INFORMED CONSENT FORM AND AUTHORIZATION TO DISCLOSE PROTECTED HEALTH INFORMATION FOR A RESEARCH STUDY

Study Title: A Prospective, Randomized, Controlled Study Assessing Vagus Nerve Stimulation in CoViD-19 Respiratory Symptoms (SAVIOR II)
Protocol Number: 2020-132-AGH
Study Sponsor: **Allegheny Health Network**
Study Physician: Tariq Cheema, MD
Study Sites: Allegheny General Hospital, 320 E North Ave, Pittsburgh, PA 15212
West Penn Hospital, 4800 Friendship Ave, Pittsburgh, PA 15224
Telephone Number: 412-322-7202
Study Device: gammaCore® Sapphire (non-invasive vagus nerve stimulator) (electroCore, Inc.)

Concise Summary

The purpose of this study is to see if using Non-Invasive Vagus Nerve Stimulation (nVNS) in patients with CoVid-19 can reduce the need for mechanical ventilation and/or reduce the number of days in the hospital. The nVNS device, gammaCore® Sapphire, is FDA cleared and commercially available for the treatment and prevention of migraine and cluster headache. However, *the device is not currently approved specifically for treating CoVid-19 associated respiratory symptoms and is considered experimental for this study.* The gammaCore is a multi-use, handheld, rechargeable, portable device that is placed on the surface of the neck. The device produces low-voltage electric signals that are transmitted to the vagus nerve. It is thought that stimulating the vagus nerve can reduce the effects of the over-active immune response to CoVid-19 and decrease bronchoconstriction (tightening of the airway).

If you decide to participate in this study you will be randomly assigned (like a flip of a coin) to one of two groups: control group (does not receive the nVNS study treatment but standard of care therapies) OR to the treatment group, (receives the nVNS therapy in addition to standard of care therapies). Both groups of patients will receive a physical exam, vital signs, blood draws and answer questions related to shortness of breath and cough. If assigned to the treatment group, you will receive daily nVNS treatments at specific times, until you are discharged from the hospital, require mechanical ventilation or if you can no longer continue.

The potential benefits may include significant reduction of days in hospital and decreased need for mechanical ventilation. The potential risks of nVNS may include: muscle twitching/discomfort/pain during stimulations, feeling of pins and needles on skin where device is applied, skin irritation/inflammation, dizziness. The potential risks from blood draws may include: pain or discomfort from needle, bleeding, infection. There is also a potential risk of loss of confidentiality.

A total of 60 patients will be enrolled in this study and all research procedures will take place at Allegheny General Hospital or West Penn Hospital. Your participation in this study will last until you are discharged from the hospital, require mechanical ventilation or can no longer continue, whichever occurs first.

If you are interested in learning more about this study please continue reading below.

INTRODUCTION

You are being asked to participate in a medical research study. Your participation in this research study is voluntary, meaning that you may or may not choose to be a part of it. To help you decide if you want to be part of this study, the risks and possible benefits of the study are described in this document so that you can make an informed decision. This process is known as informed consent. This document explains how your medical information will be used and who may see it. You are being asked to take part in this study because the study doctor feels that you may meet the qualifications of the study. You may have a copy of this document to review at your leisure or to ask advice from others.

The study doctor “Investigator” and/or study staff will answer any questions you may have about this document or about the study. Please read this document carefully and do not hesitate to ask any questions about this information. This document may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not understand. After reading the consent document, if you would like to participate, you will be asked to sign this document. You will be given a signed copy of your consent document to take home and keep for your records.

You can withdraw your consent and/or refuse treatment at any time during the study without giving a reason. This will not affect the standard of care you receive or the benefits to which you are entitled.

DESCRIPTION OF THE DEVICE:

gammaCore® Sapphire is a handheld, non-invasive, low voltage electrical device which stimulates the vagus nerve by producing weak 120 second electrical stimulation cycles that may help reduce, ease, lessen or stop your respiratory symptoms. The vagus nerve is part of the autonomic nervous system and is stimulated in the area of your left or right carotid artery on the neck. Your doctor or nurse will show you where this is. The vagus nerve is involved in many functions of the nervous system, including bronchoconstriction and gastrointestinal disorders.

The device is FDA cleared and commercially available **only** for the treatment and prevention of migraine and cluster headache**.** This device is **not** currently approved for treating CoVid-19 associated respiratory symptoms and is considered **experimental** for this study.

gammaCore® Sapphire

gammaCore® Sapphire w/Charging Station

WHAT IS THE PURPOSE OF THIS STUDY?

