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TUFTS MEDICAL CENTER
TUFTS UNIVERSITY
Cardiology

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Prevention of COVID-19 Progression Through Early Administration of Inhaled Nitric Oxide

Protocol Number: STUDY00000554

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

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have been diagnosed with Coronavirus Disease 2019 (COVID-19).

What should I know about a research study?
- Someone will explain this research study to you.
- Please also read all of the following information carefully.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can decide 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. Do not sign unless you understand the information in it and have had your questions answered to your satisfaction.
- If you sign this form and decide to take part in this research study, keep a copy of the signed form for your records. It has information, including important names and telephone numbers, which you may wish to refer to.

Why is this research being done?
The purpose of this study is to investigate the effect of inhaled nitric oxide (iNO) in the prevention of progression of COVID-19. iNO has been used by doctors for many years to treat many different conditions. If you agree to participate, you will be randomly assigned to receive either iNO or a placebo (nitrogen gas). You will have a two out of three chance of receiving iNO.

How long will the research last and what will I need to do?
Regardless of which agent (iNO or nitrogen) you are assigned to receive, we expect that it will continue for up to 2 weeks, until your condition changes or you are discharged. It will stop if your condition improves or if you require higher flow oxygen, or a breathing tube. Regardless of whether your condition improves, we will continue to observe your condition for 28 days or until you are discharged, whichever comes first.

You will be given the agent (either iNO or nitrogen) through an iNO device. Blood samples, for your routine clinical care will be collected regularly. An extra tube of blood will be collected at baseline, at 24 hours, at 72 hours and 1 week for this study as well. Regardless of whether you are receiving iNO or nitrogen, another extra blood tube will be collected at 24 hours and at one week for measurement of methemoglobin in order to monitor for iNO toxicity. The amount of oxygen in your blood will be tested continuously with pulse oximeter or arterial blood gas measurements, according to the standard of care for subjects with acute respiratory disease. A pulse oximeter is a small, lightweight device that attaches painlessly to your fingertip and is sending light through your finger to measure the amount of oxygen carried by your body. It is called “pulse” because it responds to the pulsation of your small arteries of your fingertip in order to measure the oxygen.

More detailed information about the study procedures can be found under the **“Procedures to be Followed”** section.

Is there any way being in this study could be bad for me?
Inhaled Nitric Oxide is well tolerated without significant side effects. Blood pressure drop is the most common side effect and lasts for a short period of time. Methemoglobinemia is a condition in which hemoglobin, which is the oxygen delivering molecule, is changed by the iNO and becomes unable to transfer adequate oxygen to the tissues. We will be testing your blood for this effect, which is another rare side effect of iNO, particularly with the dose being administered. Nitrogen is a non-reactive gas that makes up 78% of the air we breathe. There are no known risks to inhaling the small amount of extra nitrogen that would occur with this study. Nitrogen does not carry a risk of blood pressure drop or methemoglobinemia. Neither the iNO or nitrogen will interfere with oxygen that you may be receiving as part of your care for COVID-19.

There are some possible risks associated with having your blood drawn including bruising and/or some bleeding at the needle puncture site. Rarely an infection may develop. Lightheadedness and fainting may result from the blood sampling procedure.

More detailed information about the risks of this study can be found under the **"Risks"** 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.

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

Participation in research is completely voluntary. You can decide to participate or not to participate. Instead of being in this research study, your choices may include standard supportive care with oxygen supplementation as needed based on the severity of your clinical presentation. If in your doctor's opinion you should receive treatment with iNO, your doctor will not be prohibited to prescribe iNO to you, even if you decide not to participate in this study or even if you participate in the study and you are selected to be in the control group.

Subjects participating in this trial will not be prohibited from participating in any other trial and will be able to receive any other therapy deemed appropriate by the care team. However, additional ongoing research trials of treatments being investigated may be closed to you, since they may exclude subjects participating in other trials like this one.

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

PURPOSE OF STUDY

The purpose of this study is to investigate the effect of inhaled nitric oxide (iNO) in the prevention of progression of Coronavirus Disease 2019 (COVID-19). COVID-19 is a global pandemic which is caused by a virus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). The majority of subjects testing positive for COVID 19 do not require hospitalization but get better and appear to have complete clinical recovery without requiring any specific treatment within 2-4 weeks. One out of five subjects experience clinical worsening and require hospitalization and five out of a hundred subjects need admission to the intensive care unit. The subjects who get worse experience shortness of breath due to reduced body oxygenation and develop a specific type of lung injury called Acute Respiratory Distress Syndrome (ARDS). iNO relaxes the blood vessels of the lung and improves the oxygen delivery from the lung to the blood in subjects with ARDS. iNO has minimal effects in the tone of blood vessels outside the lungs, and as a result, it does not cause significant decrease in the blood pressure. With this study, we want to investigate whether giving iNO in the lung early will prevent the progression of COVID-19 from the early stages to more advanced disease stages and ARDS.

