Consent for Participation in Research Activities at UCONN Health

Sponsor Investigator: Dr. Liang 860-679-7541
Site Co-Investigators: Drs. Kevin Dieckhaus, Jeff Aeschlimann, Mark Metersky, Eric Mortensen, Christopher Pickett

Project Title: A randomized, open-label study of the vascular and microbiologic efficacy of dipyridamole plus standard care vs. standard care in hospitalized COVID19 patients.

Expected Duration of Participation: 9 days

IRB Study #: 20-192-2.F

Funding Source: UConn Health School of Medicine

Name of Research Participant: _____

In this consent form, "you" always refers to the subject. If you are a legally authorized representative, please remember that "you" refers to the study subject. This consent form is intended for the patient who is eligible to participate in this study. However, if the patient is incapable of providing consent due to the severity of his/her illness, the consent of a relative or other authorized representative will be sought.

If at any time during the study, the patient becomes capable of providing consent, informed consent will be sought from the subject as a condition of their continuing participation

OVERVIEW OF THE RESEARCH

You are being asked to provide consent to participate in a research study. Participation is voluntary. You can say yes or no. If you say yes now you can still change your mind later. Some key points to consider are summarized in this overview, but you should consider all of the information in this document carefully before making your decision.

This study is an open-label drug study to examine potential benefit to hospitalized COVID-19 patients. This means that you and your doctor will know if you are taking the study drug. The drug is Dipyridamole which is already FDA approved for the prevention of clots in heart valve patients. It may also have anti-viral effects. The Principal Investigator is conducting this research under an Investigational New Drug review by the FDA. Dipyridamole is not currently approved for COVID-19 patients.

This research is being done to determine if Dipyridamole is safe and effective for helping to reduce complications in those hospitalized for COVID-19. The use of this drug in January 2020, during the outbreak of the pandemic in China, was reported in a small study to reduce complications arising in those hospitalized. When given 3 times a day as a pill or liquid, if necessary, Dipyridamole has been found to protect platelets (cells that help with clotting) from being destroyed throughout the body by the virus.

Researchers are also looking to see if the drug can stop this virus from reactivating in the body, and help as people do recover. The results of this research are to be promptly shared with the FDA by the Sponsor Investigator, Dr. Liang, for possible consideration as a new use for this drug. DNA is analyzed to learn more about differences in patient susceptibility to COVID-19 and how this medicine may act in the body. Results are not disclosed you individually.

In this UConn Health Trial of Open Label Dipyridamole (TOLD) for COVID-19, 100 subjects are expected to participate. Half of the participants will have the study medication added to their UConn Health standard care for COVID-19 (taken by mouth, 3 times a day); the other half will receive standard care (without study medication).

Participation will involve your review of this form and if you are enrolled, we will collect all hospital care information about you and any possible effects on that care from Dipyridamole.
50 of the 100 UConn patients on this study will receive the drug; the other 50 will receive standard care. This is determined like a coin flip after you join. You have a 50/50 chance of receiving study drug for 7 days, while hospitalized. Your care will be monitored for 2 days after you finish the drug, as part of the study.

Up to 3 sets of research blood, nasal swab and stool sample collections will be done on day 3, day 6 and day 9. The research blood will be collected along with your Standard of Care blood draw. However, if you are discharged before **Day 9**, a final day sample set will be collected. Standard of Care blood will be collected on **Day 0** (the day you sign consent) for research purposes if not already done. Any procedures that are research related are paid for by the study. You can withdraw at any time. Women with childbearing potential will be screened with a pregnancy test.

You are asked to allow the researchers to collect and analyze all the information from your Standard, Hospital care for the next 9 days along with samples for research purposes. The research is about your infection and your body response. COVID-19 research only test results can be provided to you upon your request, at any time. After 9 days, your study participation with collection of samples, is over

The most common risk associated with the study medication in pill form is dizziness (14%). Other possible risk associated with medication are stomach ache (6%), headache (2%) and skin rash (2%). Less frequent side effects reported are: vomiting, diarrhea, flushing or itching. Potentially serious effects of the study drug are chest pain and liver function deterioration are rarely seen.

While on the study your care team providers will ask about your overall health to include any of these possible side effects. Your care by providers may stop the drug for your overall safety.

If you join the study you may leave it at any time. There will be no negative effect on the care or services provided to you UConn Health in the Hospital. If a commercially viable product is developed you will not share in any financial gains.

