**Consent Form**

**Title of Research Study:** Ultrasound Neural and Immunomodulation Treatment Evaluation Study for COVID-19 (UNITE Study (UMN-GE) for COVID-19)

**Investigator Team Contact Information:** Hubert H. Lim, Ph.D.
For questions about research appointments, the research study, research results, or other concerns, call the study team at:


Investigator Name: Hubert H. Lim, Ph.D.
Investigator Departmental Affiliation:
Department of Otolaryngology-Head and Neck Surgery
Department of Biomedical Engineering
Phone Number: (612) 626-4565
Email Address: hlim@umn.edu

Senior Researcher Name: Rachel Graham, Ph.D.
Department: Otolaryngology-Head and Neck Surgery
Telephone Number: 612-568-2246
Institutional Email Address: rgraham@umn.edu

Senior Researcher Name: Morgan Newhoff, Ph.D.
Department: Otolaryngology-Head and Neck Surgery
Telephone Number: 612-460-1576
Institutional Email Address: mnewhoff@umn.edu



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# *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 you have been diagnosed with COVID-19, and your symptoms are severe enough to require hospitalization.

## What should I know about a research study?

- Someone will explain this research study to you.
- 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?

This research is being done to study whether ultrasound treatment of the spleen can reduce the severity of COVID-19 symptoms. Ultrasound is widely used in human medicine because it is safe, non-invasive, and painless. The same kind of ultrasound that is used for imaging (for example, to visualize babies in utero) may be able to treat inflammatory diseases including COVID-19.

COVID-19 is a disease caused by infection with the SARS-CoV-2 virus. Some COVID-19 patients develop a severe respiratory disease called acute respiratory distress syndrome and this disease is caused, in part, by a significant increase in inflammatory factors. Clinical therapies that reduce these elevated inflammation factors (e.g., inflammation molecules in your body called cytokines) may be capable of diminishing symptoms in severe cases of COVID-19 by reducing inflammation.

Evidence from animal studies and a human clinical trial for the treatment of Rheumatoid Arthritis, another inflammatory condition, has shown that ultrasound applied to the spleen can suppress some of the same inflammatory factors that are believed to cause severe symptoms of COVID-19.

This study will employ ultrasound devices produced by General Electric (GE) that are currently used in hospitals and approved for diagnostic imaging by the FDA (i.e., United States Food and Drug Administration that approves the use of drugs and devices for different clinical applications in humans). The ultrasound energies applied to the spleen in this study to treat COVID-19 will not exceed what is currently approved for diagnostic imaging with those GE ultrasound devices.

## How long will the research last?

We expect that you will be in this research study until your day of discharge from the hospital. The ultrasound therapy will only be applied for 7 days (near the beginning) of your hospital stay, unless you are discharged sooner, but we will continue to record your laboratory test results and health status descriptions (e.g., body temperature) collected by your clinical care team until you are discharged from the hospital.

## What will I need to do to participate?

There will be two groups in this study. One group will receive ultrasound treatment in addition to the standard clinical care. A control group will receive standard clinical care without ultrasound treatment. If you are assigned to the ultrasound therapy group, you will be asked to permit study personnel to perform an ultrasound therapy session that lasts about 15-20 minutes per day, at approximately the same time every day, for 7 days, unless you are discharged sooner. This will involve a small, gel-coated

probe being firmly (but not painfully) pressed to your upper left abdomen over your ribs, while laying still for about 15-20 minutes on your right side (other positions are possible if you are not able to lay on your right side). This 15-20 minute period includes a period of 5-10 minutes when study personnel will use the ultrasound device to locate your spleen and to position the ultrasound probe in a proper location around the ribs area, and approximately 10 minutes for application of ultrasound to your spleen. Each day, you will be asked to have additional blood drawn during your normal daily blood draws that occur as part of your standard clinical care. If you are assigned to the control group, you will be asked to have additional blood drawn each day, for 7 days (unless you are discharged sooner), during your normal daily blood draws that occur as part of your standard clinical care.

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?