This study will be conducted entirely at Tufts Medical Center and we will enroll 42 subjects.

Inhaled nitric oxide is approved by the FDA, but is experimental as used in this study. The FDA has allowed iNO to be used for research purposes specifically for this study.

PROCEDURES TO BE FOLLOWED

The study will be performed during your hospitalization at Tufts Medical Center. After you provide informed consent to participate in the study, you will be randomized to either receive iNO or nitrogen. Regardless of which agent you are assigned to receive, the rest of your medical care will be the same as that for anyone else being treated for COVID-19.

The intervention that you will receive will be chosen by chance. Neither you nor the study doctor will choose whether you get iNO or nitrogen. You will have a two out of three chance of being given inhaled nitric oxide. This study is "blinded," which means neither you, your study doctor, nor the doctors taking care of you for COVID-19 will know whether you were randomized to receive iNO or nitrogen. This is to ensure that the clinical information collected during the study is not influenced by knowledge about whether or not you are receiving iNO. Your condition will be monitored daily (as it would for clinical purposes regardless) regardless of whether you are receiving iNO or nitrogen.

Regardless of which agent you are assigned to receive, it will be administered using the iNO pulse device at a dose of 125 mcg/kg IBW/hr. The iNO pulse device is a portable delivery system that weighs about 2.5 pounds. It has battery life of approximately 16 hours when fully charged. It supplies the agent into the nose through a nasal cannula. The cannula attaches to both the device containing the nitric oxide or nitrogen and a separate source of oxygen. The doses of the agent (either iNO or nitrogen) and oxygen can be adjusted separately, and the agent does not interfere with the delivery of oxygen. The agent will be provided for 24 hours per day. Pulse technology detects when you are about to inhale and delivers a bolus (pulse dosage) of iNO or nitrogen at the start of your breath The iNO or nitrogen will be administered for up to two weeks unless your clinical status deteriorates and you require higher flow oxygen or a breathing tube placement, in which case the study intervention will be stopped. The study intervention will also be stopped if your clinical condition, including the amount of oxygen in your blood, improves.

We will ask you to rate your shortness of breath on a 0-10 scale after you agree to enter but before you actually start receiving your assigned agent, and then at various times afterwards. This is a simple scale that poses no risk to you.

Blood samples will be collected as part of the standard of care. During these blood draws, extra tubes of blood will also be collected before the study starts, after 24 hours, after 72 hours and at one week. These samples will be tested for levels of proteins involved in inflammation, called IL6 and TNFa. This test will allow us to investigate the effect of iNO on inflammation which is thought to be an important factor leading to progression of COVID-19. Regardless of whether you are assigned to receive iNO or nitrogen, additional blood is also taken after 24 hours and at one week to measure methemoglobin levels. Drawing blood for this test will require an

additional needle stick, and will be performed by respiratory therapists that are trained in this procedure.

Each blood draw will collect 9 ccs of blood (about 2/3 of a tablespoon), to be stored in a tissue bank at Tufts Medical Center. A total of less than 6-7 tablespoons of blood will be collected over the course of the study. Blood samples deposited in the Tissue Bank will be used for the purpose of academic, scientific research and may include the analysis of expression of biological molecules including inflammatory mediators or other biological markers that will be defined in the future. Your participation in the blood banking part of the study is completely voluntary, and your participation is not a condition for enrollment in the main study or for participation in any other research study or for your future care or treatment at Tufts Medical Center or Tufts University. Blood samples may be released to outside investigators for future research studies without your additional informed consent. The released samples will be completely de-identified to protect your confidentiality. The investigators will have expertise in the measurement of the biological marker of interest and could be affiliated with a university or an independent laboratory. You will be able to withdraw your consent for future use at any time unless the tissue bank has already distributed the samples, the samples have been completely exhausted, or the code to match the sample to the subject is no longer available. Please contact Dr. Konstam if you wish to withdraw your consent to the future use of samples. The storage of samples for future research has the possible risk of loss of confidentiality. You will receive no direct benefit from participating in this banking. Once your specimens have been transferred to the tissue bank, the results of research performed on those specimens will not be communicated to you or to your primary care doctor, and/or placed in your medical record. Blood samples will be stored for at least two years.

We will also review your medical record to document information about your medical history and treatment in a computer database. All collected information will be completely de-identified to protect your confidentiality.

