Title of Research Study: Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial

Investigator Team Contact Information:

For questions about research appointments, the research study, research results, or other concerns, call the study team at:

Investigator Name: **David Boulware, MD** Investigator Affiliation: Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota	To Contact the Research Study Personnel with Questions or concerns, please email: XXXXXXXX@gmail.com

Supported By: This research is supported by the ***University of Minnesota***.

Key Information about This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

What is research?

Doctors and investigators are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Investigators learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of clinical care is to help you get better or to improve your quality of life. Doctors can make changes to your clinical care plan as needed.

Research and clinical care are often combined. One purpose of this informed consent document is to provide you clear information about the specific research activities of this study.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because either you have a confirmed diagnosis of COV-19 disease OR have been exposed to SARS-coronavirus-2 from someone who has COVID-19 disease.

What should I know about a research study?

- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The first objective is to determine whether a medication can be given to prevent COVID-19 disease in people who have been exposed to the virus but who are asymptomatic. The concept is called “post-exposure prophylaxis” — a method where medication is given to prevent an infectious disease after someone has contact with another infected person. This strategy has proven useful for diseases like influenza and bacterial meningitis.

The second objective is to determine if a medication can treat symptomatic mild COVID-19 disease to decrease the severity of illness, shorten duration of illness, and prevent hospitalization.

COVID-19 disease is caused by a virus called severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2 for short. Currently COVID-19 is infecting people across the US but no FDA-approved treatments are yet available. There are trials starting to test experimental treatments for ill, hospitalized patients; however, our study is proposing to *prevent* disease in people who have been exposed to COVID-19 or *treat* mild to moderate disease in people who are not hospitalized.

It is unknown whether you will receive any direct benefit by participating in the study, as we do not know if the study medication successfully treats or prevents disease yet. However, the data collected will be helpful in knowing how to manage COVID-19 disease moving forward.

The drug being investigated is called hydroxychloroquine (hi-drox-ee-klor-o-kwin), which is typically used to treat malaria and sometimes autoimmune diseases. It is not a new drug, having been first approved in 1955. Laboratory tests have demonstrated that it has activity against the SARS-CoV-2 virus.

How long will the research last?

We expect that you will be in this research study for 14 days. If you develop symptoms of COVID-19 or become hospitalized, we will follow you until your symptoms resolve.

What will I need to do to participate?

You will be asked to fill out an online form. We will send you the investigational drug by FedEx to be received tomorrow morning. You will need to take the drug for 5 days. We send you a brief internet-based survey about any symptoms or hospitalizations that you experienced. No blood sample collections or visits to the doctor’s office are required. You will need to:

- Take the study medicine for **five days**.
    - The first day you will take 4 tablets by mouth, then
    - 6-8 hours later take 3 tablets, then
    - Take 3 tablets once daily for 4 more days (5 days in total)

The hydroxychloroquine dose is similar to what is given for malaria treatment but higher daily doses of 3 tablets instead of 2 tablets.

- We will have a short follow up email survey for you to complete on:
    - Day 1 (to confirm you have received the medicines)
    - Day 3
    - Day 5
    - Day 10
    - Day 14

- An Additional survey at Day 21 if you are hospitalized or have pending test results at day 14. If still hospitalized at day 21, we will send follow up surveys every 2 weeks until you are discharged.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way that being in this study could be bad for me?

Hydroxychloroquine is a relatively safe drug which has been used for the prevention of malaria for over 60 years. However, like all drugs, side effects and adverse reactions are possible. Specific details are described later in the document. Some pre-existing medical conditions will prevent you from entering the study, such as if you have an abnormal heart rhythm. The dose being used and the short duration of hydroxychloroquine used in our study should also reduce the chance of an adverse event.

There has been substantial media attention on the potential dangers of abnormal heart rhythms when using very high dose chloroquine (2x higher than what is being used in our trial) with azithromycin OR using high dose hydroxychloroquine with azithromycin. On April 24, the FDA issued a caution: "The FDA is aware of reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines."

Our trial is using he normal FDA-approved dosing range of hydroxychloroquine WITHOUT azithromycin. The risk of having an abnormal heart rhythm is increased if one has:

- an abnormal heart rhythm, such as prolonged QT syndrome
- underlying heart disease
- chronic kidney disease.
- currently receiving medicines which prolong the QT interval.