You are being invited to participate in this study because you are seeking treatment for your respiratory distress as related to CoVid-19.

The purpose of the study is to investigate the safety and effectiveness of gammaCore® Sapphire in the acute and preventative treatment of acute respiratory distress syndrome (ARDS) as related to CoViD-19.

The investigator plans to enroll 60 patients into the study at Allegheny General Hospital and West Penn Hospital.

HOW LONG WILL YOU BE INVOLVED IN THIS STUDY?

Your participation in this study will last until you are discharged from the hospital, require mechanical ventilation or if you are unable to continue. There are no follow-up visits after discharge from the hospital. Detailed treatments and procedures for each study day are detailed below.

WHAT WILL I BE ASKED TO DO IN THIS STUDY?

Before you decide whether to be in this study, you should think about how the tests and study visits will affect your schedule.

To be in this study, you must agree to:

- Follow directions from your study doctor and study staff.
- Complete multiple daily entries for the duration of your stay in the hospital.

- Administer or have trained study staff assist in administering your device as per protocol.
- Share your medical information with the researchers.
- You will have blood draws, but these should be done in the routine practice of medicine

STUDY PROCEDURES:

Day of Admission (Intake and Randomization):

First, your study doctor or other study personnel will explain the study to you and you will have the chance to ask questions. You will be asked to read and sign this consent form before any study related procedures are performed. You will be given a copy of this consent document.
An evaluation will be performed to determine your eligibility to participate in the study. These include:

- A complete physical exam
- your study doctor will review any medications you are taking and your medical and surgical history
- your demographics (date of birth, sex, race, smoking status, county/region) will be recorded
- your vital signs, including height and weight, temperature, blood pressure and pulse oxidation will be measured
- you will be asked if you are short of breath and have a cough
- you will have blood drawn for research (up to an additional 35 mL) from a vein in your arm or from your central intravenous (IV) line (if applicable), during routine blood collection.
- the physician will review your test results for CoVid-19 – if positive result and you meet the remaining eligibility criteria, you will be randomized into the study
- if your Covid-19 test results come back negative, you will not continue on to randomization and you will not continue with the study

If your study doctor confirms that you are eligible to continue in the study, you will enter the randomized treatment of the study where the following will be performed:

Randomization:

The purpose of the randomized treatment is to compare two groups of subjects, one group using the gammaCore® Sapphire and the other group not using the device. Both groups will receive the standard of care treatment for CoVid-19.

Training:

A qualified member of the study team will train you on how to use the device. This training will occur at a time when you are calm and not under any significant distress. You will be encouraged to ask any member of your healthcare team, at any time during your hospitalization, for obtaining re-training on the device by a study team member, should you ever need it. A trained study team member will be available for assistance with stimulations or device re-training 24 hours/7days per week during your hospitalization. After training you will be asked a number of questions to assess your understanding and to ensure you use the device correctly.

- You will learn about the device features and how to use the device, including proper placement on the neck, adjustment of stimulation strength, and how to charge the device. Under your trainer's supervision, you will treat yourself with your assigned device so that you know proper device placement, how it feels, and approximate stimulation strength before you treat yourself.
- You will review device warnings, risks and precautions including the following:
    - Only use an electroCore-approved gel with gammaCore (this will be supplied).
    - Remove jewelry that may touch the treatment location (necklaces, earrings, etc.) before treating with gammaCore.
    - Always carefully examine the device for any signs of damage or defects before use.
    - If the device has been damaged, does not operate properly, or if you receive an error code, you must contact your study doctor or study staff immediately.
- You will review the requirements of the study, including daily treatment schedule.
- You will be invited to ask questions about the device and treatment.
- You will receive your device, device instructions, and study instructions.
- You will also be given a leaflet with instructions on how to use the study device.
- You will also receive training on how to record your treatments in a daily study log.

During the randomized treatment of the study, you will be asked to treat your respiratory distress both preventatively and when you are short of breath or are in respiratory distress (acutely).

For the preventative treatment (3 times/day): You will self-administer one treatment of gammaCore®, scheduled three times a day (morning, mid-day and 1 hour before bed at night).

- One treatment is defined as 2 consecutive stimulations: one, 2-minute stimulation on the left side of the neck, then one, 2-minute stimulation on the right side of the neck
- The preventative treatment will be done 3 times per day (morning, mid-day and 1 hour before bed at night), every day until you are discharged from the hospital or require mechanical ventilation.
- You will record the time you administered these treatments. If you are unable to do this, a research staff member who has been trained on the device can help you.