There are no expected risks that the study personnel are aware of in being in this study due to ultrasound application of the spleen. There could be some discomfort or inconvenience in laying on your side (or other designated body position) for about 15-20 minutes while the ultrasound probe is being positioned or held still over the ribs area each day for up to 7 days. The intention of ultrasound application to the spleen is to reduce inflammation in the body, so we are expecting improvements in your COVID-19 symptoms by reducing the excess inflammation in your body. However, some inflammation and immune response is needed for fighting off the virus. It's possible that anti-inflammatory or other effects on your immune system caused by ultrasound could result in an unknown infection. Your inflammatory markers will be tracked daily and monitored by study doctors. If your key inflammation and/or number of immune cells are reduced below normal ranges, we will stop treatment. 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?

Possible benefits to you include a reduction in COVID-19 symptom severity. If the study results show promise, steps towards incorporating ultrasound into COVID-19 treatment on a larger scale across hospitals could be taken, potentially benefitting others with COVID-19 in the future.

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

You are under no obligation to participate in this research. Instead of participating in this research study you may choose to undergo other investigational treatment practices without the addition of splenic ultrasound as an investigational treatment for COVID-19. You may also forgo participation in any investigational treatment practices/research studies and continue to receive standard-of-care treatment from your clinical care team.

## *Detailed Information About This Research Study*

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

### How many people will be studied?

We expect about 30 people will be in this research study. This clinical trial with the GE ultrasound device

for COVID-19 treatment is being conducted at the University of Minnesota.

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

If you are interested in participating, study personnel will conduct a screening visit to discuss your enrollment in the study.

**Screening Visit**

If you agree to be in this study, you will be asked to sign this consent form before any study related procedures take place.

The following will be completed at the screening visit:

- Questions about your medical history and medications you are using.
- A pregnancy test for women of child-bearing potential if not previously tested for pregnancy following hospital admission.

Note that these questions may be asked virtually (for example, over phone or Zoom, a secure online application) to minimize the exposure of study personnel to COVID-19.

We will evaluate your health-related data (medical history, medications, etc.). If you qualify for the study and agree to enroll, the therapy you receive will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose which therapy you receive. You will have a 50/50 chance of being assigned to one of two groups:

Group A: control group receiving your doctor's standard of care, plus a few additional blood tests;

**OR**

Group B: ultrasound therapy group with ultrasound applied to the spleen, in addition to your doctor's standard of care and a few additional blood tests.

You will be told which group has been randomly assigned to you after enrollment. Both groups will be evaluated daily for their medical progress including daily blood draws to evaluate inflammation, medical histories and current/former medications, oxygen levels, and other COVID-19 symptoms. Standard of care provided in both groups are intended to improve your health condition, in which ultrasound therapy may or may not further improve your health condition above standard of care.

### If I am assigned to Group A, the control group, what are the daily procedures?

If you are assigned to the control group, you will receive standard of care from your physician, as well as extra daily blood draws and evaluations of your medical progress.

- Additional blood will be drawn during your normal daily blood draws performed as part of your standard clinical care. This will be an additional 2 teaspoons (9.5mL).
- A photo and/or video may be taken if optional consent has been given.
- Study personnel will record your clinical laboratory results, temperature, pulse oximetry, supplemental oxygen status, and other health status descriptions already being collected as part of your standard clinical care by the hospital staff.

## If I am assigned to Group B, the ultrasound therapy group, what are the daily procedures?

**Study Days 1-7 (or Day 1 to 'day of discharge', if discharged before Day 7)**

If you are assigned to the group receiving ultrasound therapy, your experimental treatment plan will consist as follows:

- Study personnel will come to your room at approximately the same time every day.
- Your spleen will be located with ultrasound imaging, which can take 5-10 minutes, and study personnel will mark the location on your skin with a nontoxic marker. This is to identify where to place the device in subsequent visits.
- Once the spleen is located, ultrasound treatment will be performed for a period of about 10 minutes, and exact application time will be determined by trained study personnel. Thus, ultrasound application (imaging and treatment combined) will be approximately 15-20 minutes in total duration.
- You may be asked a few questions to assess your disease symptoms, and any additional effects splenic ultrasound application may be causing.
- Additional blood will be drawn during your normal daily blood draws performed as part of your standard clinical care. This will be an additional 2 teaspoons (9.5mL).
- A photo and/or video may be taken if optional consent has been given.
- Study personnel will record your clinical laboratory results, temperature, pulse oximetry, supplemental oxygen status, and other health status descriptions already being collected as part of your standard clinical care by the hospital staff.

**All Participants: Study Days 8-Hospital Discharge (only applicable if not discharged on or before Day 7)**

- A photo and/or video may be taken if optional consent has been given.
- Study personnel will remotely record your standard laboratory results, temperature, pulse oximetry, supplemental oxygen status, and other health status descriptions already being collected as part of your standard clinical care by the hospital staff.

**Table Summarizing Visits and Assessments for All Participants**

| | Screening | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Subsequent days until hospital discharge |
|---|---|---|---|---|---|---|---|---|---|
| Consent | x | | | | | | | | |
| Inclusion/Exclusion | x | | | | | | | | |
| *Pregnancy test | x | | | | | | | | |
| **Ultrasound imaging to determine spleen location (and reassessment as needed) | | x | x | x | x | x | x | x | |
| **Ultrasound treatment | | x | x | x | x | x | x | x | |
| Standard of care bloodwork and assessments | | x | x | x | x | x | x | x | x |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Blood draw for additional study metrics (9.5mL). | | x | x | x | x | x | x | x | x |
| Photo, audio and/or video collection as needed (if optional consent obtained) | | x | x | x | x | x | x | x | x |

**For women of childbearing potential if pregnancy test not previously administered following hospital admission*
***For participants randomly assigned to "treatment group"*

You will have the option to participate in the collection of photos and/or videos for the study. This may show you participating in the study visit, using the device or video testimonials before, during and after study treatment. You will be asked to document in the Optional Elements section of this form if you want to participate in the collection of photos and/or videos. You can refuse any photos or videos without affecting your involvement in the study. These photos and/or videos are voluntary and we will not record any photos or videos without your consent. You can also indicate that the photos or videos be obtained and used only if you are not identifiable in them. They may be used in presentations in our lab, scientific or collaborator meetings, as well as in research proposals, reports or publications. They will be stored on a secured server or computer and encrypted according to current University policy for protection of confidentiality. The photos or videos may be transferred to another secured server or computer but only using a secured storage device (e.g., a password protected USB drive) or by directly accessing the secured server, which requires the person to be logged onto the private network of the University of Minnesota. Images or videos stored within the study records will be destroyed after 10 years, however any photos and/or videos used in presentations, scientific meetings, research proposals, reports or publications will not be destroyed.

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

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

- If in the ultrasound therapy group, permitting and complying with study personnel applying ultrasound to your spleen once per day for 7 days for a period of about 15-20 minutes, unless you are discharged sooner.
- For both groups, permitting the clinical care team to withdraw additional blood during your daily blood draws for a period of 7 days, unless you are discharged sooner.

## *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, your academic standing as a student, or your present or future employment.

If you decide to leave the research study, contact the investigator or study personnel. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed. If you stop being in the research, information about you that has already been collected may not be removed from the study database.

## 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 risks for participation are:

- A risk of pain associated with the study's blood draws, although these will already occur as part of your standard clinical care, and they are not being conducted separately for this study.
- If in the ultrasound therapy group, there could be some discomfort or inconvenience in laying on your side (or other designated body position) for about 15-20 minutes while the ultrasound probe is being positioned or held still over the ribs area each day for up to 7 days. The ultrasound probe pressed against your ribs area may also cause some discomfort over time.
- The intention of ultrasound application to the spleen is to reduce inflammation in the body, so we are expecting improvements in your COVID-19 symptoms by reducing the excess inflammation in your body. However, some inflammation and immune response is good for fighting off the virus. It's possible that immune alterations caused by ultrasound could make you more susceptible to unknown infections. Blood work will be tracked daily and monitored by study doctors, and if your key inflammation and immune cells are reduced below normal ranges, we will stop treatment.
- Privacy and confidentiality risks: There is some risk of a data breach involving the information we have about you. We comply with the University's security standards to secure your information and minimize risks, but there is always a possibility of a data breach.

In addition to the risks listed above, this research may hurt you in ways that are unknown if you are in the ultrasound therapy group. These might be minor or severe. Note that the GE ultrasound device has obtained FDA approval for human use for diagnostic imaging applications and different locations on the body, including the abdomen and ribs area, in which there have been no reported major health issues on the FDA website or to the best of the investigators' knowledge. The treatment paradigm in this study will use ultrasound energies below the levels approved for diagnostic imaging. Therefore, there are no expected risks beyond those listed above that the study personnel are aware of in this study.

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

The research may also hurt a pregnancy or fetus in ways that are unknown if you are in the ultrasound therapy group. You should not be or become pregnant while on this research study. If you become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You might be required to stop participation in this study; however, other clinical care options will be discussed with you at that time if necessary.

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

Taking part in this research study will not lead to any additional costs to you. You and your insurance company will be charged for the standard health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services are performed in a research study. Please note that the research study sponsor (University of Minnesota, and health care system) will pay for any health care services and tests that are done as part of the research; you will not be responsible to pay for those additional services and tests.

## What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information, although we cannot promise complete confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution , including those that have responsibilities for monitoring or ensuring compliance (such as the Quality Assurance Program of the Human Research Protection Program (HRPP)). The funding agency for this study is the Department of Defense (DOD) may also have access to research records. Additionally, your de-identified research data may be shared outside of the University of Minnesota with other research partners and collaborators.

Your participation in this research will involve the collection and processing of your personal data, as described above and in any HIPAA Authorization Form we have provided to you. Please indicate whether you consent to the collection and processing of your personal data by placing your initials underneath the appropriate selection.

**____Yes, I consent to the collection and processing of my personal data.**

**____No, I do not consent to the collection and processing of personal data.**

(Your consent is entirely voluntary but declining to provide it may materially impede your ability to participate in this research and receive any research-related treatment.)

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), and the United States 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.

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

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

We will use, store, and may share data and/or blood specimens for future research. They may be shared with researchers and institutions outside of University of Minnesota. This could include for profit companies. We will not ask for your consent before using or sharing them. We will remove identifiers from your data and/or blood specimens, which means that nobody who works with them for future research will know who you are. Therefore, you will not receive any results or financial benefit from future research done on your specimens or data.

**____Yes, I consent to the storage of blood specimens for future research.**

**____No, I do not consent to the storage of blood specimens for future research.**

(Your consent is entirely voluntary but declining to provide it may materially impede your ability to participate in this research)

## Will anyone besides the study team be at my consent meeting?

You may be asked by the study team for your permission for an auditor to observe your consent meeting. Observing the consent meeting is one way that the University of Minnesota makes sure that your rights as a research participant are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not document any personal (e.g., name, date of birth) or confidential information about you. The auditor will not observe your consent meeting without your permission ahead of time.

## 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). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. 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.
- 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 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.

## Can I be removed from the research?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal could include worsening of COVID-19 symptoms such that your condition no longer fits into the study criteria, reduction of inflammation below normal levels, or inability or unwillingness to permit study personnel to perform treatment or collect outcome measures.

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

In the unlikely event that this research activity results in an injury, or injury occurs during study participation, treatment will be available, including first aid, emergency treatment and follow-up care 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.

## Will I be compensated for my participation?

You will not be compensated for participation in this study.

## Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

## 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 or meetings with partner institutions and funding agencies (including the Defense Advanced Research Projects Agency (DARPA) and General Electric (GE) research). Information that makes it easy to identify you (such as your name and contact information, SSN 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.

## Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

| **Yes, I agree** | **No, I disagree** | |
|---|---|---|
| _____ | _____ | The investigator may audio, photo and/or video record me to aid with data analysis. The investigator will not share these recordings with anyone outside of the immediate study team. |
| _____ | _____ | The investigator may audio, photo and/or video record me for use in scholarly presentations, publications or demonstrations. My identity may be shared as part of this activity. |
| _____ | _____ | The investigator may use de-identified audio, photo and/or video recordings of me in scholarly presentations, publications or demonstrations. My identity will not be shared as part of this activity. |

## Consent Signatures:

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

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

**WITNESS STATEMENT:**
The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is unable to read the information

☐ The participant is visually impaired

☐ The participant is non-English speaking

☐ The participant is physically unable to sign the consent form. Please describe:

_____

☐ Other *(please specify)*:

_____

## For the Consent of Non-English Speaking Participants when an Interpreter is Used:

A**s** someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

_____ _____
Signature of Interpreter Date

_____
Printed Name of Interpreter

**OR:**

## Statement from a Non-Interpreter:

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

_____ _____
Signature of Individual Date

_____
Printed Name of Individual