbate this problem. 3. Not only is the medication itself different, but so is the dose. The daily dose in the Brazil study was very high. 4. The PATCH study populations are different from the Brazil study which involved individuals hospitalized for COVID-19, which is not the case here.

Appendix 4: PATCH 3 Job Aid

PATCH3 STUDY LEAD JOB AID

A PATCH3 AUTOMATIC STUDY EXCLUSIONS

Consumer Language for Enrollment Exclusions • These exclusions are automatic during the online enrollment experience in the enrollment portal • If indicated exclusion response is selected, it is an automatic exclusion from the study	**Automatic Portal Exclusion**
Are you a health care worker scheduled to working an average of 20 hours a week for the next 2 months?	**If NO**
Are you currently asymptomatic and presume not to have COVID?	**If NO**
Have you had a fever within the last four days? [yes/ no]	**If NO**
Do you require hospitalization? [yes/ no]	**If YES**
Are you able to self-quarantine at home for 14 days? [yes/ no]	**If NO**
Have you been tested for COVID-19? [yes/ no]	**If NO**

B AUTOMATIC CLINICAL EXCLUSIONS

Consumer Language for Enrollment Exclusions • These exclusions are automatic during the online enrollment experience in the enrollment portal • If "yes" to any, it is an automatic exclusion from the study.		**Automatic Portal Exclusion**
Protocol Language: Allergy to hydroxychloroquine, 4 aminoquinolines, or quinine	**Do you have an allergy to hydroxychloroquine (HCQ), aminoquinolines, or quinine?** [yes/ no]	**X**
Protocol Language: Patients with G6PD deficiency	**Do you have a G6PD deficiency?** [yes/ no]	**X**
Protocol Language: Pregnant or lactating or positive pregnancy test during pre-medication examination	**Are you pregnant?** [yes/ no]	**X**
	Are you breast feeding? [yes/ no]	**X**
Protocol Language: Receiving any trial treatment drug for 2019-ncov within 14 days prior to screening evaluation (off label, compassionate use or trial related)	**Have you been in any other drug trial for COVID-19?** [yes/ no]	**X**
Protocol Language: Patients with serious intercurrent illness that requires active infusional therapy, intense monitoring, or frequent dose adjustments for medication including but not limited to infectious disease, cancer, autoimmune disease, cardiovascular disease.	**Are you on any IV or other serious medications, such as chemotherapy?** [yes/ no]	**X**
Protocol Language: Patients who have undergone major abdominal, thoracic, spine or CNS surgery in the last 2 months, or plan to undergo surgery during study participation.	**Have you had any surgery in the last two months?** [yes/ no]	**X**
Protocol Language: Patients currently taking digoxin	**Do you take the medication, digoxin or lanoxin?** [yes/ no]	**X**
(From Medication Section)	**Have you ever had a seizures?** [yes/ no]	**X**

(From Medication Section)	**Have you ever had a transplant?** [yes/ no]	**X**
Protocol Language: History or evidence of increased cardiovascular risk including any of the following: • Left ventricular ejection fraction (LVEF) < institutional lower limit of normal. Baseline echocardiogram is not required; • Current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation; • History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment; • Current ≥ Class II congestive heart failure as defined by New York Heart Association.	**Do you have any heart disease such as congestive heart failure, history of heart attack, angina, arrhythmias or atrial fibrillation (also called AFib)?** [yes/ no]	**X**

C STUDY LEAD DECIDED EXCLUSIONS

Consumer Language for Enrollment Exclusions

- These exclusions will be asked prior to the consent call through the study enrollment portal. "Yes" response do not trigger an automatic exclusion.
- "Yes" responses require a live conversation between the prospective participant and the study lead during live consent.
- If a medical consult is needed, then the study lead will conduct a medical consult with study PIs. Track all medical consult language in the study portal.
- Call the prospective study participant back with the final decision (yes or no) on enrollment. If he/she is eligible, then finish study consenting, and trigger tablet + journal shipment