For the (acute) treatment of shortness of breath or respiratory distress (up to 9 times per day): You will *also* administer the gammaCore® treatment, as needed, when you are short of breath and/or are in respiratory distress.

- First, notify your nurse, doctor or another healthcare provider, that you are feeling short of breath.
- You can then administer the treatment the same way as preventative (2 consecutive stimulations (one on each side of the neck)

- If after 20 minutes, you are still short of breath, give yourself another two stimulations on each side of your neck.
- You can do this up to 9 times each day. If you or your physician feel that the additional treatments do not appear to be providing benefit/relief of symptoms, there is no need to continue with additional acute treatments. However, if it there appears to be benefit, you can administer more, as needed up to 9 times per day (or 18 stimulations). Your healthcare team may also treat your acute shortness of breath or respiratory distress, with standard of care therapies.

A study member will also complete details in the daily log to include:
- Oxygen requirements, oxygen saturation level and Clinical Evaluation Scale

In the Hospital, Daily until Study Completion
- you will be reminded to continue completing your study log
- you will be provided with further device or study log training, if necessary
- your vital signs will be measured
- you will be asked if you are short of breath and have a cough
- you will have research blood samples drawn (up to 35 mL) from a vein in your arm or from your central intravenous (IV) line (if applicable) before 10:00 am. This research blood draw will occur at the same time as your routine (non-research) blood draws on odd days.
- one of your blood samples will be frozen and may be used by the study team for additional research in the future. This sample will be labelled without your identifying information. Please review the section below: *WHAT HAPPENS TO MY COLLECTED SAMPLES AND DATA?*
- you will continue to self-administer VNS treatments, daily, as follows:
    - **For the preventative treatment (3 times/day)**: You will self-administer one treatment of gammaCore®, scheduled three times a day (morning, mid-day and 1 hour before bed at night), as previously described, every day until you are discharged from the hospital or require mechanical ventilation.
    - You will record the time you administered these treatments. If you are unable to do this, a research staff member who has been trained on the device can help you.

    - **For the (acute) treatment of shortness of breath or respiratory distress (up to 9 times per day):** You will *also* administer the gammaCore® treatment, as needed, when you are short of breath and/or are in respiratory distress, as previously described. You may continue these treatments every day until you are discharged from the hospital or require mechanical ventilation, up to 9 times per day.
    - Your healthcare team may also treat your acute shortness of breath or respiratory distress, with standard of care therapies.
    - You will record the time you administered these treatments. If you are unable to do this, a research staff member who has been trained on the device can help you.

Study Completion
There are three possible scenarios in which the study period for you will end:
1. You will be discharged from the hospital

2. You are placed on a mechanical ventilator
3. You can no longer continue with the treatments

The following assessments will occur upon study completion:

- your vital signs will be measured
- you will be asked if you are short of breath and have a cough
- you will asked to complete a Clinical Evaluation Scale
- you will have research blood samples drawn (up to 35 mL) from a vein in your arm or from your central intravenous (IV) line (if applicable) before 10:00 am. This blood draw will occur at the same time as your standard of care blood draws
- your study log will be reviewed
- you will be asked if you have experienced any adverse events
- you will return your device to study staff

Adverse Reactions:

- Notify your study doctor immediately if experiencing any symptoms or side effects from the stimulation treatment.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

You may experience side effects and complications associated with gammaCore Sapphire. These are anticipated to resolve shortly after discontinuation of the stimulation procedure without medical intervention. Occurrence of several of these events can be lessened by repositioning the device on the neck and/or decreasing the stimulation intensity. Training on the positioning of the device and controlling the stimulation intensity will be conducted at the time the device is provided to you. In addition, the device is supplied with detailed instructions for use. The potential anticipated side effects include, but are not limited to:

- Muscle twitching, discomfort, or pain during stimulations
- Tingling, pricking or a feeling of “pins and needles” on the skin where the device is applied (paraesthesia or dysaesthesia) lasting beyond the treatment period
- Skin irritation/inflammation
- Dizziness
- Application site discomfort (4.85%)
- Application site irritation/redness (3.74%)
- Local pain, face/head/neck area (including toothache) (3.00%)
- Muscle twitching and/or contractions, face/head/neck area (including facial droop and/or lip pull) (3.47%)
- Headache/migraine (2.56%)
- Dizziness (2.00%)

  Tingling, pricking or a feeling of “pins and needles” on the skin where the device is applied (1.63%)

Risks associated with blood draws

- Pain or discomfort from needle
- Bleeding
- Infection

Privacy risk

- The research staff will take every measure possible to protect your confidentiality. Please refer to the confidentiality and HIPAA section below for more information about your personal health information. Participating in research may involve a loss of privacy and the potential for a breach in confidentiality.