All of these conditions are excluded from trial participation. Three interim analysis to date have not revealed any safety concerns.

Aside from possible medication side effects, there are no direct harms of this internet-based study. As there is no known way to prevent or treat COVID-19 disease, there are no standard medicines that other people are receiving in your situation. Any personal medical information collected will be kept confidential.

More detailed information about the risks of this study can be found under ***"What are the risks of this study? Is there any way being in this study could be bad for me? (Detailed Risks)" and in the "What happens to the information collected for the research?" section***

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits from study participation include preventing COVID-19 disease or reducing the severity of COVID-19 disease. There is also an important benefit to others and the medical community at large, as a medication that proves effective in preventing or reducing the severity of COVID-19 could have worldwide importance.

More detailed information about the benefits of this study can be found under ***"Will being in this study help me in any way? (Detailed Benefits)"***

What happens if I do not want to be in this research?

As there are currently no FDA-approved medications for the treatment or prevention of COVID-19 disease, there are no known alternatives other than deciding not to participate in this research study. Deciding not to participate in the trial will otherwise not affect your ability to receive supportive medical care from a doctor or hospital if you were to become sick. If you did develop COVID-19 disease, you would likely remain eligible for any treatment trial that was ongoing at a hospital.

If you wish to stop taking the study medicine, you may do so; however, the investigators would ask to continue to follow you to collect your clinical outcome through Day 14 – do you become ill? Do you become hospitalized?

Detailed Information About This Research Study

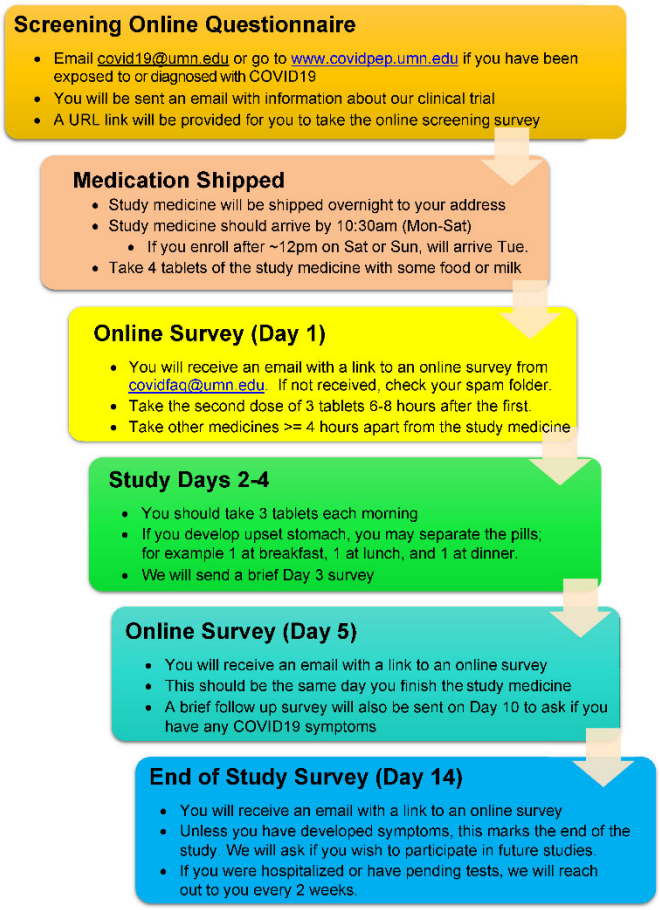
The following is more detailed information about this study in addition to the info listed above.

How many people will be studied?

We expect up to 2500 people may be in this research study.

What happens if I say "*Yes, I want to be in this research*"?

You will first answer an online questionnaire about your health history to determine if you can participate in this study. If you are deemed eligible and consent for study participation, then you will be randomly assigned to receive either hydroxychloroquine or a vitamin, which you will take for 5 days. Once assigned, the medication will be sent by FedEx overnight to you. You are to start the medication as soon as you receive it. Then you will fill out a survey on Days 1, 3, 5, 10, and 14 reporting any COVID-19 symptoms, medicine side effects, or hospitalizations that have occurred.