DISEASE EXCLUSIONS

Protocol Language	Study Portal Language		
Eye Disease: Known retinal disease including but not limited to macular degeneration, retinal vein occlusion, visual field defect, diabetic retinopathy	**Do you have eye disease?** [yes/ no]		
	(if yes) **Please describe.** [open text]		
	INCLUDED IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**
	Wears eye glasses		Any eye disease

Protocol Language	Study Portal Language		
Lung Disease: History of interstitial lung disease, severe emphysema or asthma, or chronic pneumonitis unrelated COVID-19.	**Do you have lung disease, such as asthma or emphysema?** [yes/ no]		
	(if yes) **Please describe.** [open text]		
	INCLUSION IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**
	If moderate or controlled	If in question, then medical consult	If severe, then exclude

Protocol Language	Study Portal Language		
Porphyria and Psoriasis: Due to risk of disease exacerbation patients with porphyria or psoriasis are ineligible unless the disease is well-controlled, and they	**Do you have porphyria?** [yes/ no]		
	Do you have psoriasis? [yes/ no]		
	INCLUSION IF:	**MEDICAL CONSULTATION IF:**	**EXCLUSION IF:**

are under the care of a specialist for the disorder who agrees to monitor the patient for exacerbations.	If moderate or controlled	If in question, then medical consult	If severe, then exclude

MEDICATION EXCLUSIONS

Study Portal Language	**Please list all medications that you are currently taking** [text fields- one per medication]
• The following medications are not allowed during the study. • The sponsor must be notified if the participant receives any of these during the study. • Participants must be instructed not to take any medications, including over the counter products, without first consulting with the investigator. • IF a study participant sees another provider, they are instructed to bring their study journal to this provider visit. • IN ADDITION, the participant should contact the study lead any time they seek medical treatment.	

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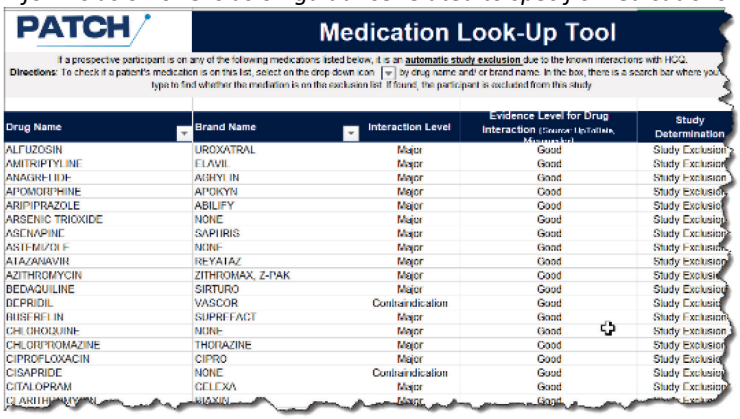
Live attenuated vaccines	• **(Exclude)** If using live attenuated vaccines during the study through 180 days after the last dose of both drugs. Examples include: MMR, Zostavax, Polio, Varicella • **(Include)** If using non-living vaccines. Examples include: Flu vaccine, Pneumonia vaccine
Insulin or antidiabetic drugs	• **Reduce dosage consideration.** As HCQ may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.
Arrhythmogenic	• **Drugs that prolong QT intervals.** • HCQ can prolong the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. • Also, there may be an increased risk of inducing ventricular arrhythmias if HCQ is used concomitantly with other arrhythmogenic drugs

Antiepileptics	• **Side effect.** The activity of antiepileptic drugs might be impaired if co-administered with HCQ.
Cyclosporin	• **Side effect.** An increased plasma cyclosporin level was reported when cyclosporin and HCQ were co-administered

*See **medication look up tool***
for inclusion or exclusion guidance related to specific medications



PATCH

Medication Look-Up Tool

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Drug Name	Brand Name	Interaction Level	Evidence Level for Drug Interaction (Source: UpToDate, Micromedex)	Study Determination
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CLARITHROMYCIN	BIAXIN	Major	Good	Study Exclusion