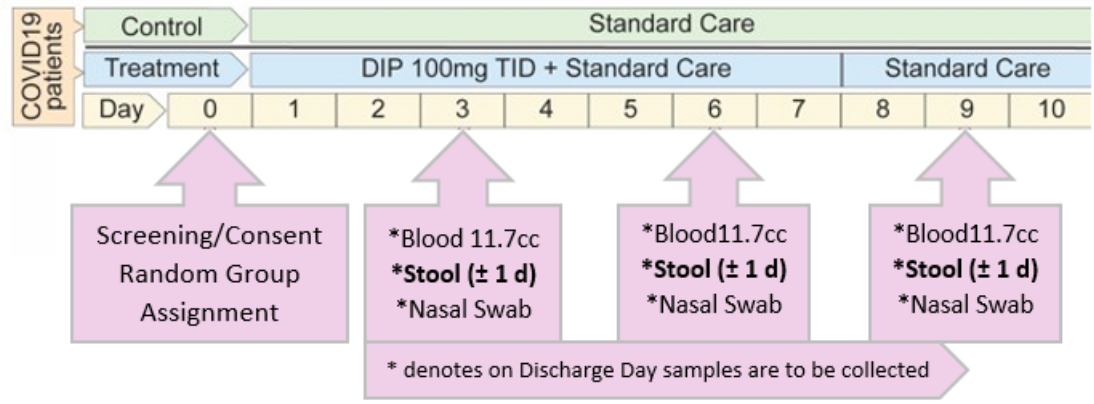
Why am I Invited to Participate?

You are 18 year old and hospitalized at UConn Health with COVID-19.

What Procedures Will Be Done?

You are asked to review and sign this consent to participate in the study.

After that, the study team will inspect all your hospitalization records for up to 9 days. There are no study visits. All patients get Standard Clinical Care with their providers giving the care for COVID19 in Hospital. After joining, ½ of patients will be assigned to receive the study drug. The use of the study drug, when assigned is considered experimental at this time. At 3, 6 and 9 days (+ or – 1 day) after starting the study, samples of blood, nasal swab and stool are obtained when for research analyses. All samples are obtained by your providers when available. The research swab (when available) and stool samples are collected to examine COVID-19 viral shedding; the blood tests for the research are included in monitoring your overall health while hospitalized.



Screening (day 0): All patients that have met enrollment criteria will be approached for informed consent. Standard care and all medical information will be documented in UConn Health's electronic medical record (EPIC). A review of previous drug and non-drug treatments within past 30 days and current medications will be conducted. Adverse events going forward from review of EPIC record and by inquiry of Provider Investigator as warranted will be documented.

What Alternative Procedures or Treatments Are Available To Me?

There is no FDA approved therapy for COVID-19. You may decline participation. You may choose to be in another study if available to you

What Are the Costs To Me For Participating In This Study?

There is no charge for participating in this research study. There is no charge for the sample collections conducted as part of your hospital care and there are no charges to you or your insurance for participating in this research. Regular standard of care charges for hospital treatment are billed to your insurance. This study is funded by a grant from the University of Connecticut, School of Medicine.

Is Participation Voluntary?

Participation in this study is voluntary. Before making a decision about whether to participate in this research study, read this consent form carefully and discuss any questions you have with an investigator listed above. You may also want to talk with family members, your primary care physician or a friend before making a decision.

If you decide to participate in the study, you are free to withdraw from it at any time. If you choose to withdraw from this study, the data and any specimens that have already been collected from you prior to withdrawing will continue to be used and remain in our study Research database.

If you decide not to participate and withdraw from the study, your decision will not affect your present or future medical care you receive at UConn Health and there will be no penalty or loss of benefits to which you are otherwise entitled.

How Many People Will Participate?

We expect 100 people to enroll in this study. By chance, 50 will receive the study drug added to their Standard Care.

How Long Will My Participation In This Study Last?

Your information will be collected for up to 9 days. Research samples are collected on day 3, day 6 and day 9 (+ or – 1 day); they will be collected on your last hospital day if necessary. Each day, the Study Team staff with the Investigators will review your hospital care progress in the EPIC medical record for this research. They will collect information about your condition and blood work and interact with your providers to monitor your safety whether on the drug or not. If you withdraw from the study we continue to collect medical record information, if you permit, until discharge or day 9, whichever is later. If you are discharged, recovered before 9 days, we will call you for follow up information, if you allow.

We will follow-up by phone at 30 and 60 days after study enrollment (Day 1) to check on your wellbeing. If we cannot contact you, we will check EPIC medical records and/or public health records if needed.

You can receive results of your research COVID-19 tests from the Hospitalization whenever you request from the study team. If you are a Department of Corrections participant, you will not be contacted after discharge.