WITHDRAWAL

If you are eligible to participate and decide to be in the study, the Principal Investigator may still choose to discontinue the inhaled agent (either iNO or nitrogen) if he thinks it is in your best medical interest. You can also leave the research at any time and it will not be held against you. If you refuse to participate in the study or stop being in this study, it will not affect your care or treatment outside this study, payment for your health care, or your health care benefits.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

If you withdraw from the study or the Principal Investigator decides to discontinue administration of iNO or nitrogen, any data collected from you before your withdrawal will still be used for the study. If the Principal Investigator decides to discontinue iNO or nitrogen administration, we will continue to follow you and collect clinical data in order to investigate your response to the intervention.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, these data will be handled the same as research data.

If you withdraw from the study the study investigators will not access your medical record or other confidential record requiring your consent.

RISKS

Inhaled Nitric Oxide is generally well tolerated without significant side effects. Blood pressure decrease is a rare side effect and lasts for a brief period of time. Methemoglobinemia is another rare side effect. In this condition, the hemoglobin, which is the oxygen delivering molecule, is changed by the iNO and becomes unable to transfer adequate oxygen to the human tissues. Methemoglobinemia is unusual when iNO is administered within the dose range used for this study. Methemoglobin level in the blood will be measured 24 hours and one week after initiation of iNO treatment and iNO will be discontinued if methemoglobin level exceeds 5%. iNO may increase the risk of kidney dysfunction, especially with prolonged use. Kidney disfunction appears to be rare and temporary. Finally, the risk of death from iNO administration is extremely low, especially for the dose range used for this study.

The FDA categorizes iNO into category C with regards to safety for use during pregnancy. This means that there are no well-controlled studies that have been done in humans. Therefore, this study drug may be used if the potential benefits to the mother outweigh the potential risks to the unborn child. In addition, there are no adequate data from the use of iNO during breastfeeding. Based on that, we have decided to exclude from this study women who are pregnant or actively breastfeeding.

Nitrogen is a non-reactive gas that makes up 78% of the air we breathe normally. There are no known risks to inhaling the small amount of additional nitrogen that you would receive through the device if you are assigned to receive nitrogen. Nitrogen has been used in a similar way in other research studies investigating the iNO pulse device and no risks have been observed for the participants assigned to receive nitrogen in those studies.

All or almost all needle sticks for blood draw will occur, regardless, as part of your standard care. There are some possible risks associated with having your blood drawn including bruising and/or some bleeding at the needle puncture site. Rarely an infection may develop. Lightheadedness and fainting may result from the blood sampling procedure.

There is also a possible risk of breach of confidentiality. Storing your medical information and storing samples for future research includes the possible loss of confidentiality. To minimize this risk, information that personally identifies you as a subject is not being captured. All stored samples will be completely de-identified and no research results will be placed in your medical records or communicated to you or to your treating physician. Study data will be stored in a secure, password-protected database accessible by only the research team on password-protected hospital computers in locked offices.

RESEARCH RELATED INJURY

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of being in this research study. You or your insurance carrier will be required to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment, and professional services are available to you, just as they are to the general public. The institution will not pay for your treatment if you become ill or injured as part of this study.

Due to the coronavirus public health crisis, the federal government has issued an order that may limit your right to sue if you are injured or harmed while participating in this COVID-19 clinical study. If the order applies, it limits your right to sue the researchers, healthcare providers, any study sponsor or manufacturer or distributor involved with the study. However, the federal government has a program that may provide compensation to you or your family if you experience serious physical injuries or death. To find out more about this "Countermeasures Injury Compensation Program" go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

COSTS

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only. These include the measurement of inflammatory mediators in the collected blood samples. You or your insurance provider will not have to pay for the iNO or nitrogen while you take part in this study.

PAYMENT

Study subjects will not be paid for their participation in the study.

PRIVACY AND CONFIDENTIALITY

All information collected during the study is confidential to the extent permitted by law. The blood samples will be labeled with a number, not your name, and only authorized personnel working on the study will have access to the code that links the number with your identity. The results of studies using material from the Tissue Bank may be presented at meetings or in publications, however, your identity will not be revealed. You will not be contacted at any time by the Tissue Bank or anyone who receives your samples from the tissue bank.

If you decide to take part in this research study, your personal information will not be given to anyone unless we receive your permission in writing. It will only be given if the law requires it. It will also only be given for regular hospital treatment, payment, and hospital management activities.