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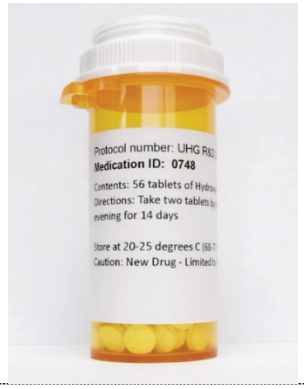
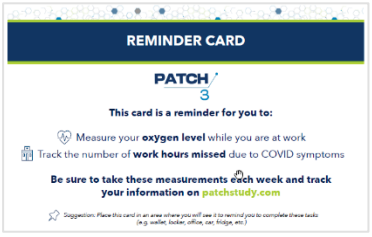
- Please tell them if you have any other **problems with your health** or the way you feel during the study, whether or not you think these problems are related to the study drugs.

Serious	Protocol Language
Side effects occurring at a frequency which cannot be estimated from available data	• **Convulsions** • **Heart problems** (e.g. breathlessness with exercise or even at rest, swelling of the legs, ankles and feet, irregular heartbeats that feel rapid or pounding, chest pain, sudden fainting) • **Hypoglycemia** (low blood sugar) (e.g. sweating, shakiness, weakness, dizziness, fast heartbeat, nausea, irritability, blurred vision, confusion, loss of consciousness) • **Increased sensitivity to sunlight**. Skin rash due to sunlight can be reduced by appropriate use of sunscreen creams • **Liver problems** with symptoms such as: unusual tiredness, nausea, vomiting, abdominal pain, or jaundice (yellow discoloration of the eyes or skin) • Long-lasting **involuntary muscle contraction**; impairment of voluntary movements, tremor • **Lowered blood cell counts** (e.g. fatigue, weakness, increase susceptibility to infections or bleeding) • **Muscle weakness** • **Psychosis** (e.g. hallucinations, loss of contact with reality) • Severe **breathing problem** (bronchospasm, angioedema) • Severe **skin problem** • **Suicidal thoughts**
Rare	**Protocol Language**
These occurring in 0.1 to 1% of participants receiving this drug	• **Dizziness** • **Hair loss** or bleaching of hair • Loss of **skin pigment** or increase in skin pigment (bluish-black color) • **Nerve and muscle disorders** (e.g. tingling, numbness, burning pain, weakness, cramps, and spasms • Ringing in the **ears**, decreased hearing
Common	**Protocol Language**
These occur in 1 to 10% of participants receiving this drug	• **Diarrhea** • **Vomiting** • Loss or **lack of appetite** (anorexia) • **Headache** • Nervousness, **emotional changes** • Rash, **itchy rash** • **Visual problem:** blurred vision, difficulty focusing, seeing halos around lights, especially at night, seeing light flashes and streaks, night blindness, visual field loss, change in eye color (eye pigmentation), difficulty focusing eye, difficulty reading (skipped words). • **Notes on Vision:** HCQ may rarely cause problems with your vision. A review of over 1000 patients taking HCQ found that this side effect occurred in only 1 patient and only after they had taken the drug for 7 years. Vision problems include visual disturbances such as flickering or flashing lights, dimming of your vision (things appear darker) and decreased vision that could progress to blindness.
Very Common	**Protocol Language**
These occur in 10% or more of participants receiving this drug	• Nausea • Stomach pain • Stomach cramps

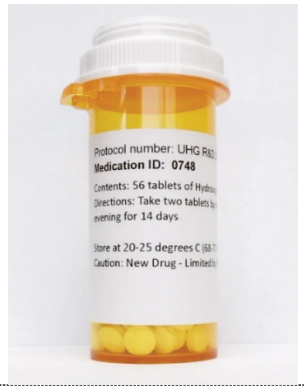
F. PATCH3 HEALTH CARE WORKER WELCOME KIT

Shipment 1:

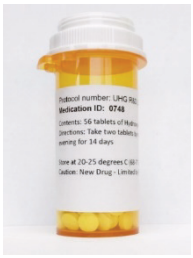
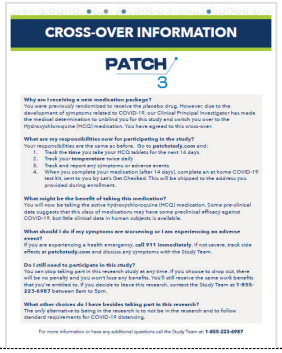
Content	Description
	**THE MEDICATION BOTTLE** **Blinded - 90 tabs** Medication ID: [bottle serial number] Contents: 90 tablets Instructions: Take 3 tablets in the AM daily for a total of 30 days. One refill will be shipped to you. Store at [insert storage instructions from the manufacturer] Caution: New Drug - Limited by Federal (or United States) law to investigational use
	**THE HYDOXYCHLOROQUINE MEDICATION GUIDE** • The HCQ Medication Guide opens with: "You have received your medication tablets in this box. These tablets may be a placebo or they may be the active hydroxychloroquine (HCQ) medication. Below is a list of possible side effects from taking active HCQ."
	**THE STUDY JOURNAL** • 15 page Study Journal • Includes a variety of study information, contact information, FAQ, reminders and study tracking examples
	**A THERMOMETER** • A thermometer will be sent to all health care worker participants to track their temperature • It will be all white
	**PEN** • An ink pen will be sent to all health care workers to use with the study journal

	**REMINDER CARD** • The reminder card is to help remind health care workers to get their weekly oxygen level checked at work and track the number of hours they missed due to their own COVID-19 symptoms

Shipment 2:

Content	Description
	**THE MEDICATION BOTTLE** **Blinded - 90 tabs** Medication ID: [bottle serial number] Contents: 90 tablets Instructions: Take 3 tablets in the AM daily for a total of 30 days. One refill will be shipped to you. Store at [insert storage instructions from the manufacturer] Caution: New Drug - Limited by Federal (or United States) law to investigational use
	**THE HYDOXYCHLOROQUINE MEDICATION GUIDE** • The HCQ Medication Guide opens with: "You have received your medication tablets in this box. These tablets may be a placebo or they may be the active hydroxychloroquine (HCQ) medication. Below is a list of possible side effects from taking active HCQ."

PATCH3 HEALTH CARE WORKER CROSSOVER KIT

Content	Description
	**CROSSOVER MEDICATION** **Unblinded Active HCQ - 42 tabs** Medication ID: [bottle serial number] Contents: 42 tablets Directions: Take 3 pills in the AM daily for 14 days. No refill. Store at [insert storage instructions from the manufacturer] Caution: New Drug - Limited by Federal (or United States) law to investigational use
	**CROSSOVER GUIDE** This guide is to support the health care worker with instructions when crossing over from placebo to HCQ should they qualify.

E FREQUENTLY ASKED QUESTIONS (FAQ)

Type of Question	Question	Response
Study Info	What is the PATCH Study?	PATCH, also known as Prevention and Treatment of COVID-19 with Hydroxychloroquine (HCQ), is a research study that is being conducted by ProHEALTH NY, University of Pennsylvania, and UnitedHealth Group Research & Development to determine if HCQ can be an effective antiviral medication for preventing and treating COVID-19.
Study Info	What will be expected of me if I decide to participate in this study?	A package will be sent to you with either HCQ active or placebo pills. We ask that you take your medication according to the package direction, check your temperature twice daily or report symptoms of fever, record and report any adverse events, and upload this information daily through the study portal at patchstudy.com for the full duration of this study. You'll also be asked to get your swab samples taken at the end of the study.
Study Info	Can anyone join?	The **PATCH2** Study is focused on recruiting patients who are: • between the ages of 50-75 years of age • experiencing COVID-19 symptoms such as cough, fever, and/or sore throat • being sent home for a 14-day self-quarantine after being tested for COVID-19