Pregnancy:

It is unknown whether gammaCore Sapphire can harm an unborn child if used during pregnancy. If you are pregnant, you will not be allowed to participate in this study.

WHAT ARE THE POTENTIAL BENEFITS?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include:

- Symptoms associated with your condition may reduce, ease, lessen and/or stop
- No mechanical respirator required
- Reduction of number of days in hospital

Even if you do not benefit personally from taking part in the study, your participation may help other patients with the same disease. The information we gain from this study can help us better understand and treat ARDS as it relates to CoViD-19.

WHAT ARE THE ALTERNATIVES?

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive will continue and nothing will change. If you choose not to participate in this research study, you will be offered the treatment that is routinely offered for your CoViD-19 symptoms, and your doctor will discuss your options with you.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about the new information and discuss with you whether or not you want to continue in the study. If you decide to continue in the study, you will be asked to sign an updated consent form.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

You will continue with standard treatment as directed by your study doctor.

IS THERE FINANCIAL COMPENSATION PROVIDED?

You will not be paid to participate in this research study.

ARE THERE COSTS FOR PARTICIPATING?

This kind of research study is not expected to result in any costs to you or your insurance company. If you require medical care for your CoVid-19 or other health problems, as part of your routine care (care you receive even if you do not participate in this research study), either you or your insurance carrier will be billed for these charges.

The study device (gammaCore® Sapphire) and any additional **study-related** tests (blood draws, questionnaires) that is required for this study will be provided to you at no cost.

There are certain tests and examinations that are part of the normal standard of care for patients diagnosed with CoVid-19. The cost for the standard of care items will be billed to you or your insurance company as usual. If you require additional medical care for your CoVid-19 or other health problems, as part of your standard medical care, either you or your insurance carrier will be billed for these additional charges.

Please also talk with the study doctor about any expected added costs or health insurance problems.

WHAT IF I AM INJURED?

If you are injured or made sick while taking part in this research study, emergency medical treatment will be provided at the usual charge. No funds have been set aside by Allegheny Health Network or Allegheny Health Network Research Institute to pay you in case you are injured. You do not waive any of your legal rights to compensation, if any, by signing this form.

IS PARTICIPATION VOLUNTARY?

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your involvement will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should notify the study doctor as soon as possible.

The study doctor may stop your participation in the study at any time if the doctor decides that it is in your best interest. The study doctor may also do this if you do not follow instructions. If you have other medical problems or side effects or your symptoms worsen, the doctor may remove you from the study. If any adverse event (side-effect) is ongoing when you withdraw your consent, the physician may continue to follow-up with you until the adverse event or side-effect is resolved or is stable and needs no further follow-up.

WHAT HAPPENS TO MY COLLECTED SAMPLES AND DATA?

The private information and bio-specimens may be used by your study team for additional research in the future without obtaining additional consent from you. Any information that directly identifies you will be removed from the data and specimens before they are stored in

locked freezers and used for future research. The research team will label the data and specimens with a unique code and only the investigator and the designated research staff will have access to the link between the code and your identity.

Biospecimens collected from you for this research may be used to develop new tests, drugs, or devices. The researchers, their organizations, or possibly other entities may potentially profit from the use of the data, biospecimens or discoveries from this research. You will not share in the profits of these discoveries or benefit financially from them.

The specimens will be banked at Allegheny General Hospital in locked freezers that are accessible only to the members of the study team, indefinitely. Researchers will not perform any genetic testing on samples for the purposes of this study or for any future testing. However, as more data becomes available (through peer reviewed publicly-available scientific literature) about the mechanisms by which the immune system reacts to the virus, the investigator may initiate additional studies at Allegheny General Hospital (Neuroscience Institute, Institute of Cellular Therapeutics) to address hypotheses that are currently, and possibly in the future, relevant to how the immune systems are changed in virus-infected patients who may exhibit co-morbidities at the time of when they were in-study (e.g. obesity, diabetes, hypertension, cardiovascular disease, neurologic conditions). This will not be done prior to new IRB submission and approval. You will not receive the results, including your individual results, of any of the tests performed during these future research studies.