We will make every effort to keep your information private, but it cannot be completely guaranteed. Certain government agencies, like the Office for Human Research Protections,

Department of Health and Human Services, U.S. Food and Drug Administration, and the Institutional Review Board of Tufts Medical Center and Tufts University Health Sciences, may check records that identify you. This might include your medical or research records and the informed consent form you signed. The records of this study might also be reviewed to make sure all rules and guidelines were followed.

For any questions about this, please contact Dr. Patrice Nickens, desvignp@nhlbi.nih.gov.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this web site at any time.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

If you sign this document, you give permission to the Principal Investigator named above and research staff at Tufts Medical Center as well as other individuals at Tufts Medical Center who may need to access your information to do their jobs (such as for treatment, payment (billing) or health care operations) to use or disclose (release) your health information that identifies you for the research study described above.

The parties listed in the preceding paragraph may disclose the health information described below to the following persons and organizations for their use in connection with the research study:

- Individuals or organizations working under the direction of the Principal Investigator(s) for the study,
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories on behalf of Tufts Medical Center or Tufts University Health Sciences.
- Other researchers and institutions that are conducting or participating in this study,
- The study sponsor and any companies that they use to oversee, manage, or conduct the research.
- The Office for Human Research Protections in the U.S. Department of Health and Human Services, the United States Food and Drug Administration (FDA) and other federal and state agencies that have the right to use the information as required by law, and
- The members and staff of any Institutional Review Board (IRB) and a study safety monitor, not otherwise involved in the study.

The health information that we may use or disclose (release) for this research study includes all information in your medical record related to the diagnosis and management of COVID-19, including the record of your care, as well as any information collected or created during the course of this study.

Tufts Medical Center is required by law to protect your health information. By signing this document, you authorize Tufts Medical Center or Tufts University Health Sciences to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You may not be allowed to see or copy the information described on this form as long as the research is in progress, but you have a right to see and copy the information upon completion of the research in accordance with hospital policies.

Tufts Medical Center may not withhold or refuse to provide you with clinical care based on whether or not you sign this form.

This authorization does not have an expiration date. You may change your mind and revoke (take back) this authorization at any time. Even if you revoke this authorization, this site's clinical, administrative and research staff may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this authorization, you must write to: HIPAA Privacy Officer for Research, 800 Washington Street, Box 5100, Boston, MA 02111. If you revoke this authorization, you may no longer be allowed to participate in the research described in this form.

WHOM TO CONTACT

If you have questions, concerns, or complaints, or think the research has hurt you, please contact the Principal Investigator, Dr. Marvin Konstam, at Tufts Medical Center as soon as possible at 617-636-6293 or via the hospital page operator at 617-636-5114. You can also feel free to contact any member of the research team below:

- Project Coordinator: Abbey Haynes (617-636-4990)
- Co-Investigator: Gaurav Gulati, MD (pager number: 617-705-1904)
- Co-Investigator: Mehak Dhande, MD (pager number: 617-705-1282)

If you have question about your rights as a research study subject, call the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of people who take part in the studies. Federal law requires the IRB to review and approve any research study involving humans. This must be done before the study can begin. The study is also reviewed on a regular basis while it is in progress. This research study has been reviewed and approved by the IRB of Tufts Medical Center and Tufts University Health Sciences.

Documentation of Consent

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered to my satisfaction. I agree to take part in this study.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

_____ _____ _____
Participant's Signature Date Time

I consent that my de-identified blood samples can stored in a central tissue bank at Tufts Medical Central.

___YES ___NO

I consent that my de-identified blood samples may be used for future research by investigators.

___YES ___NO

_____ _____
Participant's Signature Date

I have fully explained to _____ the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____
Date Principal Investigator or Representative's Signature

Witness Signature:

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

_____ _____ _____
Witness' Signature Date Time

_____
Witness Printed Name

_____ _____ _____
Legally Authorized Representative's Signature Date Time

_____
Legally Authorized Representative's Printed Name

_____
Assent

Assent
- ❑ Obtained
- ❑ Not obtained because the capability of the subject is so limited that the subject cannot reasonably be consulted.

Check the relationship of the legally authorized representative to the subject (list is in order of recognized hierarchy):

- ☐ 1. The health care agent, upon proper invocation of the health care proxy
- ☐ 2. Legally appointed guardian or conservator
- ☐ 3. Spouse
- ☐ 4. Adult children – (majority consensus encouraged)
- ☐ 5. The subject's parent – (consensus encouraged)
- ☐ 6. Adult siblings – (majority consensus encouraged)

I have fully explained to _____ the nature and purpose of the
Legally Authorized Representative

above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____	_____
Printed Name of Principal Investigator or Person Conducting the Informed Consent Discussion	Position

_____	_____
Date	Signature of Principal Investigator or Person Conducting Informed Consent Discussion