Medication Dosing: If you are selected by chance to receive the drug, you will take 100 mg 3 times a day in pill form, for 7 days, when you are randomized to the Standard Care plus Dipyridamole group. If you are on a breathing tube initially or at some point, you are unable to swallow the medication. There is a liquid form which may be given to you when your standard care includes a tube passed through your nose into your stomach for nutrition and medications.

What Drug Will I Be Asked to Take? Is it Safe?

If you choose to participate in this study you may be assigned to take study medication- Dipyridamole which goes by the brand name, Persantine. For this research, all medicines and treatments which your providers consider using to treat you in the Hospital are permissible except overlapping use of other COVID-19 research drugs under another research study. All medication that you use will be recorded to our Research Records.

There may be risks related to use of Dipyridamole that are not now known. You will be notified of any new significant findings regarding the medication that might affect your willingness to continue in the study.

What is Dipyridamole?
Dipyridamole has FDA approval now when it is added to treatment with the blood thinner (warfarin) for the prevention of clotting complications with cardiac valve replacement. The investigators at UConn Health are familiar with its use. It is also FDA approved for combination with aspirin to reduce the risk of stroke in patients who have had transient ischemia (TIA) of the brain or stroke due to clotting.

What are Potential Risks and Side Effects Associated with Dypyridamole?

Side effects are usually mild and don't last long. In studies looking at long term use of Dipyridamole tablets, initial side effects usually disappear.

The following reactions were reported in two heart valve replacement studies, comparing Dipyridamole tablets and warfarin (Blood thinner) therapy to either warfarin alone or warfarin with placebo:

Dizziness (13.6% vs. 8.2%)
Abdominal distress (6.1% vs. 3.5%)
Headache (2.3% vs. 0.0%)
Rash (2.3% vs. 1.1%)

Other reactions from uncontrolled studies include- diarrhea, vomiting, flushing and pruritus.

In addition, chest pain related to the heart and liver test elevations have been reported rarely.

Safeguards Taken:

You will be asked by your providers each day if you are experiencing any potential medication related adverse effects, as above or otherwise, as part of Standard Care. If you experience any side effects, you may also contact the study coordinator by Dr. Bruce Liang at 860-679-7541.

<u>What Other Types of Risk Are Involved If I Choose To Participate?</u>
<u>Risks Associated with Confidentiality</u>

- Your participation is confidential. There is a chance that people outside of the research teammay learn of your participation in a study. Despite our best efforts we cannot guarantee 100% confidentiality.
    - ***Safeguards Taken:*** Paper research records will be locked in a secure location in the Clinical Research Center, apart from your medical record. The records will be identifiable, which means they will include a research code such as "753-XXX". Your name and/or medical record number may be on some documents, such as the consent form and any images of it, as transmitted by fax or electronically, via cell phone image obtained and then provided to study team by email. All UConn Health issued phones and fax machines are secure. If you are the LAR providing consent, your device may not be secure to guarantee confidentiality. All electronic files (e.g., emails, database, spreadsheet) containing identifiable information will be retained in study files which are password protected and encrypted. Any computer receiving or hosting such files will also have password protection. Only research staff will have access to the electronic files. A master list that links the code on the paper records to your name will be kept in electronic format.
- The research samples will be labeled with your research code only. You cannot be identified since

lab researchers will not have access to the master list which contains your personal information. .

Risks Associated with Blood Draws, Nasal Swabs and Stool Collection:

- Arrangements are made so that your study blood tube (about ¾ of tablespoon on day 3, 6 & 9) is taken as part of your scheduled blood draw to monitor your progress. There is a total of about two and half tablespoons of blood needed for this study. There can be some mild discomfort during the blood draw, if not done through a line you may already have. Some people develop a bruise at the needle site; some people report dizziness or even faint after having their blood drawn; and, some people develop minor infections. You may be uncomfortable temporarily while nasal swab is being obtained, but this is not harmful. There is no discomfort to you associated with our collection of a stool sample for research.
- ***Safeguards Taken:*** If you do not have an IV to draw sample, the area where the blood drawing needle is to be inserted will be wiped with a disinfectant before the needle is inserted. Only sterile needles will be used. The puncture site will be covered with a bandage. Experienced staff draw your blood obtain your swab and let them know if you if you feel faint and you can be assisted. You may decline if you wish.