The experimental treatment you get will be chosen by chance, like flipping a coin. Neither you nor the research study doctor will choose what experimental treatment you get. You will have an equal (50%) chance of being given either treatment. Neither you nor the study doctor will know which experimental treatment you are getting.

No in-person visits or blood draws are required. All data will be collected by you reporting information in online questionnaires.

If you do become ill with COVID-19 symptoms or your symptoms worsen, you should contact your local doctor and/or local Department of Health.

Please call your doctors for medical care. If you become sick, we would recommend continuing the study medication, unless directed by your local doctor.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

1. Check tomorrow to make sure you receive the shipped medication at ~10:30am Mon-Sat (via Fedex)
2. Take your medication each day
3. Fill out at least five online questionnaires on Day 1, 3, 5, 10, and 14. Each survey should take ~2 minutes to complete on average.
4. If you do become symptomatic or are hospitalized, we will send additional surveys 2 weeks later (Day 28) to ask how long it took you to recover.

There are two optional sub-studies that you may participate in of:

- Checking for antibodies at Day 14 via the collection of a dried blood spot and returning
- Cardiac monitoring with daily electrocardiograms (EKGs) to assess for any change in heart rhythm.

More details on these sub-studies are on the final two pages.

What happens if I say "Yes", but I change my mind later?

- If you take part in this research study, and want to leave, you should tell us. Your choice not to be in this study will not negatively affect your right to any present or future medical care.
- If you stop the study, you should continue to follow the direction of your own doctor or public health officials.
- If you stop participating in the research study, information about you that has already been collected may not be removed from the study database. This is per U.S. FDA rules.
- **If you have severe side effects from the study medicine and wish to stop the medicine, you may stop the medicine and still remain in the study.** You're ongoing participation in reporting these side effects is very important. **Even if you do not take the study medicine or stop the study medicine, we would like for you to complete the follow up surveys, please.**
- If you stop being in the research, you will be asked if the investigators can continue to collect information from you about your clinical outcome through 14 days. You may choose to decline.

What are the risks of being in this study? Is there any way being in this study could be bad for me? (Detailed Risks)

- The main side effects of hydroxychloroquine include nausea (and upset stomach), decreased appetite, headache, rash, itching, and blurred vision. Central nervous system effects can include: ringing in the ears, irritability, nervousness, emotional changes, nightmares, or vertigo. All these symptoms should resolve once the drug is stopped. Dividing up the doses into multiple doses per day can decrease gastrointestinal side effects, such as nausea.
- More serious reactions are rare but possible; typically these occur in people taking the drug for much longer periods of time than as directed in this study, generally for >1 year. These include vision damage, heart rhythm problems, low blood sugar, and muscle weakness.

Persons with psoriasis may experience temporary skin worsening while taking the medication.

- Persons with diabetes should be aware that hydroxychloroquine may lower their blood sugars, and you should monitor your blood sugars frequently.
- Persons with a previous allergy to chloroquine or hydroxychloroquine should avoid the drug.
- Persons with Glucose-6-phosphate deficiency (G6PD), a blood disorder, may have increased risk of hemolytic anemia when taking hydroxychloroquine. Symptoms of hemolytic anemia include fatigue, shortness of breath, pale skin, and yellowing of skin or eyes.
- Persons with existing eye disease of the retina should not take hydroxychloroquine. Long-term use >1 year can be associated with rare retinal eye problems. Eye problems have not been reported with short-term use.
- Persons taking medications for abnormal heart rhythms may be ineligible for the study (more information below). Long term use >1 year has been associated with prolongation of the heart QT interval. Very high doses (2x higher than what is being used in this study) can be toxic or when used in combination with azithromycin – thi scna prolong the QT interval.
    - The QT interval is a feature on the electrocardiogram (i.e, “EKG”) that can provide valuable information. When the QT interval is longer than normal, this indicates that the heart muscle is taking longer than normal to recharge. If the QT interval is very long, the heart can develop fast beats, which can be potentially dangerous.
    - Azithromycin is prohibited in this study because of the concern for causing abnormal heart rhythms.
- Persons with porphyria cutanea tarda may develop fever and liver injury with high dose hydroxychloroquine use, such as given in this study. Persons with known porphyria are excluded.
- Persons with epilepsy or an otherwise low seizure threshold may be at greater risk of seizures while receiving hydroxychloroquine.
- Persons with structural heart disease, ischemic heart disease, or an abnormal heart rhythm called QT prolongation are not eligible to participate.
- Persons taking medications for significant heart rhythm problems are ineligible for the study due to increased risk for heart rhythm abnormalities. The most common medications are:
    - Flecainide (Tambocor)
    - Procainimide (Procan)
    - Propafenone (Rythmol)
    - Amiodarone (Cordarone, Pacerone)
    - Quinidine
    - Digoxin
- Other medicines which can prolong the heart QT interval – and are prohibited -- are:
    - Antimicrobials: levofloxacin, ciprofloxacin, moxifloxacin, **azithromycin,** clarithromycin, erythromycin, ketoconazole, itraconazole, or mefloquine
    - Antidepressants: amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, or venlafaxine
    - Antipsychotic or mood stabilizers: haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone
    - Methadone