WILL MY INFORMATION BE KEPT CONFIDENTIAL

Your identity and medical records and data related to this study will be kept confidential, except as required by law and except for inspections by the U.S. Department of Health and Human Services (HHS), the U.S. Food and Drug Administration, Allegheny Health Network, the Allegheny Health Network Research Institute, the AHN RI Institutional Review Board (the committee formed to protect the rights and welfare of human subjects involved in research activities being conducted under its authority) and the AHN Compliance Office. Results of the research may be published for scientific purposes or presented to scientific groups, however, your identity will not be revealed.

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."

Federal law provides additional protections of your personal health information. These are described below in the HIPAA Authorization Statement below.

Authorization to Use and Disclose Individually Identifiable Health Information for a Research Study (HIPAA Authorization Statement)

Before you can take part in this research study, the Allegheny Health Network is required to obtain your authorization to use and/or disclose (release) your health information. This section describes to you how, and to whom, your health information will be used and/or disclosed (shared) while you are participating in this research study. It is important that you read this carefully. Allegheny Health Network and its' researchers are required by law to protect your health information.

The following is a list of health information that will be used and/or disclosed:

- Medical/surgical history, co-morbidities
- Basic demographic information (date of birth, race, sex, smoker, county/region)
- Medications
- Clinical evaluation scale scores
- Results of physical examinations, vital signs and blood tests
- Total number of gammaCore doses administered
- Survival
- Admission to ICU
- Dependence on ventilator
- Adverse event and/or side-effects information
- Discharge information including date of discharge

The following is a list of entities that may use and/or disclose your health information as part of this study:

Internal Oversight
Those who oversee the study will have access to your health information, including the following:
- Allegheny Health Network
- Allegheny Health Network Research Institute
- AHN Compliance Office
- The AHN IRB
- Study Doctor and Study Staff

Governmental Oversight
Your health information may also be shared with government agencies that have oversight of the study or to whom access is required under the law:
- U.S. Department of Health and Human Services (HHS)
- U.S. Food and Drug Administration (FDA)

In order to participate in this study, you must agree to share your health information with the persons and organizations listed above. If these persons or organizations that you authorize to receive and/or use protected health information, are not health plans, covered health care providers or health care clearinghouses subject to federal health information privacy laws, they may further disclose the protected health information and it may no longer be protected by the federal health information privacy laws.

Expiration of Authorization
This authorization will not expire unless you revoke it in writing. You may revoke or end this authorization by writing to the Principal Investigator at the address listed on the first page of this consent.

If you revoke your authorization, you will also be removed from the study. Revoking your authorization only affects the use and sharing of your health information after the written request is received. Any health information obtained prior to receiving the written request may be used to maintain the integrity of the study.

IS MY HEALTH INFORMATION PROTECTED AFTER IT HAS BEEN GIVEN TO OTHERS?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. This is a risk that your information will be released to others without your permission.

If you agree to participate in this study, you will receive a signed and dated copy of this consent form for your records.

WHOM DO I CONTACT IF I HAVE QUESTIONS OR NEED ADDITIONAL INFORMATION?
If you have questions, concerns, or complaints, or think the research has hurt you, you should contact the principal investigator: **Tariq Cheema, MD at 412-322-7202**

This research has been reviewed and approved by **AHN RI Institutional Review Board.** You may talk to them by calling this toll free number, **1-844-577-4621**, for any of the following:

- 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 subject.
- You want to get information or provide input about this research.

AUTHORIZATION

By signing this document (authorization), you authorize that your health information can be used and/or disclosed as described.

Your access to your protected health information created or obtained by Allegheny Health Network in the course of the research (that includes treatment) may be temporarily suspended for as long as the research is in progress. By signing this document, you are agreeing to the denial of access to your protected health information, created for the research, while you are participating in this research study. Your access to your protected health information will be reinstated upon completion of the research.

If you choose to not sign this document, you will not be permitted to participate in this research study.

Your signature below indicates your permission to take part in this research and to the use and disclosure of your protected health information:

_____	_____
Signature of Subject	Date
_____	_____
Printed Name of Subject	Time – include AM/PM
_____	_____
Signature of Witness to Signature	Date
_____	_____
Printed name of Witness to Signature	Time – include AM/PM
_____	_____
Signature of Physician Investigator	Date
_____	_____
Printed Name of Physician Investigator	Time – include AM/PM