		The **PATCH3** Study is focused on recruiting health care workers (MD, DO, PA, NP, RN or other members of the medical care team with significant COVID-19 exposure) who are: • not diagnosed with COVID-19 or PCR negative • exposed to patients with COVID-19 • asymptomatic (no cough, fever or sore throat) • scheduled to work 20+ hours per week for the next two months
Study Info	How can I enroll and participate in this study?	If you are interested in learning more and want to enroll in this research study, go to our study portal at **patchstudy.com**. You will then be asked to create a user profile and answer a few eligibility questions. If eligible, you will sign a consent form via the study portal and provide a valid shipping address to receive your tablets and study materials. Once completed, call us at **1-855-223-6987** between 8am to 5pm to confirm your enrollment and consent to our study.
Study Info	What happens to my data, who sees it, and how is it used?	To ensure your privacy, a study ID will be used in place of your name whenever researchers outside of the clinic access your information. Your information may be shared with individuals and organizations that conduct or watch over this research. Sharing your health data will be in accordance with the consent form and applicable data privacy laws. The data collected will be used in analysis to determine the efficacy of HCQ as an antiviral medication for COVID-19.
Study Info	Will being in this research benefit me?	There is no anticipated benefit for you directly. There may be future benefits for society based on the outcomes of the research for those who are at risk of infection.
Study Info	Are there risks to being in this research study?	The risks of this research are mainly related to taking Hydroxychloroquine (HCQ). The side effects of HCQ are well known and include: • Potential drug interactions with other medications. The study team will review the list of medications that should not be taken with HCQ before confirming that you are eligible to participate. If you take any of the drugs that may interact with HCQ you will not be eligible to participate. Because of this risk of drug interactions, it is important for you to inform the study team of all drugs, vitamins, and supplements you are currently taking or if you receive any new prescriptions during the course of the study.
Study Info	Who can I contact if I have more questions?	For additional questions or you want to learn more, please reach out to our Study Team at **1-855-223-6987** between 8am to 5pm**.**
PATCH3	What is the PATCH3 Study?	PATCH, also known as Prevention and Treatment of COVID-19 with Hydroxychloroquine (HCQ), is a research study that is being conducted by ProHEALTH NY, University of Pennsylvania, and UnitedHealth Group Research & Development to determine if HCQ can be an effective antiviral medication for preventing COVID-19.
PATCH3	How long will I be required to participate?	We expect that your taking part in this research will last for 9 weeks, including additional follow-up visits.

PATCH3	What will be expected of me if I decide to participate in this study?	A package will be sent to you with either HCQ active or placebo pills. We ask that you take your medication according to the package direction, check your temperature twice daily or report symptoms of fever, measure your oxygen level weekly while at work, track the number of work hours missed due to COVID-19 symptoms, and record and report any adverse events, and upload this information daily through the study portal at **patchstudy.com** for the full duration of this study. You'll also be asked to get your swab samples taken at the end of the study.
PATCH3	What happens if I sign-up and change my mind later?	You can stop taking part in this research at any time. If you choose to drop out, there will be no penalty and you won't lose any benefits. You'll still receive the same work benefits that you're entitled to. If you decide to leave this research, contact the research team at **1-855- 223-6987** between 8am to 5pm.
PATCH3	What happens to my data, who sees it, and how is it used?	To ensure your privacy, a study ID will be used in place of your name whenever researchers outside of the clinic access your information. Your information may be shared with individuals and organizations that conduct or watch over this research. Sharing your health data will be in accordance with the consent form and applicable data privacy laws. The data collected will be used in analysis to determine the efficacy of HCQ as an antiviral medication for COVID-19.
Medication Info	What is Hydroxychloroquine?	Hydroxychloroquine, also known as HCQ, is an antiviral medication that has been used for many years for the treatment of other illnesses such as malaria, lupus, and rheumatoid arthritis. Chloroquine derivatives have shown preclinical efficacy against COVID-19, but little clinical data is available.
Medication Info	How do I take the HCQ active or placebo medication?	You must be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels, gastric bypass, and lap banding.
Medication Info	What happens if I miss a dose?	Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.
Medication Info	What if I am taking other medication(s) for a different condition or using over-the-counter product(s)?	Please let the Study Team know what other medications you are currently taking before starting the study. We also ask that you do not to take any medications, including over-the-counter products, without first consulting with the Study Team.
Medication Info	What should I avoid while taking hydroxychloroquine?	Avoid taking an antacid or Kaopectate (kaolin-pectin) within 4 hours before or after you take hydroxychloroquine. Some antacids can make it harder for your body to absorb hydroxychloroquine.
Medication Info	What medications are not allowed during the study?	Please make the Study Team aware at **1-855-223-6987** during your call between 8am to 5pm if you are taking any investigational or off-label antiviral therapy such as: 1. Active cancer treatments (e.g. chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy). 2. Immunosuppressive medications, including, corticosteroids at doses exceeding 10mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-alpha blockers. 3. Live attenuated vaccines

Medication Info	How do you determine who gets the HCQ active or placebo drug?	You will be randomized by using computer generated randomization numbers.
Adverse Event	What are some common side effects of hydroxychloroquine?	Mild and transient headache, dizziness, and gastrointestinal complaints (diarrhea, loss of appetite, nausea, abdominal cramps and, on rare occasions, vomiting).
Adverse Event	What are some rare side effects of hydroxychloroquine?	Cardiomyopathy (chronic disease of the heart muscle) has been rarely reported with high daily dosages of hydroxychloroquine.
Adverse Event	What should I do if I experience side effects?	If severe, such as bluish lips or face; new confusion/dizziness or inability to arouse; persistent pain or pressure in the chest (not caused by coughing); and difficulty breathing (including severe shortness of breath and single word speech), **call 911 immediately.** If not severe, track side effects at **patchstudy.com** and discuss symptoms during your next study call.
Adverse Event	What happens if I overdose?	Seek emergency medical attention or call the Poison Help line at **1-800-222-1222**. An overdose of hydroxychloroquine can be fatal, especially in children. Hydroxychloroquine overdose must be treated quickly. You may be told to induce vomiting right away (at home, before transport to an emergency room). Ask the poison control center how to induce vomiting in the case of an overdose. Overdose symptoms may include drowsiness, vision changes, slow heart rate, chest pain, severe dizziness, seizure (convulsions), or shallow breathing.
Adverse Event	What is an adverse event?	An **adverse event (AE)** is any symptom, sign, illness or experience that develops or worsens during the course of the study. An adverse event does not need to be directly related to the study treatments. The following examples are considered adverse events: • If you experience an illness during the study • If you have a diagnostic procedure and the results are abnormal • If you seek an additional treatment during the study based on a diagnostic test
Adverse Event	What if my partner or I become pregnant?	Under FDA guidelines, that is considered an adverse event. Please call the study team at **1-855-223-**6987 between 8am and 5pm.
Adverse Event	What should I do if I experience an adverse event?	If you are experiencing a health emergency, **call 911**. Please do share any adverse event with your study team. • Please track all adverse events in the study portal at patchstudy.com • You can also call the study team to discuss your adverse event at 1-855-223-6987 between 8am and 5pm.
Adverse Event	What will happen if I report an adverse event during the study?	We care about your health and safety. • A study lead will follow up with you to gather more information and determine if any changes need to be made to the medicine you are taking.

		• Additionally, the information will be analyzed as part of the study results.
Adverse Event	What should I do if I have an adverse event, but it is the end of the study?	During your last call with the study team, please make a plan for follow-up. Our study team will continue to follow up with you until your adverse event is resolved. We also encourage you to share events with your personal physician.
HCQ vs CQ	What is the difference between the recently published study in Brazil and the PATCH studies being conducted at ProHEALTH?	There are several key but crucial differences between the recently published study in Brazil and the PATCH studies: 5. The Brazil study involved chloroquine, not hydroxychloroquine. Chloroquine is chemically similar to hydroxychloroquine but the two have very different safety records at high doses with hydroxychloroquine being the safer of the two. 6. Participants in the Brazil study were taking two additional antibiotics (Ceftriaxone and Azithromycin) which are known to exacerbate this problem. 7. Not only is the medication itself different, but so is the dose. The daily dose in the Brazil study was very high. 8. The PATCH study populations are different from the Brazil study which involved individuals hospitalized for COVID-19, which is not the case here.