- Sumatriptan, zolmitriptan

Due to avoidance of any *possible* increased risk of harm, if you are currently using these medicines, you are not eligible to participate.

- Some persons will receive a vitamin instead of hydroxychloroquine. Oral vitamins are considered safe, though can occasionally cause upset stomach. The vitamin being given will not interfere with any current vitamin that you may take.
- There is a risk that you may have a bad outcome with COVID-19 disease. This risk exists whether you are in the trial or not. We cannot predict for sure who will have mild or severe disease after infection from the virus. However, we do have evidence that persons >65 years old may be at higher risk for more severe disease. It is unlikely that this trial will worsen that risk in any way.
- There is some risk of a data breach involving the information we have about you. We comply with the University's data security standards to secure your information and minimize risks.

What do I need to know about reproductive health and/or sexual activity if I am in this study?

Pregnant women may participate in the trial.

Hydroxychloroquine is Pregnancy Category: C – Use with caution if benefits outweigh risks. Hydroxychloroquine crosses the placenta. Animal studies show evidence of fetal harm when used in high doses and for prolonged durations with associated neurological disturbances and interference with hearing, balance, and vision in the fetus. There is no data in animals that short term use, such as for the treatment of malaria (or as in this study), causes fetal toxicity.

In humans, a 2009 comprehensive review of the published literature reported that hydroxychloroquine is not associated with any increased risk of congenital defect, spontaneous abortion, fetal death, pre-maturity, or decreased numbers of live births in pregnant women with autoimmune diseases.

The effect of SARS-CoV-2 on pregnancy is not known. The U.S. Food and Drug Administration (FDA) recommends contraception use for all women of childbearing potential for the next 6 weeks. This is recommended but not required for your participation.

If you are or become pregnant while participating in this research study, we ask to be able to send you a short survey ~1 month after your delivery to collect information on the outcomes of your pregnancy.

Breastfeeding: Small amounts of hydroxychloroquine enter into breast milk. Small studies have reported no harmful effects in infants whose mothers' breastfed while taking hydroxychloroquine with no evidence of vision, hearing, or growth problems in infants who were followed up to one year of age.

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you. You will not be charged for the study medications or the cost to ship them to you.

What happens to the information collected for the research, including my

health information?

We try to limit the use and sharing of your information, including research study records, any medical records and any other information about you, to people who have a need for this information. But we cannot promise complete confidentiality.

If you participate in this study, your information, including your health information, will be used and shared for purposes of conducting this research. As described later in this Consent Form, your information may also be used and shared for publishing and presenting the research results. If you sign this Consent Form, you are giving us permission to use and share your health information for these purposes. We ask for access to your medical records to verify test results and review hospitalizations, you are giving permission to any health care providers who are treating you to share your medical records with us.

What health information will be made available?

Health information about you to be used and shared for the research includes those items checked by the research team below:

☒ Your medical records, which may include records from hospital and clinic visits, emergency room visits, medical history and physical exams, medications, progress notes, lab and pathology reports. These records may be used and shared for as long as this research continues. We will limit any request to 5 days prior and 90 days after study entry.

☒ Information collected as part of this research study, including research procedures, research visits, and any optional elements of the research you agree to, all as described in this Consent Form. This information might not be part of your medical record, and may include things like responses to surveys and questionnaires, and information collected during research visits described in this Consent Form.

Who will access and use my health information?