Risks related to Genetic (DNA) Testing:

- The principal risk of genetic testing is a loss of confidentiality, with sensitive information concerning your genetic risk for disease becoming known. Such information, if available to you, could cause distress and if available to health or life insurers could adversely affect your access to insurance or its benefits.
- Variation in some genes is known to be directly related to risk for certain illnesses, and other genes we may encounter in our study with your DNA may be shown at some point in the future, to be related to illness. For example, genetic research could potentially reveal that you are at risk for certain diseases or that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers.
- ***Safeguards Taken (related to genetic testing):*** To guard against these risks, confidentiality will be closely protected. All study information will be kept in a research record. The research record is separate from your medical record (EPIC). The research record is not available to insurance companies.
- We will not make any of our genetic testing results available to you, nor will we add them to your medical record
- If you want to know your risk for genetic diseases, we can refer you to a genetic counselor. You (or your insurance carrier) would be responsible for the cost of any genetic counseling.
- While complete confidentiality of research records cannot be guaranteed 100%, we strongly protect our information and work constantly so that these safeguards will prevent any research genetic testing information that could cause you trouble in the future, from becoming known to anyone other than the scientists working on this study.

What Are the Benefits Of Participating In This Study?

You may benefit from UConn Health Standard Care and the medical treatment during the 9 day study. You may have a good response to the study medication, if received. However, it is also possible that you may receive no direct health benefit from being in this study and it is possible that your health may decline.

Other people who have COVID-19 requiring hospitalization may benefit in the future from the information learned from this study. However, there is also the possibility that no benefit will come from conducting this study.

Benefits related to genetic testing: You will not directly benefit from genetic testing done on your coded blood to explore immune or other response functions of people with COVID-19. Potential societal benefits may include a greater understanding of the genetic basis of susceptibility to or risks from COVID-19.

Will I Be Compensated For Participating In This Study?

There is no compensation available for participation in this study.

How Will My Personal Information Be Protected?

- The following procedures will be used to protect the confidentiality of your data. Information related to your participation in this study will be kept in a research record, separate from you medical records. The image of this consent form and the orders for the study drug, may be part of your EPIC medical record to alert your care providers.
- The study staff (principal investigator, co-investigators, research coordinator) will keep all research records (including any codes to your data) in a locked cabinet in a locked room. Each participant will have a unique sequentially assigned 3 digit study number. All research records will be labeled with this study ID (eg 753-XXX) rather than your name or other personal identifier.
- A master key that links your name and your study ID will be securely maintained (in locked file) during the study but will be destroyed when the study and data analysis are completed.
- All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be encrypted and only be assessable via password protected logon to prevent access by un-authorized users. Samples and any research data that will be shared with others outside the immediate study team will be coded with a study ID in place of your name to protect your identity.
- Any research lab results will be stored in your research record and upon completion of the study, the link between your personal identity and research information will be destroyed.
- We will do our best to protect the confidentiality of the information we gather from you but we cannot guarantee 100% confidentiality. You should know that the Department of Health and Human Services, the Food and Drug Administration (FDA), and UConn Health's Institutional Review Board and/or Human Subjects Protection Program may inspect records. They may inspect records to ensure that the study is being done correctly.
- A description of this clinical study will be available on http://ClinicalTrials.gov, as required by U.S. Law. The web site will not include information that can identify you. Following completion of this study, the web site will include a summary of study results. You can search the web site at any time.
- At the conclusion of this study the researchers intend to publish one or more articles on their findings. Information will be presented in summary format and you will not be identified in any publications or presentations.

What Will Happen to the Blood, Swab and Stool Samples I Give During the Study?

Once obtained, all blood samples (biochemical, proteins, DNA, RNA or plasma or serum from blood) stool samples (and DNA extracted from stool) and the infectious organisms/material (RNA) from swabs will become the property of UConn Health.

They will be used for research laboratory testing at UConn Health related to this study and/or will be stored in the laboratory of Dr. Liang, for later testing. Some are also distributed to Jackson Laboratories and the University of Michigan researchers. Your sample will be marked with your study ID but not your name or any other personal identifiers.

The link between your personally identifiable information and your assigned study ID will not be shared with anyone outside of the UConn Health research team, assisting in conduct of this study. The samples processed by collaborating scientists at Jackson Laboratory may include a code to allow results to be included in the research records when COVID-19 related testing is done there.

Prior to closure of the study, the link between your personal identity and your samples and information collected from you will be destroyed so that there will be no way, not even through codes, to link the samples and study results back to you.

The de-identified sample materials-DNA, RNA, blood cells, serum/plasma may be kept in storage indefinitely or until fully utilized by the Sponsor Investigator. These de-identified samples and any anonymized study information in the database, from you, may potentially be shared with other researchers and used in other projects. If such future research is done, additional informed consent will not be sought.

Your genomic data and health information will not be labeled with or contain your name or other information that could be used to identify you. However, it is possible that the information from your genome, when combined with information from other public sources could be used to identify you, though we believe it is unlikely that this will happen. Any researchers approved to access information in the database will agree not to attempt to identify you.

What Happens to the Blood, Stool and Swab Samples if I Withdraw from the Study?

If you choose to withdraw from the study, we will retain your samples in a coded format while the study is open. No further research will be conducted but we will use results of any sample data obtained before the time we are notified of your withdrawal.
The samples will be de-identified upon completion of the study and used as described above.

What Happens if I Withdraw from the Study or I am discharged before 9 days?

If you choose to withdraw from this study the data which has already been collected will continue to be used and remain in the research study database. We would like to be able to contact you in follow up if you are willing to continue to provide follow-up data for two days of information about status and any adverse events.

If you choose not to participate in the follow-up phase, your medical information or other confidential records will no longer be accessed for purposes of this research. However, investigators on this study may continue to review the study data collected prior to your withdrawal, and may consult public records, such as those establishing survival status.

Please indicate below whether you are willing to be contacted if discharged before Day 9 by the researchers in the future.

I **agree** for the researchers contact me for the follow-up _____(initials)
I **do not** agree for the researchers to contact me for follow up _____(initials)

What If I Decide To Stop Participating In The Study?
You are free to stop taking part in this study at any time. If you decide to stop taking part in the study, your care and relationship with your doctors or the UConn Health will not be affected in any way. If you decide to withdraw we ask that you let us know by calling the Sponsor Investigator Dr. Liang at 860-679-7541.

Can Someone Else Make Me Stop Participating In This Study?
The Sponsor Investigator or Co-Investigators listed above may stop your participation in this study at any time, with or without your consent.

Reasons that might lead the study doctor to stop your participation in the study include:

1) if in their judgment medical, health problems should be addressed on an urgent basis including intensive treatment such that you are not able to express your consent to participate or withdraw; 2) if you experience a significant serious drug side effects, likely attributed to Dipyridamole; 3) there may be other reasons that are not specified here.

Will I Find Out the Results Of This Research Study?
We intend to publish results of this study shortly after we complete full analyses.

What If I Experience An Adverse (Bad) Event or Injury Related To My Participation?
All research involves a risk that something bad might happen to you. In spite of all safety measures, you might develop a reaction or injury from participating in this study.

If you have an adverse event or study related injury, you should tell a Co-Investigator or Study staff or the Sponsor Investigator, Dr. Liang as soon as possible. You may contact Dr. Liang by calling 860-679-7541.

If the Sponsor Investigator determines that an injury you have experienced is possibly related to the study drug and requires medical intervention, you will receive care needed at UConn Health.

Financial compensation for such things as lost wages, disability or discomfort due to study drug injury is not offered. However, by signing this form you do not give up any of your legal rights.

UConn Health does not provide insurance coverage to compensate for injuries incurred during this research. However, compensation may still be available. A claim may be filed against the State of Connecticut seeking compensation. For a description of this process contact a representative of the UCH Institutional Review Board at 860-679-4849 and 860-679-8729.

UConn Health does not offer free care. However, treatment for a research related injury can be obtained at the UConn Health for the usual fee.

What If You Learn About Something That May Make Me Change My Mind?
We will tell you about any new information that may affect your willingness to participate. If you still want to participate we may ask you to sign a new consent form.

What if I Have Questions?
The Sponsor Investigator and Co-Investigators listed above and study staff are willing to answer any questions you have about the research. You are encouraged to ask questions before deciding whether to take part. You are also encouraged to ask questions during your study participation.

If you have questions, complaints or concerns about the research, you should call Dr. Liang, the Sponsor Investigator at 860-679-7541. If you have questions about your rights as a research subject you may contact the Institutional Review Board at 860-679-8729 or 860-679-4849.

You may also call the Institutional Review Board if you want to talk to someone who is not a member of the research team in order to pass along any suggestions, complaints, concerns or compliments about your involvement in the research, or to ask general questions or obtain information about participation in clinical research studies.

Please do not call the IRB number for medical related issues.

Consent To Participate:

By signing this form you acknowledge that you have read, or have had read to you, this informed consent document, have talked with research personnel about this study, have been given the opportunity to ask questions and have them satisfactorily answered, and voluntarily consent to participate in this project as described in this form.

By signing this form the individual obtaining consent is confirming that the above information has been explained to the subject and that a copy of this document along with a copy of the Research Participant Feedback Form, will be provided to the participant The handout regarding the Genetic Information NonDiscrimination Act has also been provided to the subject.

Role	Printed Name	Signature	Date	Time
Subject				
Legally Authorized Representative				

Co-investigator /Coordinator				
Witness (if telephonic)				