If you agree to participate in this study, your information will be shared with:

- The University of Minnesota research team and any institutions or individuals collaborating on the research with us;
- Others at the University of Minnesota and M Health/Fairview who provide support for the research or who oversee research (such as the Institutional Review Board or IRB which is the committee that provides ethical and regulatory oversight of research at the University, systems administrators and other technical and/or administrative support personnel, compliance and audit professionals (Such as the Quality Assurance Program of the Human Research Protection Program (HRPP)) , individuals involved in processing any compensation you may receive for your participation, and others);
- The research sponsor(s), any affiliates, partners or agents of the sponsor(s) involved in the research, organizations funding the research, and any affiliates, partners or agents of the funding organization(s) involved in the research, including state health departments;
- Organizations who provide accreditation and oversight for research and the research team, and others authorized by law to review the quality and safety of the research (such as U.S. government agencies like the Food and Drug Administration, the Office of

Human Research Protections, the Office of Research Integrity, or government agencies in other countries); and

- The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential. Specifically, your records may be audited to determine whether all information provided by you is correct.

Additional sharing of your information for mandatory reporting

If we learn about any of the following, we may be required or permitted by law or policy to report this information to authorities:

- Current or ongoing child or vulnerable adult abuse or neglect;
- Communicable, infectious or other diseases required to be reported under Minnesota's Reportable Disease Rule;
- Certain wounds or conditions required to be reported under other state or federal law; or
- Excessive use of alcohol or use of controlled substances for non-medical reasons during pregnancy.

How will my information be used in publications and presentations?

We may publish the results of this research in scientific, medical, academic or other journals or reports, or present the results at conferences. Information that makes it easy to identify you (such as your name and contact information, and medical records number) will not be part of any publication or presentation. If you have an extremely unique or rare condition that is not shared by many others, it is possible that some people may be able to determine your identity even without these identifiers.

What will be done with my data and specimens when this study is over?

Your data will not be used for any future research after this study is complete.

Do I have to sign this Consent Form and give my permission to make my information, including my health information, available for use and sharing?

No, you do not have to sign this Consent Form. But if you do not sign, you will not be able to participate in this research study. Treatment available outside of the study, payment for such treatment, enrollment in health insurance plans and eligibility for benefits will not be impacted by your decision about signing this Consent Form.

Does my permission for making my health information available for use and sharing ever expire?

Yes, we will limit collection of data to 90 days from entering the study.

May I cancel my permission for making my health information available for use and sharing?

Yes. You may cancel your permission at any time by writing to the researcher at the email address on the first page of this Consent Form. If you cancel your permission, you will no

longer be in the research study. If you cancel your permission, any health information about you that was already used and shared may continue to be used and shared for the research study and any optional elements of the study to which you agree in this Consent Form.

What happens to my health information after it is shared with others?

When we share your information with others as described in this Consent Form, privacy laws may no longer protect your information and there may be further sharing of your information.

Will I be able to look at my records?

The research team will allow you to see the information collected for this study.

A description of this clinical trial is available at: www.ClinicalTrials.gov/ct2/show/NCT04308668 as required by U.S. Law. This Web site will not include your name or any other direct identifiers such as your contact information. The Web site may include a summary of the results of this research. You can search this Web site at any time.

Will I receive research test results?

When the study is complete, we will email a summary of results to all participants' email addresses. You will not know if you got the hydroxychloroquine or the vitamin.

If you participate in the optional dried blood spot collection to check for antibodies at Day 14, we seek to return results to you within 4-6 weeks.

Will I be compensated for my participation?

There is no payment for study participation. The study medicine will be provided free of charge.

Whom do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP) at the University of Minnesota. To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-XXX-XXXX (Toll Free: 1-888-XXX-XXXX) or go to z.umn.edu/XXXXXX. You are encouraged to contact the HRPP **if**:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team at XXXXXXX@gmail.com (please email study related questions here first)
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The Human Research Protections Program (HRPP) may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for

study team contact information and “Whom do I contact if I have questions, concerns or feedback about my experience?” of this form for HRPP contact information.

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, you should seek first aid and emergency treatment from your healthcare provider, as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

If you develop new or worsening symptoms concerning for COVID19 disease (such as fever, cough, shortness of breath, sore throat, muscle aches, or fatigue) you should call your healthcare provider or local health department for testing and further instructions.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant