CLINICAL INVESTIGATION PLAN (CIP)

Title: A Prospective, Randomized, Controlled Study Assessing Vagus Nerve Stimulation in CoViD-19 Respiratory Symptoms (SAVIOR II)	
Clinical Investigation Number:	2020-132-AGH
Clinical Investigation Medical Device:	gammaCore® Sapphire
Indication:	Acute Respiratory Distress Syndrome
Device Class:	IIa
Version:	18
Date:	10 Dec 2020
	NCT#04382391
Principal Clinical Investigator:	Dr. Tariq Cheema
Sponsor:	Allegheny Health Network Allegheny General Hospital 320 E North Avenue Pittsburgh, PA 15212 USA

This clinical investigation will be performed in compliance with ICH GCP following US Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Parts 50, 56, 312) and applicable regulatory requirements.

1 SYNOPSIS

CLINICAL INVESTIGATION TITLE: A Prospective, Randomized, Controlled Study Assessing Vagus Nerve Stimulation in CoViD-19 Respiratory Symptoms (SAVIOR II)

CLINICAL INVESTIGATION CODE:
2020-132-AGH

CLINICAL INVESTIGATIONAL MEDICAL DEVICE(S):

gammaCore Sapphire® (non-invasive vagus nerve stimulator)

OBJECTIVES:

The aims of this study are to summarize and compare the incidence of clinical events and pro-inflammatory cytokine levels in patients randomized to use of gammaCore Sapphire plus standard of care vs standard of care alone in patients hospitalized for CoViD-19. In addition, this study is intended to demonstrate the safety of gammaCore Sapphire use in patients hospitalized for CoViD-19.
Specific clinical events to be summarized include, but are not limited to:

- Changes in oxygen support requirements (no oxygen support, low-flow oxygen support, nasal high-flow oxygen support, noninvasive mechanical ventilation, and invasive mechanical ventilation)
- Changes in O_2 saturation
- PaO2/FiO2 ratio
- Proportion of subjects requiring mechanical ventilation
- Days to onset of mechanical ventilation
- Live discharge from the hospital
- Patient length of stay
- Mortality
- Shortness of Breath
- Clinical improvement Scale

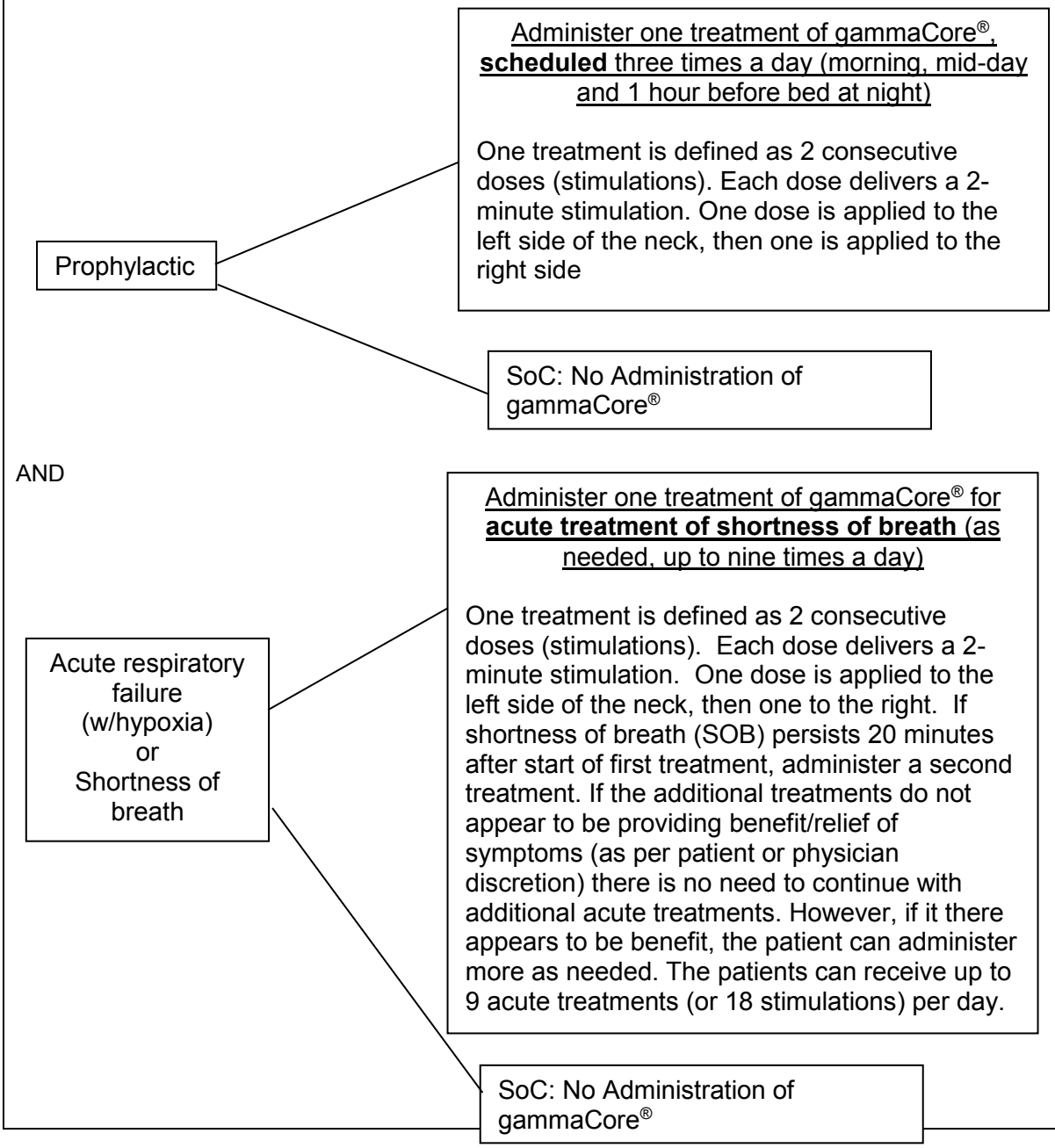
Specific laboratory measurements to be summarized include, but are not limited to:

- TNF-α
- IL-1β
- IL-6
- CRP
- Ferritin
- D Dimer

- Pro-Calcitonin

OVERALL CLINICAL INVESTIGATION DESIGN:

The study is a prospective, randomized, controlled investigation designed for comparison of two groups for the reduction of respiratory distress in a CoViD-19 population, using gammaCore Sapphire® (nVNS) plus standard of care (active) vs. standard of care alone (SoC), the control group. The gammaCore® (nVNS) treatments will be used acutely and prophylactically.



INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

All patients must meet the following inclusion criteria to be included in this study:

1. Patients (age 18 years and older) who have tested positive or suspected/presumed positive for CoViD-19 (PCR real time test)
2. Patients with cough, shortness of breath or respiratory compromise (RR>24/min, increased work of breathing.)
3. O_2 Saturation less than or equal to 96% on room air or sensation
4. Agrees to use the gammaCore Sapphire device as per protocol and to follow all of the requirements of the study including recording required study data
5. Permission for early am blood draw to freeze for subsequent lab tests and sequencing as related to CoViD-19 sequelae
6. Patient is able to provide signed and witnessed Informed Consent

Exclusion Criteria

Patients meeting any of the following criteria cannot be included in this research study:

1. On home/therapy oxygen (i.e. for COPD patients) at baseline prior to development of CoViD-19
2. Already using gammaCore® (nVNS) for other medical conditions
3. A history of aneurysm, intracranial hemorrhage, brain tumors, or significant head trauma
4. Known or suspected severe atherosclerotic cardiovascular disease, severe carotid artery disease (e.g., bruits or history of transient ischemic attack or cerebrovascular accident), congestive heart failure, known severe coronary artery disease, myocardial infarction documented within past 90 days, or current or recent history of life-threatening arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, second or third-degree heart block, uncontrolled atrial fibrillation or

uncontrolled atrial flutter)

5. Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia (as per investigator discretion)
6. Current implantation of an electrical and/or neurostimulator device, including but not limited to a cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant
7. Current implantation of metal cervical spine hardware or a metallic implant near the gammaCore® stimulation site
8. Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled and prisoner)
9. Compromised access to peripheral veins for blood sampling.
10. Pregnant women
11. Patients with active cancer or those who have had recent cancer treatment

CLINICAL INVESTIGATION PROCEDURE OVERVIEW:

Enrollment / Admission Day - Day 0

Study patient must meet all of the following inclusion criteria and none of the exclusion criteria

- Patient must sign Informed Consent and witness to signature must occur
- Randomization – Upon meeting all eligibility requirements (including verification of +CoViD-19 testing), patient's will be randomized 1:1 into either the control group or the treatment group
- Intake Collection of:
    - Basic Demographics
        - Date of Birth (DOB), Race, Sex, Smoking Status, County/Region
    - Medications, Co-morbidities

- CoViD-19 Test Results (Positive / Presumed Positive)

- Study Measurements:
  - Height/Wt (BMI)
  - Temperature
  - Blood Pressure
  - O_2 Saturation
  - PaO2/FiO2 ratio
  - Shortness of Breath (Yes / No)
  - Cough (Yes / No)

- Clinical Labs
  - Immunokine panel (TNF-**α,** IL-1β, IL-6)
  - Frozen blood sample
  - Leukocyte flow cytometry
  - Pro-Calcitonin
  - CRP
  - Ferritin
  - D Dimer
  - Complete hematology panel (CBC with differential)
  - Comprehensive metabolic panel
  - Serum or urine hCG (for any woman who might be pregnant)

- Device training: Patient receives device training on gammaCore® Sapphire device and receives first treatment with trained study staff*

- VNS Stimulation Supervised**, record date and times of stimulations

- Daily Tx Log Completion
  - Oxygen Required, Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow), Ventilator Dependence, Date and time of Ventilation, Patient discharge home, Date and time of Discharge, Survival

- Clinical Improvement Ordinal Scale

- Adverse event assessment

* For those patients allocated to non-invasive vagus nerve stimulation, the patient will be instructed by a study physician or study personnel on the gammaCore® technique. They will be instructed to use it according to the specified protocol, which will be available at bedside.

**** Protocol:**

Prophylaxis: Administer gammaCore® Sapphire daily, prophalytically, scheduled three times a day (morning, mid-day and 1 hour before bed at night). One treatment is defined as 2 consecutive doses (stimulations). Each dose delivers a 2-minute stimulation. One stimulation is applied to the left side of the neck, then one is applied to the right. This would be a total of 6 treatments (2 stimulations x 3 times per day).

For acute respiratory distress or shortness of breath (SOB): Administer one treatment of gammaCore® for acute treatment of shortness of breath (as needed, up to nine times a day). One treatment is defined as 2 consecutive doses (stimulations). Each dose delivers a 2-minute stimulation. One stimulation is applied to the left side of the neck, then one to the right. If shortness of breath (SOB) persists 20 minutes after start of first treatment, administer a second treatment. If the additional treatments do not appear to be providing benefit/relief of symptoms (as per patient or physician discretion) there is no need to continue with additional acute treatments. However, if it there appears to be benefit, the patient can administer more as needed. The patients can receive up to 9 acute treatments (or 18 stimulations) per day.

Day 1 - 3

For days 1 through 3, the following assessments will be recorded each day:

- Study Measurements:
    - Height/Wt, BMI, Temperature, Blood Pressure, O_2 Saturation, PaO_2/FiO_2 ratio, Shortness of Breath, Cough
- Labs (Research) Early am blood draw (before 10 am) ***Day 1 and 3 only** (then drawn on all odd days)*
    - Immunokine panel (TNF-α, IL-1β, IL-6), Frozen blood sample, Leukocyte flow cytometry
- Labs (Standard of care) ***Day 1 and 3 only** (then drawn on all odd days)*
    - Pro-Calcitonin, C-reactive protein, Ferritin, D Dimer, CBC with differential
- Comprehensive metabolic panel ***Day 3 only** (then drawn on all odd days)*
- VNS Stimulation supervised
    - Total number of gammaCore® treatments administered, Date and times of stimulations
- Daily Tx Log
    - Oxygen Required, Oxygen level (%), Ventilator Dependence, Date and time of Ventilation, Patient discharge home, Date and time (in 24 hour

format) of Discharge, Survival

- Clinical Improvement Ordinal Scale
  - Concomitant medication and adverse event assessments

All <u>Even</u> Days Starting Day 4

- Study Measurements
  - Temperature, Blood Pressure, O2 Saturation, Shortness of Breath, Cough
- VNS stimulations
  - Total number of gammaCore® treatments administered with Date/time
- Daily Tx Log
  - Oxygen Requirements, Oxygen level (%), Ventilator Dependence, Date and time of Ventilation, Patient discharge home, (if applicable) Date and time of Discharge, Survival
- Clinical Improvement Ordinal Scale
  - Concomitant medication and adverse event assessments

All <u>Odd</u> Days Starting Day 5

Same as Days 1 and 3

Study Completion

The last day of the study will be determined by discharge, transition to mechanical ventilation and/or if the patient is unable to continue i.e. death or feasibility impossible. The following will be recorded:

- Study Measurements:
  - Height/Wt, BMI, Temperature, Blood Pressure, O_2 Saturation, PaO_2/FiO_2 ratio, Shortness of Breath, Cough
- Labs (Standard of care)
  - Pro-Calcitonin, C-reactive protein, Ferritin, D-Dimer, CBC with differential,

Comprehensive metabolic panel

- Labs (Research) Early am blood draw (before 10 am)
  - TNF-α, IL-1β, IL-6
- VNS stimulations
  - Total number of gammaCore® treatments administered, dates/times
- Daily Tx Log
  - Oxygen Required, Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow), Ventilator Dependence (Yes / No), Date and time of Ventilation, Patient discharge home (Yes / No), Date and time (in 24 hour format) of Discharge, Survival (Yes / No) with Date and Time of Death
- Clinical Improvement Ordinal Scale
- Concomitant medication and adverse events assessment

2 TABLE OF CONTENTS

Section Page

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
CAP	Cholinergic Anti-inflammatory Pathway
CIP	Clinical Investigation Plan
CRF	Case Report Form
DMC	Data Monitoring Committee
FAS	Full analysis set
FEV1	Forced Expiratory Volume
IEC	Independent Ethics Committee
IL	Interleukin
nVNS	Non-Invasive Vagus Nerve Stimulation
PPS	Per protocol set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOB	Shortness of Breath
SoC	Standard of Care
IRB	Institutional Review Board
UAE	Unanticipated Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VNS	Vagus Nerve Stimulation
WOB	Work of Breathing

4 CLINICAL INVESTIGATORS AND CLINICAL INVESTIGATION ADMINISTRATIVE STRUCTURE

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5 INTRODUCTION

5.1 Background

Vagus nerve stimulation (VNS) has an established history of reducing airway distress. VNS has at least two mechanisms of action that may profoundly affect respiratory function in patients with respiratory distress due to CoVID-19.

First, vagus nerve stimulation modulates bronchoconstriction[1-3], acute stimulation has demonstrated a marked improvement in Work of Breathing (WOB) as well as Forced Expiratory Volume (FEV_1) in patients with severe respiratory distress due to airway reactivity. This effect appears to occur via an afferent response to stimulation of the vagus nerve.

Second, and perhaps more importantly, VNS has been shown to be a potent moderator of pathologic immune reactions, specifically suppressing pro-inflammatory cytokine levels via activation of the Cholinergic Anti-inflammatory Pathway (CAP). VNS is currently being studied to modulate pro-inflammatory cytokines patterns and concentrations in a variety of acute and progressive inflammatory conditions, ranging from septic shock and asthma to stroke, rheumatoid arthritis and Inflammatory Bowel Disease.[4-8]. VNS has been studied in animal models of acute septic shock, consistently demonstrating life-saving potential. In one such study, cecal ligation and puncture was used to induce a septic state in an animal model. VNS reduced the expression of cytokines which was tightly associated with survival.[9] Specifically, in animal and human models, this neuromodulatory therapy has the capacity to reduce the expression of inflammatory mediators, including TNF-α, IL-6 and IL-1β. These are precisely the same cytokines which are elevated in ARDS and other inflammatory disorders. In all cases, the therapy has shown considerable promise as a potential alternative to steroids (having potent anti-inflammatory activity but without the adverse side effects of steroids) and biologic therapies targeting pro-inflammatory cytokines (broadly – e.g., tofacitinib, or specifically – e.g., adalimumab, etanercept, and infliximab).

Viral-induced acute respiratory distress syndrome (ARDS), including those caused by SARS CoV-1 and MERS are characterized by a massive systemic pro-inflammatory state. Although a pro-inflammatory environment is required to control the rate of infection as well as the eradication of infected and compromised cells, the massive response to these viruses, primarily due to leukocytes of the innate arm of the immune system, is part of the problem as a significant number of tissues are damaged and lost secondary to the infected tissues in a by-stander and collateral manner.[10-28] A simple, drug-free approach to attenuate this systemic inflammation would be of significant benefit to the progression of the syndrome and potentially improve the overall recovery of the patients.

For these reasons, we propose that VNS may ameliorate the over-activity of the pro-inflammatory immune condition in CoViD-19 patients, thus conferring a superior therapeutic option especially for elderly patients and those presenting with respiratory illness in setting of comorbid conditions who experience severe symptoms. These groups are at particularly high risk of requiring mechanical ventilation, developing ARDS, experiencing severe cytokine storm and have a higher mortality rate.

Non-Invasive Vagus Nerve Stimulation (nVNS)

Historically, VNS was delivered using implanted signal generators coupled to leads having electrodes that wrap around the vagus nerve. The vagus nerve is located within the carotid sheath, and thus the implantation surgery is complicated with inherent risks, particularly in the critically ill. More recently, a non-invasive approach to vagus nerve stimulation (nVNS) was cleared by the FDA for the acute treatment of pain associated episodic cluster and migraine headaches and the prevention of cluster headaches and migraine headaches. This device, gammaCore® (electroCore, Inc., Basking Ridge, NJ) is handheld and requires no surgery or implants. The device is applied by healthcare providers or patients to the skin at the neck over the vagus nerve to deliver periodic treatments of VNS non-invasively.

An Emergency Use Application for use of VNS in CoViD-19 patients was granted by the FDA on July 10, 2020.

With respect to bronchoconstriction, early studies demonstrated modulation of airway reactivity in hospitalized asthmatic patients, improving various measures of airway patency.[2,29]

Non-invasive VNS (nVNS) is a safe method of stimulating the vagus nerve, with minimal side effects. It does not require surgery or an invasive procedure that would otherwise limit its utility in the critically ill. The stimulation can be either self-administered or administered by a health care practitioner. There are numerous studies with both implanted and nVNS in multiple animal models and humans that have demonstrated a modulation of the inflammatory cascade with an improvement in survival.

gammaCore® (nVNS) has been studied in approximately 2,000 patients as part of clinical trials with an excellent safety profile. It is available through commercial insurers and the private pay market, and is listed on the federal supply schedule available for purchase by the VA and Department of Defense and also carries a CE mark for distribution abroad. More than ten thousand patients have been successfully treated in the United States and abroad.

CoViD-19 Respiratory Issues Involve Virally-triggered Severe (Lethal) Cytokine Expression

COVID-19 (coronavirus disease 2019) is caused by SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) and is related to the coronavirus which caused SARS in 2003 (SARS CoV-1). The virus is transmitted either through airborne droplets (e.g. coughing or sneezing) or direct contact (e.g. through a surface containing the virus), with a mean incubation period between 4 and 7 days (range 2 days to > 2 weeks). As of April 3, 2020, there are over a million confirmed cases and rising with 55,000 individuals deceased to date. This gives a current mortality rate of 5.3 %, although the base case of confirmed cases may be markedly underestimated. Elderly and those with comorbid conditions including heart disease, diabetes, and asthma seem to have a higher mortality rate.

Many CoViD-19 patients experience moderate to severe respiratory symptoms, including shortness of breath and impaired oxygen saturation. Eighty-eight percent (88%) of patients present with respiratory symptoms. A significant and increasing number of CoViD-19 patients require hospitalization, and progress to being intubated and/or ventilator dependent. Given the

rapid spread of this contagion, concern exists that the international healthcare systems do not have the number of ventilators and/or ICU beds to meet the expected demand in the coming months.

The most critically afflicted can experience pneumonia and/or ARDS. Accumulating evidence suggests that this subgroup with severe CoViD-19 likely have a cytokine storm syndrome, a hallmark of ARDS that includes dramatic increase in the expression of pro-inflammatory cytokines, mainly TNF-α, IL-6 and IL-1β among others. Elevations in IL-6 seem to be a particularly poor outcome indicator of respiratory compromise. It is believed that the mortality of ARDS is at least partially the result of an over activity of the patient's immune system.[30] Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed CoViD-19 cases in Wuhan, China, included elevated ferritin (mean 1297·6 ng/ml in non-survivors *vs* 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001)[31], suggesting that mortality and respiratory decompensation may be due to virally driven hyperinflammation.

Therapies that could block the cytokine storm may help improve survival and decrease the need for ventilator use and prolonged respiratory support. Other companies are in fact developing pharmaceutical approaches for the treatment of cytokine storm[32], or plasma infusions from those who have recovered from the virus. At this point there is no cure or vaccine for the virus and neither is there a treatment approach to dampen the systemic inflammation.

Proposal to Use gammaCore® nVNS to Reduce Severe Respiratory Disease Associated with CoViD-19

Given the CE mark and excellent safety profile, including the twenty year history of the use of VNS to block the over production of pro-inflammatory mediators via the CAP (cholinergic anti-inflammatory pathway), and the lack of other effective or reasonable options during this pandemic we propose deploying gammaCore® (nVNS) devices for prophylactic use to those who have been diagnosed as infected with the virus, but before the cytokine storm begins to cause and/or exacerbate the severe respiratory distress syndrome. The hypothesis is that the administration of non-invasive VNS using gammaCore®, during and following severe infection with CoViD-19 may prevent the worsening inflammatory response and acute injury associated, thus decreasing ventilator dependence and mortality of the virus. If utilized early enough in the course of disease we hope to reduce ventilator dependence and improve survival with a scientifically driven safe and cost-effective approach. Furthermore, through additional acute utility of gammaCore® (nVNS) in cases of ARDS and cytokine storm we aspire to effectively blunt the pro inflammatory response, reduce mortality and liberate patients from mechanical ventilation earlier which will assist in deploying the ventilator to other patients in need during the CoViD-19 pandemic.

electroCore has designed a non-invasive vagus nerve stimulation (nVNS) device called gammaCore®. The gammaCore® (nVNS) device is a handheld, battery-powered unit that produces a proprietary electrical waveform in the vicinity of the vagus nerve in the neck. Each dose (or stimulation) is relatively brief (120 seconds) and the user maintains control over the stimulation intensity.

gammaCore® is currently commercially available for the treatment of cluster and migraine headaches, and broad safety data with thousands of patients treated in the US Europe and the UK in both clinical trials and routine clinical care.

Treatment paradigms have been developed and tested in clinical trials to support FDA clearance for the acute treatment of pain associated with episodic cluster and migraine headaches, and the prevention of cluster and migraine headache. This experience demonstrates that nVNS may be administered safely in up to 24 two-minute doses (stimulations) per day. We thus have data to draw on as to how to effectively stimulate the vagus nerve. Given the multiple modes of action with blocking the CAP, and acute bronchodilatation, using a similar treatment paradigm for a trial to evaluate nVNS treatment of ARDS is reasonable. The device should be used both prophylactically and acutely early in the course of the disease prior to mechanical ventilation, and once trained, treatment can be fully managed by either a healthcare professional or the patient. If one waits until mechanical ventilation has started, it is less likely that a therapy will be able to block the cytokine storm and outcomes will be less profound.

With respect to the theoretical cardiac and respiratory side effects of non-invasive treatment, historically, stimulation of the vagus nerve is associated with adverse side effects, including bradycardia and bronchoconstriction. These effects were shown to be the result of in discriminant stimulation of all fibers in the vagal bundle (the vagus nerve is primarily comprised of A and C fibers), which could be avoided by specifically tuning the electrical signals to selectively stimulate only the A fibers. This is possible because of the difference in electric field strengths necessary to activate the different fiber types.[34]

The intensity, pulse duration and frequency of gammaCore® (nVNS) stimulation parameters have been optimized to induce signals in the large, myelinated Aβ fibers of the cervical branch of the vagus nerve. Since gammaCore® activates only the low threshold afferent Aβ fibers, versus the high threshold efferent C-fibers that innervate the heart, there is no known risk for adverse cardiac or other systemic parasympathetic effects.

electroCore has conducted pre-clinical studies to assess the potential risk of vagus nerve overstimulation on the heart and airways. Several studies were conducted in beagle dogs with hypersensitized airways (worst case for airway reactivity) at maximum stimulation output for 2 minutes. Review of heart rate and airway resistance before, during and after stimulation indicated that there were no significant adverse changes associated with stimulation.[37] These results are consistent with the human clinical experience with the gammaCore® device. Regarding the theorized mechanism of action, afferent fibers from the vagus nerve enter the brain and synapse onto the nucleus tractus solitarius (NTS) in the brain stem[1], making connections with many structures in the brain including the locus coeruleus (LC), the periaqueductal gray (PAG) and the raphe nucleus (RN).[35] These structures are known to control the release of key inhibitory neurotransmitters. Numerous animal and clinical studies over the last 25 years have implicated the activity of these structures, in particular the LC, in the mechanism of action of VNS to inhibit seizures.[36]

Clinical Use for Clinical Care

Given the lack of other effective and/or reasonable options for a patient with CoViD-19 respiratory distress and the anticipated demands on our healthcare system, considering gammaCore® (nVNS) therapy, we propose, is a reasonable approach. To achieve goal of decreasing health care burden with patient benefit of decreasing ventilator dependency, inflammatory response and mortality, plan to use it early in course of disease i.e. prior to severe respiratory distress and the need for mechanical ventilation.

The presumptive mechanisms of bronchodilatation and modulation of the cytokine storm would suggest that early intervention is ideal in improving pulmonary function and avoiding respiratory depression.

1) Prevention. Mitigation of pro-inflammatory immunokine release would be best achieved with two doses (stimulations), consisting of a two-minute stimulation, on each side of the neck three times a day (am, afternoon and an hour before bed). This would be a total of 6 treatments (2 stimulations x 3 times per day) of stimulation as a prophylactic/preventive measure. This dosage is well below the known safety dosage threshold.
2) In addition, patients may receive additional treatments when experiencing acute respiratory distress. Similarly, one treatment is two doses (stimulations). Each treatment (consisting of two-minute stimulation on each side) is performed on the neck. If shortness of breath (SOB) persists 20 minutes after start of first treatment, administer a second treatment. Maximum number of acute treatments per day is 9. This is symptomatic control and can be used to improve FEV_1, Work of Breathing or dyspnea.

6 CLINICAL INVESTIGATION OBJECTIVES

The aims of this study are to summarize and compare the incidence of clinical events and pro-inflammatory cytokine levels in patients randomized to use of gammaCore Sapphire plus standard of care vs standard of care alone in patients hospitalized for CoViD-19. In addition, this study is intended to demonstrate the safety of gammaCore Sapphire use in patients hospitalized for CoViD-19.
Specific clinical events to be summarized include, but are not limited to:

- Changes in oxygen support requirements (no oxygen support, low-flow oxygen support, nasal high-flow oxygen support, noninvasive mechanical ventilation, and invasive mechanical ventilation)
- Changes in O_2 saturation
- PaO2/FiO2 ratio
- Proportion of subjects requiring mechanical ventilation
- Days to onset of mechanical ventilation
- Live discharge from the hospital
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Specific laboratory measurements to be summarized include, but are not limited to:

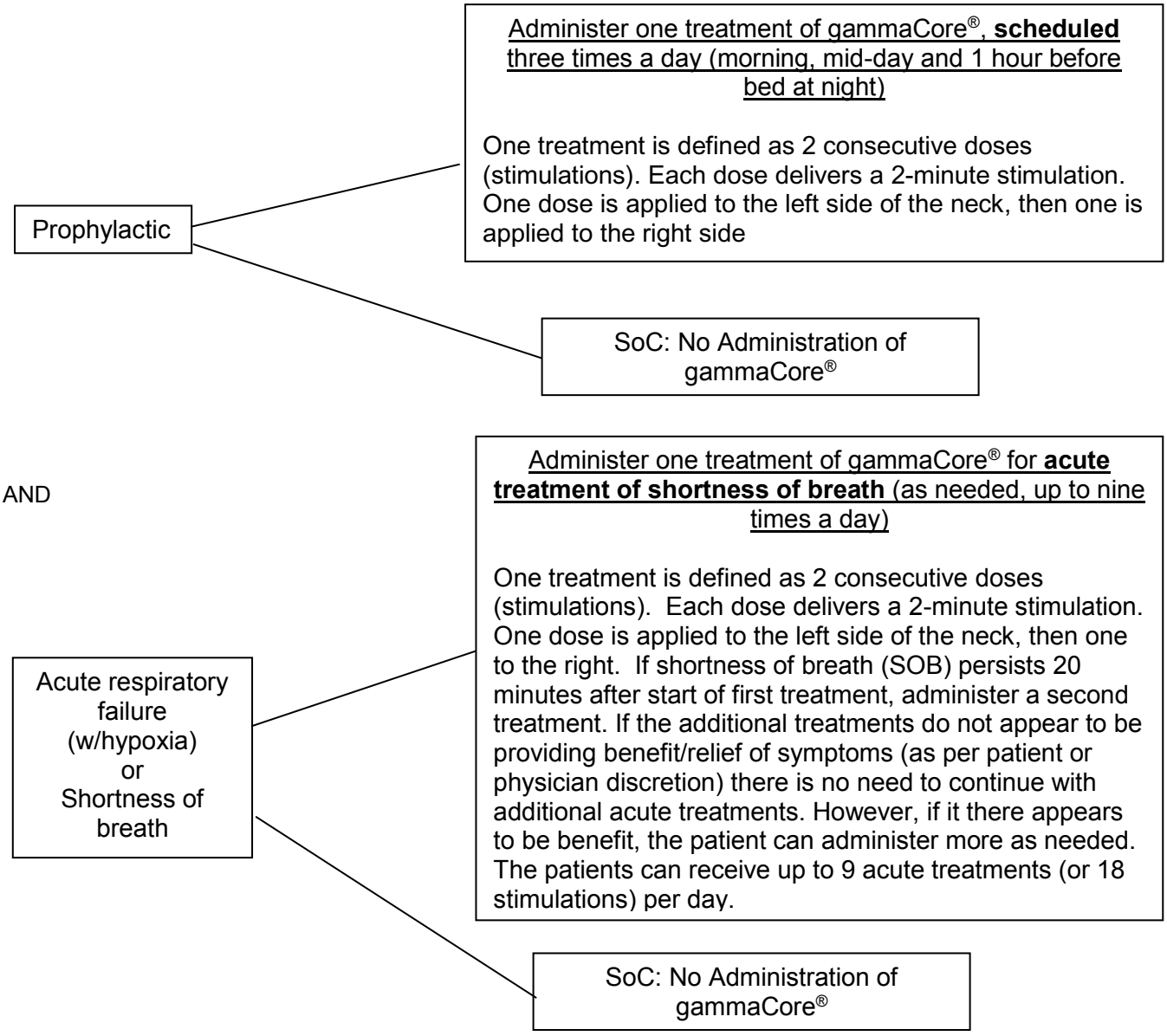
- TNF-α
- IL-1β
- IL-6
- CRP
- Ferritin
- D Dimer
- Pro-Calcitonin

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 Overall Clinical Investigation Design

The study is a prospective, randomized, control investigation designed for comparison of two groups for the reduction of respiratory distress in a CoViD-19 population, using gammaCore® Sapphire plus standard of care (active) vs. standard of care alone (SoC), the control group. The gammaCore® treatments will be used acutely and prophylactically.

Figure 1 Overall Design



7.2 Clinical Investigation Procedures and Definitions

Once the patient is admitted to the hospital, the institution shall follow their standard protocol for their CoVid-19 patients. The investigator shall administer the consent form, conduct the intake and randomize the patient 1:1 into each of the two study arms prior to baseline measurements. Once qualified, the patient shall be trained on the use of gammaCore® and provided an initial treatment. For every day the patient is in the hospital but not on mechanical ventilation, the administration of gammaCore®, prophylactically and acutely, will be recorded on the daily study log as per protocol treatment.

7.2.1 Schedule of Clinical Investigation Events

7.2.1.1 Intake / Admission (Day 0)

Upon hospital admission, after the patient and the Investigator have signed the Informed Consent Form, the patient will be randomized 1:1 into one of the two treatment arms. Patient's severity of condition will be classified based on age, co-morbidities, and oxygen saturation as moderate or severe. To prevent allocation bias, the patient will be assigned to the test or control arm of the study based on severity of classification in a 1:1 ratio. Thereafter, the study physicians and/or attending physicians participating in the study and if feasible, will conduct a complete physical examination and obtain vitals. Medical and demographic information in the EMR pertinent to this trial and the patient's treatment will also be captured into the CRFs.

The following Intake and collection of data will then be conducted:

- Intake Collection of:
    - Basic Demographics
        - Date of Birth (DOB), Race, Sex, Smoking Status, County/Region
    - Medications, Co-morbidities
    - CoViD-19 Test Results (Positive / Presumed Positive)
- Study Measurements:
    - Height/Wt (BMI)
    - Temperature
    - Blood Pressure
    - O_2 Saturation
    - PaO2/FiO2 ratio
    - Shortness of Breath (Yes / No)
    - Cough (Yes / No)
- Clinical Labs
    - Immunokine panel (TNF-**α,** IL-1β, IL-6)
    - Frozen blood sample†
    - Leukocyte flow cytometry
    - Pro-Calcitonin

  - CRP
  - Ferritin
  - D Dimer
  - Complete hematology panel (CBC with differential)
  - Comprehensive metabolic panel
  - Serum or urine hCG (for any woman who might be pregnant)

- Device training: Patient receives device training on gammaCore® Sapphire device and receives first treatment with trained study staff *
  - nVNS Stimulation Supervised**
  - Study log completion: patient will record date and times of stimulations.
  - Daily Tx Log Completion
    - Oxygen Required, Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow), Ventilator Dependence, Date and time of Ventilation, Patient discharge home, Date and time of Discharge, Survival
- Clinical Improvement Scale
  - Adverse event assessment

* For those patients allocated to gammaCore (nVNS), the patient will be instructed by a study physician on the gammaCore® technique. They will be instructed to use it according to the specified protocol, which will be available at bedside. Re-training on the device or study log completion can occur at any time the patient requests further instruction or clarification and/or if research staff feels re-training is necessary during supervised stimulations.

Instructions for the use of the device will be kept in each patient's room and will not be re-used for any other patient, or removed from the patient room for any reason, throughout their study participation.

Study team will provide each patient with a laminated study log for individual patient room, each day, to log their treatments. This log will cleaned for reuse each day for each patient, then discarded per institutional policy and will not be used by any other patient. A duplicate paper study log will be located on the outside of the room, whereas a trained study investigator will transpose the data entered on the log from the patient's room, onto a CRF, with their signature and date, each day while patient is on study.

**** Protocol:**

Prophylaxis: Administer gammaCore® Sapphire daily, prophalytically, scheduled three times a day (morning, mid-day and 1 hour before bed at night). One treatment is defined as 2 consecutive doses (stimulations). Each dose delivers a 2-minute stimulation. One dose is applied to the left side of the neck, then one is applied to the right. This would be a total of 6 treatments (2 stimulations x 3 times per day).

For acute respiratory distress or shortness of breath (SOB): Administer one treatment of gammaCore® for acute treatment of shortness of breath (as needed, up to nine times a day). One treatment is defined as 2 consecutive doses (stimulations). Each dose delivers a 2-minute stimulation. One dose (stimulation) is applied to the left side of the neck, then one to the right. If shortness of breath (SOB) persists 20 minutes after start of first treatment, administer a second treatment. If the additional treatments do not appear to be providing benefit/relief of symptoms (as per patient or physician discretion) there is no need to continue with additional acute treatments. However, if it there appears to be benefit, the patient can administer more as needed. The patients can receive up to 9 acute treatments (or 18 stimulations) per day.

Determination of benefit/relief of symptoms will be determined collaboratively between patient and a research investigator who is caring for the patient. Should the acute treatments not provide any relief, the research investigator will determine if/what standard of care therapies are necessary, to treat symptoms. If patient remains in stable condition, they can continue with prophylactic treatments (3xday), when/if possible. Once symptoms are treated (standard of care) and patient is stable again, they can resume the acute treatments (up to 9x day) and continue with this process, until study completion (until they are placed on mechanical ventilation, are discharged, or can no longer continue with treatments, per patient or physician discretion/withdrawal from study).

The devices are pre-programmed to not allow more than 30 stimulations in a 24 hour period. This is a safeguard with the device that cannot be changed. Once the maximum daily number of treatments has been reached, the device will not deliver any more stimulations until the following 24-hour period. (The stimulation automatically stops 120 seconds after the device is powered on).

† Frozen blood sample - Cryopreserved leukocytes will be used in future studies, under peer-reviewed funding support, to determine changes in leukocytes not measured during this trial (e.g. Tregs, Bregs, dendritic cells) as well as transcriptomes (RNA-Seq) and epigenotypes.

7.2.1.2 Days 1 – 3

For days 1 through 3, the following assessments will be recorded each day:

- Study Measurements
    - Height/Wt, BMI
    - Temperature
    - Blood Pressure
    - O_2 Saturation
    - PaO_2/FiO_2 ratio
    - Shortness of Breath (Yes / No)
    - Cough (Yes / No)
- Labs to be drawn early am **(before 10 am) on odd days only**

- Immunokine panel, specifically TNF-α, IL-1β, IL-6
- Frozen blood sample
- Leukocyte flow cytometry
- Pro-Calcitonin
- C-reactive protein
- Ferritin
- D-Dimer
- CBC with differential
- Comprehensive metabolic panel ***Day 3 only**(then drawn on all odd days)*

- VNS Stimulation supervised
  - Total number of gammaCore® treatments administered
  - Date and times of stimulations
- Daily Tx Log (Oxygen dependence & data, ventilator dependence & data, discharge data, survival)
  - Oxygen Required (Yes / No)
  - Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow)
  - Ventilator Dependence (Yes / No)
  - Date and time of Ventilation
  - Patient discharge home (Yes / No)
  - Date and time (in 24 hour format) of Discharge
  - Survival (Yes / No)
- Clinical Improvement Scale
- Concomitant medication assessment
- Adverse event assessment

7.2.1.3 All Even Days Starting Day 4

For all days starting on day 4, lab work is not required, only the following assessments will be recorded each day:

- Study Measurements
  - Temperature
  - Blood Pressure

  - O_2 Saturation
  - Shortness of Breath (Yes / No)
  - Cough (Yes/No)
- nVNS stimulations
  - Total number of gammaCore® treatments administered
  - Date and times of stimulations
- Daily Tx Log
  - Oxygen Required (Yes / No)
  - Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow)
  - Ventilator Dependence (Yes / No)
  - Date and time of Ventilation
  - Patient discharge home (Yes / No)
  - Date and time (in 24 hour format) of Discharge
  - Survival (Yes / No)
- Clinical Improvement Scale
- Concomitant medication assessment
- Adverse event assessment

7.2.1.4 All Odd Days Starting Day 5

For all odd days starting on day 5, the following assessments will be recorded each day:

- Study Measurements
- Labs to be drawn early am **(before 10 am)**
  - Immunokine panel, specifically TNF-α, IL-1β, IL-6
  - Frozen blood sample
  - Leukocyte flow cytometry
  - Pro-Calcitonin
  - C-reactive protein
  - Ferritin

  - D-Dimer
  - CBC with differential
  - Comprehensive metabolic panel
- nVNS stimulations
  - Total number of gammaCore® treatments administered
  - Date and times of stimulations
- Daily Tx Log
  - Oxygen Required (Yes / No)
  - Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow)
  - Ventilator Dependence (Yes / No)
  - Date and time of Ventilation
  - Patient discharge home (Yes / No)
  - Date and time (in 24 hour format) of Discharge
  - Survival (Yes / No)
- Clinical Improvement Scale
- Concomitant medications
- Adverse event assessment

7.2.1.5 Day of Study Completion

The last day of the study will be determined by discharge, transition to mechanical ventilation and/or if the patient is unable to continue. The following will be recorded:

- Study Measurements
  - Height/Wt, BMI
  - Temperature
  - Blood Pressure
  - O_2 Saturation
  - PaO_2/FiO_2 ratio
  - Shortness of Breath (Yes / No)
  - Cough (Yes / No)
- Labs
  - Pro-Calcitonin
  - C-reactive protein

    - Ferritin
    - D Dimer
    - CBC with differential
    - Comprehensive metabolic panel
- nVNS stimulations
    - Total number of gammaCore® treatments administered
    - Date and time of stimulations
- Daily Tx Log
    - Oxygen Required (Yes / No)
    - Oxygen level (%) based on device type (HFNC / NC / Bipap / Optiflow)
    - Ventilator Dependence (Yes / No)
    - Date and time of Ventilation
    - Patient discharge home (Yes / No)
    - Date and time (in 24 hour format) of Discharge
    - Survival (Yes / No) with Date and Time of Death
- Clinical Improvement Scale
- Concomitant medication assessment
- Adverse event assessment

7.2.2 Clinical Investigation Flow Chart

Procedures and outcome measures will be collected as described in the clinical investigation flow chart shown in Table 1.

Table 1 Clinical Investigation Flow Chart

	Study Visit (D=Day)								
Protocol requirements	Admission/ D0	D1	D2	D3	D4	D5	D6	D7	Study Termination[e]
Informed Consent	X								
Inclusion/ Exclusion criteria	X								
Randomization	X								
Complete physical exam	X								
Enter Device #	X								
Intake[a]	X								
Study Measurements[b]	X	X	X	X	X	X	X	X	X
Pro-Calcitonin, C-reactive protein, ferritin, D-dimer, CBC w/dif	X *(+ serum/urine hCG for women who may be pregnant)*	X		X		X		X	X
Comprehensive metabolic panel	X			X		X		X	X
Study labs drawn before 10am (Frozen blood sample, Immunokine panel (Luminex) including (TNF-α, IL-1β, IL-6), Leukocyte flow cytometry	X	X		X		X		X	

	Study Visit (D=Day)								
Protocol requirements	Admission/ D0	D1	D2	D3	D4	D5	D6	D7	Study Termination[e]
Device training[c]	X								
nVNS Stimulation Supervised[c]	X	X							
VNS Stimulation[c]		3X +prn	3X +prn	3X +prn	3X +prn	3X +prn	3X +prn	3X +prn	X
Clinical Improvement Scale	X	X	X	X	X	X	X	X	X
Daily Tx Log completed[d]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X	X	X	X

[a] Includes collection of basic demographics (DOB, Race, Sex, Smoking Status, County/Region), medications, comorbidities CoViD-19 test results)
[b] Includes height/weight (BMI), temperature, blood pressure, O_2 saturation, PaO_2/FiO_2 ratio, shortness of breath assessment, cough assessment
[c] For the active study arm. Includes record of treatment (time and number of doses administered)
[d] The following parameters will be recorded daily: Oxygen dependence & data, ventilator dependence & data, discharge data, survival, device treatment record (active study arm only)
[e] Study completion will be determined by discharge, transition to mechanical ventilation and/or if the patient is unable to continue

7.3 Discussion and Justification of Clinical Investigation Design, Including the Choice of Control Groups

The study design (randomized, including a control group) was chosen to evaluate the usefulness of the gammaCore® Sapphire device for symptom improvement in patients suffering CoViD-19 related respiratory distress compared to standardized institution treatment only.

During hospitalization, the study patients, if able, will administer gammaCore® as prescribed for all acute respiratory attacks or shortness of breath, and also prophylactically. If patients are unable, study personnel may assist.

7.3.1 Prior and Concomitant Medication and Procedures

Medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator.

The study team will document all concomitant medication usage during the investigation in the CRF.

7.4 Selection of Population for the Clinical Investigation

7.4.1 Number of Patients

After the first 20 patients have been enrolled and completed the study at Allegheny General Hospital, the investigator will conduct an interim analysis and submit findings to the IRB for approval to increase the enrollment up to 60 patients (30 patients per arm). Up to 90 patients are expected to be screened.

7.4.2 Inclusion Criteria

The patients have to meet all of the following criteria to be eligible to enter the investigation:

1. Patients (age 18 years and older) who have tested positive or suspected/presumed positive for CoViD-19 using PCR real-time test
2. Patients with cough, shortness of breath or respiratory compromise (RR>24/min, increased work of breathing)
3. O_2 Saturation less than or equal to 96% on room air or sensation
4. Agrees to use the gammaCore Sapphire device as per protocol and to follow all of the requirements of the study including recording required study data
5. Permission for early am blood draw to freeze for subsequent lab tests and sequencing as related to CoViD-19 sequelae
6. Patient is able to provide signed and witnessed Informed Consent

7.4.3 Exclusion Criteria

Patients meeting any of the following criteria cannot be included in this research study:

1. On home/therapy oxygen (i.e. for COPD patients) at baseline prior to development of CoViD-19
2. Already using gammaCore® for other medical conditions
3. A history of aneurysm, intracranial hemorrhage, brain tumors, or significant head trauma
4. Known or suspected severe atherosclerotic cardiovascular disease, severe carotid artery disease (e.g., bruits or history of transient ischemic attack or cerebrovascular accident), congestive heart failure, known severe coronary artery disease, myocardial infarction documented within past 90 days, or current or recent history of life-threatening arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, second or third-degree heart block, uncontrolled atrial fibrillation or uncontrolled atrial flutter)
5. Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia (as per investigator discretion)

6. Current implantation of an electrical and/or neurostimulator device, including but not limited to a cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant
7. Current implantation of metal cervical spine hardware or a metallic implant near the gammaCore® stimulation site
8. Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled and prisoners)
9. Compromised access to peripheral vein for blood
10. Pregnant women
11. Patients with active cancer or those who have had recent cancer treatment

Before enrollment into the study, patients must meet all of the following inclusion criteria and none of the following exclusion criteria.

7.4.4 Removal of Patients from the Clinical Investigation

Patients are free to discontinue participation in the investigation at any time, without prejudice to further treatment. Patients who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any adverse event (AE)/adverse device effect (ADE) and, if possible, be assessed by a Clinical Investigator.

Patients may be withdrawn from investigation treatment and assessments at any time, if deemed necessary by the Clinical Investigator.

Specific reasons for withdrawal of patients from this investigation are:

- The decision of a patient to withdraw from the investigation (including if the patient withdraws informed consent)
- Unacceptable adverse event
- Patient lost to follow-up; or
- Patient is non-compliant with study procedure

In case of withdrawal, AEs/ADEs should be followed up.

Incorrectly enrolled patients will be withdrawn from further investigation and assessments. A protocol deviation will be submitted to the IRB via a prompt report form.

7.5 Identification and Description of the Clinical Investigational Medical Device

7.5.1 Identification of the Clinical Investigational Medical Device

gammaCore Sapphire (non-invasive vagus nerve stimulator) is a multi-use, handheld, rechargeable, portable device consisting of a rechargeable battery, signal-generating and amplifying electronics, and a control button for the patient to control the signal amplitude. The device provides visible (display) and audible (beep) feedback on the device and stimulation status. A pair of stainless-steel surfaces, which are the skin contact surfaces ("stimulation surfaces"), allows the delivery of a proprietary electrical signal. The patient will apply electroCore-approved gel to the stimulation surfaces to maintain an uninterrupted conductive path from the stimulation surfaces to the skin on the neck. Tubes of electroCore-approved gel will be provided with each unit. The stimulation surfaces will be capped when not in use. gammaCore® produces a low-voltage electric signal consisting of five 5000-Hz pulses that are repeated at a rate of 25 Hz. The waveform of the electric pulses is approximately a sine wave with a peak voltage limited to 24 Volts when placed on the skin and a maximum output current of 60mA.

The signal is transmitted through the skin of the neck to the vagus nerve. gammaCore® allows for the patient to appropriately position and adjust the stimulation intensity level as instructed by the research team. Each stimulation is designed to be applied for 2 minutes, after which the device automatically stops delivering the stimulation. Each device allows for multiple treatments.

gammaCore® can deliver up to thirty 120–second stimulations within a 24-hour period. Once the maximum daily number of treatments has been reached, the device will not deliver any more stimulations until the following 24-hour period. (The stimulation automatically stops 120 seconds after the device is powered on). The gammaCore® Sapphire device includes a charging station to hold and charge the device.

Figure 1. gammaCore® Sapphire

Figure 2. gammaCore® Sapphire with Charging Station

The patient will apply conductive gel (supplied with the device) to the stimulation surfaces and then hold the nVNS device on the skin over the vagus nerve on the neck (between the trachea and the sternocleidomastoid muscle, over the carotid pulse). Details of device placement and operation will be provided in the Instructions for Use (IFU).

The gammaCore Sapphire device produces a proprietary, low voltage electric signal that generates an electric field in the vicinity of the vagus nerve when the device is placed in the intended location.

7.5.2 Packaging and Labelling of the Clinical Investigational Medical Device

The commercial packages will be used in this Clinical Investigation, all device packaging will be marked “For Clinical Investigation Only”.

7.5.3 Installation and Use of the Clinical Investigational Medical Device

A qualified research personnel (i.e. device trained) will train the study patients before they can start self-administration of stimulations. The gammaCore® Sapphire device will be used following the treatment assigned in this protocol.

7.5.4 Compliance with Device Usage

Patient will record all use of the device in a study log, trained study staff can assist the patient, as necessary. Compliance will be assessed in the hospital setting by the research staff.

7.6 Risk and Benefits of the Investigational Device and Clinical Investigation

The gammaCore Sapphire is being trialled for the acute and prophylactic treatment of CoViD-19 induced respiratory distress. The anticipated benefits include:

- No mechanical respirator required
- Significant reduction of number of days in hospital

There are no significant risks identified with the participation in this study however study patients can rarely experience transient symptoms such as:

- 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

Study subjects will be exposed to potential risks and complications associated with gammaCore. These are anticipated to resolve shortly after discontinuation of the stimulation procedure without medical intervention or clinical sequelae. Occurrence of several of these events can be mitigated by the user repositioning the device on the neck and/or decreasing the stimulation intensity. Training on the positioning of the device and controlling the stimulation intensity is conducted at the time the device is provided to the subjects. In addition, the device is provided with detailed Instruction for Use. These potential anticipated adverse events include, but are not limited to:

- 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 (paresthesia/dysesthesia) (1.63%)

NOTE: When all available safety data was pooled from all studies, the following AEs occurred in >1% of patients, but less than < 5% (there were no reported side effects that occurred in >5% of study patients) All adverse events occurred in at least 1 in 100 (1%) patients and are therefore "common".

Risks associated with blood draws

- Pain or discomfort from needle
- Bleeding
- Infection

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

The product will be used at the hospital.

Each device is for single patient use. No device sharing will be done. Every patient will have an individual device throughout the study. It will be stored in patient room throughout the duration of the study and at completion will be discarded by study staff, according to institutional policy and following all regulations for disposal of infectious waste and electrical equipment.

All patients must undergo training at the hospital before starting treatment with the device in order to learn and optimize where and how to stimulate. Written information will also be provided.

All research staff included in study will be trained in the use of device. Patients will administer their own treatment unless unable to do so safely. Treatment can be administered by trained research staff, if necessary and with patient permission.

Site will be instructed to contact electroCore immediately if the product malfunctions and does not work as expected or if the device have been damaged or is suspected to have been damaged in some way. If patients are using it without clinical supervision, patients will report any product malfunctions to the PI and/or research staff. Should any type of malfunction occur, the patient would discontinue use of the device and the research staff will assess for any adverse events. Any device deficiencies/malfunctions will be reported to the PI, the IRB via a prompt report form and the device manufacturer. The device will be quarantined by the research staff and a new device will be provided to the patient.

The benefits of this study are estimated to outweigh the risks as the patient's improvement is expected to be considerably greater than any expected side effects..

7.7 Performance and Safety Endpoints, Variables and Measurements

7.7.1 Patient Characteristics

Date of Birth (DOB), Race, Sex, Smoking Status, County/Region

7.7.2 Objectives

The aims of this study are to summarize and compare the incidence of clinical events and pro-inflammatory cytokine levels in patients randomized to use of gammaCore Sapphire plus standard of care vs standard of care alone in patients hospitalized for CoViD-19. In addition, this study is intended to demonstrate the safety of gammaCore Sapphire use in patients hospitalized for CoViD-19.
Specific clinical events to be summarized include, but are not limited to:

- Changes in oxygen support requirements (no oxygen support, low-flow oxygen support, nasal high-flow oxygen support, noninvasive mechanical ventilation, and invasive mechanical ventilation)
- Changes in O_2 saturation
- PaO2/FiO2 ratio
- Proportion of subjects requiring mechanical ventilation
- Days to onset of mechanical ventilation
- Live discharge from the hospital
- Patient length of stay
- Mortality
- Shortness of Breath
- Clinical improvement Scale

Specific laboratory measurements to be summarized include, but are not limited to:

- TNF-α
- IL-1β
- IL-6
- CRP
- Ferritin
- D Dimer
- Pro-Calcitonin

7.7.3 Safety Variables and Measurements

The primary safety measure for this study is the incidence and occurrence of SAEs related to the study treatments.

7.7.4 Other Variables and Measurements

Comorbidities known to influence course of CoViD-19 including asthma or other underlying pulmonary disorders, diabetes and cardiac disease will be recorded.

7.7.5 Appropriateness of Measurements

The evaluative measurements include changes in oxygen support, O2 saturation and shortness of breath, the need and onset of mechanical ventilation, clinical improvement assesement and mortality. We will also correlate these with cytokine suppression. It is possible that those who have a drop, or do not have an increase in cytokine activation will have a higher survival and lower need for oxygen requirments and/or mechanical ventilation. These will permit evaluation of the objectives for the study.

The safety measurements are typical for a clinical trial and permit evaluation of the safety of the device.

7.8 Adverse Events/Adverse Device Effects and Device Deficiencies

The definitions and procedures for reporting adverse events (AE), adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE) and are presented in the sections below. It is of utmost importance that all staff involved in the investigation are familiar with the definitions and procedures and it is the responsibility of the Clinical Investigator to ensure this.

7.8.1 Adverse Event/Adverse Device Effect Definitions

Adverse Event

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research

Adverse Device Effect

Adverse event related to the use of an investigational medical device.

Note 1: This definition includes any event resulting from insufficiencies or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event that is a resulting from a user error or from intentional misuse of the investigational medical device.

7.8.2 Serious Adverse Event/Serious Adverse Device Effect/Unanticipated Adverse Device Effect Definitions

Serious Adverse Event

An adverse event is considered serious and should be reported to IRB when the patient outcome is:

- **Death**
- **Life-threatening** - the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
- **Hospitalization (initial or prolonged) -** admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- **Disability or Permanent Damage -** if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- **Congenital Anomaly/Birth Defect -** suspected exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- **Required Intervention to Prevent Permanent Impairment or Damage (Devices)** - medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- **Other Serious (Important Medical Events)** - the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Serious Adverse Device Effect

A SADE is an ADE that results in any of the consequences characteristic of an SAE or that might lead to any of these consequences if suitable action is not taken, if intervention is not made or if circumstances are less opportune.

7.8.3 Unanticipated serious adverse device effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.

7.8.4 Reporting of Adverse Events/Adverse Device Effects

7.8.4.1 Methods for Eliciting Adverse Events/Adverse Device Effects

All patients will be carefully monitored for the occurrence of AEs during the investigation period from the run-in to the completion of follow up. The Clinical Investigator will collect AE information using non-leading questions such as “have you experienced any new health problems or worsening of existing conditions”. Events directly observed or spontaneously volunteered by patients will also be recorded.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the patient or reported in response to an open question by the Clinical Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the CRF and should include the following information.

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding the medical device
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event and will be assessed as:

Mild
The AE does not interfere in a significant manner with the patient’s normal functioning level. It may be an annoyance.

Moderate
The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe
The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description.

Causality (Adverse Device Effects/ADE)

Causality will be assessed as:

- Related (definitely, possible or probable) - A causal relationship between the clinical investigational medical device and the AE is at least a reasonable possibility, i.e. there is evidence or argument suggesting a causal relationship.
- Not related - There is no indication that the AE was caused by the clinical investigational medical device.

7.8.4.2 Follow-up of Patients with Adverse Events

Any AE that is ongoing when the patient is withdrawn from the investigation should be followed-up until the AE is resolved or the Clinical Investigator decides that the AE is stable and needs no further follow-up. The date when the Clinical Investigator considers one of these outcomes to have occurred for the last ongoing AE for a patient will be considered the last visit for this patient, and the outcome should be recorded in the CRF.

7.8.5 Reporting of Events

INTERNAL: REPORTABLE EVENTS THAT OCCUR AT THE PI's RESEARCH SITE or are ASSOCIATED WITH THE PI			
Event	**Examples** (not all-inclusive)	**How to Report**	**Report Timeframe**
Serious Adverse Event (SAE)	○ Pneumonia resulting from study drug administration ○ Significant allergic reaction resulting from study drug(s) ○ Cardiovascular event induced by study drug(s)	*Prompt Report Form* Copy of SAE Report to Sponsor Copy of subject's signed ICF	5 days
Unanticipated Adverse Device Event (UADE)	○ Guide wire breaks during insertion and cannot be retrieved ○ Revision surgery to replace component ○ Cardiovascular event induced by study device	*Prompt Report Form* Copy of UADE (Device SAE) Report to Sponsor Copy of subject's signed ICF	5 days
SAE or UDAE resulting in death	○ Any death related or possibly related to use of investigational drug or device	*Prompt Report Form* Copy of SAE Report to Sponsor Copy of subject's signed ICF	24 hour phone notice 5 days: written report
Deaths within 30 days of study treatment (all others reported at continuing review)	○ Any death that occurs within 30 days of receiving study drug/device/intervention, regardless if PI determined death is "unrelated" and/or "expected" (this excludes MINIMAL RISK STUDIES such as registries or observational studies).	*Prompt Report Form* Copy of SAE Report to Sponsor	5 days
Major Protocol Deviation/ Violation	○ Failure to obtain informed consent ○ Omitting study procedure(s) required by-approved protocol ○ Drug dispensing/dosing error ○ Failure to securely control the study product ○ Deviation necessary to eliminate an apparent immediate hazard to a participant	*Prompt Report Form*	5 days
Research Complaint	○ Complaint from a participant regarding a research-related injury or study activities ○ Complaint from study personnel regarding fabrication of data or research misconduct	*Prompt Report Form*	5 days
Adverse Monitoring or Audit Reports, or Enforcement Action	○ Reports of study monitor visits or sponsor audits with findings that require action at this site to address potential risks to participants or others. ○ Suspension or restriction of medical license ○ FDA Form 483 or Warning Letter	*Prompt Report Form* Copy of reports, audits, etc.	24 hour phone notice: suspensions or FDA 483 5 days: monitoring or audit reports
Other Unanticipated Problem	○ Participant becomes incarcerated ○ Breach of participant confidentiality (e.g., breach of secured database) ○ Study personnel misconduct that adversely affects the study	*Prompt Report Form*	5 days
Recalls / Withdrawals / Clinical Holds	○ Correspondence communicating a Regulatory Agency or Sponsor mandated marketing recall, withdrawal, or clinical hold	*Prompt Report Form* Copy of the correspondence	5 days
Reports, publications, or interim results or findings	○ DSMB reports and recommendations ○ Regulatory Agency Public Health Advisory ○ "Dear Healthcare Professional" Letter	*Prompt Report Form* Copy of report, publication, interim finding, etc.	10 days
All Adverse Events (regardless if serious, related or expected) **that do not meet Prompt Reporting criteria as described above**	○ If applicable, a summary report of all adverse events should be provided to the IRB at least annually. ○ The specific format of this report should be described in the Local Data Safety Monitoring Plan at the time of initial review. Many protocols will require only written verification on the *Protocol Renewal Form* (e.g. All adverse events have been reviewed by [the PI & study coord] and appear to be occurring at the frequency and intensity as is expected in this subject population)	*Protocol Renewal Form* (if applicable)	Continuing review (if applicable)

7.8.6 Device deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented on a separate DD form and provided to IRB via prompt report and electroCore within 24 hours of the event.

7.9 Data Quality Assurance

7.9.1 Monitoring, Audits and Inspections

During the investigation, the PI will be responsible for the monitoring of the clinical trial to ensure the research team is following all aspects of the CIP. All data must be accurately recorded in the CRF. Source data verification (a comparison of data in the CRF with the patient's medical records and other records at the investigation site) with access to records may also be performed by the institution's Quality Coordinator.

Authorized representatives of Regulatory agencies may visit the site to perform audits or inspections, including source data verification.

7.9.2 Patient Records and Source Data

Data may be recorded directly in the CRF, which will then be considered as source data.
It is the responsibility of the Clinical Investigator to record essential information in the medical records in accordance with national regulations and requirements, including:

- Investigation code
- Patient screening number and/or patient number
- That informed consent for participating in the study was obtained
- Diagnosis
- All data entry days during the investigation period
- All AEs/ADEs
- Treatments
- The SN number of the device

The Clinical Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs. Signed CRFs will be collected and monitored on a regular basis.

7.9.3 Access to Source Data and Documentation

The Clinical Investigator should guarantee access to source documents for the Quality Coordinator and auditors as well as for inspection by appropriate regulatory agencies, and the IRB/IEC, if required.

7.9.4 Training of Staff

The Clinical Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

7.9.5 Data and Quality Management

The data collection tool for this trial will be using CRFs. Patient data necessary for analysis and reporting will be entered into a validated database or data system. Data management and handling will be conducted according to the investigation specific Data Management Plan, developed, managed and controlled by Institution.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in an investigation specific Data Management report.

7.9.6 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will meet quarterly with the investigators and study coordinator to review study data and any major adverse events. The board will conduct interim monitoring of AEs/SAEs, oversight and analysis of study information and data to ensure the continuing safety of research participants, efficacy of the study intervention, appropriateness of the study, continued relevance of the study question, and integrity of the accumulating data throughout the life of the clinical trial. The board will be comprised of three physicians specializing in pulmonology. A summary of the DSMB findings will be submitted to the IRB with the annual renewal.

7.10 Statistical Methods and Determination of Sample Size

7.10.1 Statistical Evaluation of Performance and Safety Variables

This section provides a summary of the statistical methodology that will be used by the Institution. A more detailed description of analysis methods will be provided in a separate statistical analysis plan (SAP).

7.10.1.1 Data Sets to be Analysed

The intention to treat (ITT) population includes all randomized subjects with at least 1 verified treatment post-training during study period. The ITT population will be analyzed using the subject's randomized treatment regardless of which treatment the subject actually received.

Subjects with major protocol deviations will be excluded from the per-protocol (PP) analysis set. Subjects not taking the study treatment in the prescribed manner more than 33% of the time will be excluded from the PP analysis set. Additional subjects with exclusionary protocol deviations will be identified prior to database finalization and unblinding. Analyses for the PP will be conducted according to the randomized treatment.

All subjects entering the study will be included in the safety population. Analyses for safety population will be conducted according to the treatment actually received.

Definitions

Generally, a baseline measurement refers to the last non-missing assessment made before the first administration of study treatment (at e.g. screening and baseline).

7.10.1.2 Summary Statistics

Data will be presented using summary statistics. For example, categorical data may be presented as proportions and counts; continuous data may be presented with the mean, median, minimum, maximum, and/or standard deviations. Kaplan-Meier methodology may be used to present time to event data. All comparisons between active and control groups are nominal in nature; confidence intervals and p-values may be presented, but are not intended for inferential purposes.

7.10.1.3 Analysis of Objectives

Full details will be described in the Statistical Analysis Plan (SAP).

7.10.1.4 Demographic and Other Baseline Characteristics

Full details will be described in the Statistical Analysis Plan (SAP).

7.10.1.5 Extent of Device Usage

Exposure to treatment/device will be presented by using summary statistics for number of days with study treatment by each device group.

7.10.1.6 Adverse Events/Adverse Device Effects

Device-related serious adverse events will be tabulated. The overall incidence of device-related serious adverse events will be summarized and presented as a proportion and respective 95% exact binomial confidence interval. Additionally, an overview of events, to include total numbers of events, and total number of subjects with events will be tabulated and presented for all AEs, serious AEs, and device-related AEs and device-related serious AEs, as well as deaths. Events will be presented overall and by study arm.

7.10.2 Handling of Drop-outs and Missing Data

Outliers will be included in summary tables and listings, and will not be handled separately. Available data from prematurely withdrawn patients will be included in the analysis as far as possible. If data are only partially completed, the available data will be reported as an per protocol evaluation

7.10.3 Determination of Sample Size

This is one of the first studies of GammaCore Vagus Nerve Stimulation treatment in COVID-19. There is no published data on anticipated effect size in humans. Hence, a formal power analysis could not be done.

Data will be presented using summary statistics. For example, categorical data may be presented as proportions and counts; continuous data may be presented with the mean, median, minimum, maximum, and/or standard deviations. Kaplan-Meier methodology may be used to present time to event data. All comparisons between active and control groups are nominal in nature; confidence intervals and p-values may be presented, but are not intended for inferential purposes.

7.10.4 Interim Analysis

An analysis of safety and feasibility was conducted on the first 20 patients who completed the hospitalization period. Only minor protocol deviations were noted with one SAE unrelated to device use. Neither incidence was a reportable event to the IRB.

7.10.5 Procedures for Reporting any Deviations from the Original Statistical Analysis Plan

Any deviation(s) from the original statistical analysis plan will be described and justified in a CIP Amendment and/or in a revised statistical analysis plan and/or in the final report, as appropriate.

7.11 Amendments to the Clinical Investigation Plan

Any change to the approved CIP must be documented in a written and numbered CIP amendment with a justification for the amendment. Changes to the CIP will only be implemented after written agreement has been obtained between the Principal/Coordinating Clinical Investigator and the IRB. electroCore will also be notified of any amendments or changes to the IRB approved CIP.

An amendment to the CIP may require notification or approval from IRB/IEC and, in many countries, the Competent Authority before implementation. Local requirements shall be followed.

7.12 Deviations from the Clinical Investigation Plan

Every effort should be made to comply with the requirements of the protocol. If the changes or deviations may affect the rights, safety, or welfare of participants, IRB/IEC approval is required. Deviations will be recorded with an explanation for the change. Corrective action will be implemented to avoid repeat deviations.

The reasons for any patient's withdrawal and discontinuation from the investigation will be recorded. If such discontinuation is because of problems of safety or lack of effectiveness, the patient will still be followed up in the investigation, if possible.

7.13 Report and Publication

The CIP shall specify whether the results of the investigation will be submitted for publication or the extent to which and conditions under which the results of the clinical investigation will be offered for publication.

At the completion of the study, the Clinical Investigator may collaborate with the device manufacturer, electroCore, to review and use the data collected for publication purposes. If/when the Clinical Investigator chooses to publish results of the study, the PI wil provide electroCore with the final clinical study report summarizing the study and the results prior to publication.

All publications and presentations must be based upon the clinical investigation report.

8 ETHICS

8.1 Institutional Ethics Review

The final CIP, including the final version of the Patient Information and Consent Form, must be approved in writing by an IRB/IEC before enrollment of any patient into the investigation. The Clinical Investigator is responsible for informing the IRB/IEC of any amendment to the CIP, as per local requirements.

8.2 Ethical Conduct of the Clinical Investigation

The investigation will be conducted in compliance with applicable regulatory requirements and with the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association (Appendix A).

8.3 Patient Information and Consent

All patients will receive written and verbal information regarding the investigation prior to any investigation-related procedures. This information will emphasise that participation in the investigation is voluntary and that the patient may withdraw from the investigation at any time and for any reason. All patients will be given the opportunity to ask questions about the investigation and will be given sufficient time to decide whether to participate in the investigation.

Before any investigation-related procedures, the informed consent will be signed and dated by the patient , a witness to signature, and by the Clinical Investigator who gave the patient the verbal and written information.

The consent specifies that data will be recorded, collected, processed and used in accordance with patient consent and applicable law.

9 PATIENT PROTECTION PROCEDURES

9.1 Procedures in Case of Medical Emergency

The Clinical Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

9.2 Patient Data Protection

Minimal necessary data will be collected and stored on a hospital password protected research drive only accessible to the research staff. Risk of breach of confidentiality of this data has been minimized as much as possible. We have used the “minimum necessary” standard in choosing specific and pertinenet data paramenters for this research.

All key research team members having access to clinical data (containing PHI) being collected and analysed currently work within our system. Data containing PHI will be stored on secure, password-protected computers by the team and when necessary, will be securely emailed to other team memebers using only AHN.org email acconts (as per AHN IT Security Policy). Team members will use secure computers and systems to access and work with study spreadsheet data/files. When any information is shared with the sponsor, this will be de-identified. PHI will not be shared with the sponsor.

At the conclusion of data analysis for the protocol, identifiers will be stripped from the compiled datasheet to anonymize the dataset by the PI, or other team member with the goal that the data will be presented formally. Patient identifiers will be deleted and the dataset anonymized as soon as possible. We will comply with the AHNRI IRB “Records Retention” SOP #72 Section 4.6.1 which states “…for research involving PHI performed at AHN, the records will be retained for 10 years after the study is completed.”

10 REFERENCES

In order to determine the scientific background for this clinical investigation as well as to assess risks/benefits of the device, a literature review was conducted and a Clinical evaluation has been performed according to MDD.

The literature listed below was critically evaluated before serving as background information

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11 CLINICAL INVESTIGATION PLAN - INVESTIGATOR AGREEMENT FORM

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Tariq Cheema, MD

Principal Investigator

AHN Allegheny General Hospital

Signature: _____ Date: _____

12 APPENDICES

Helsinki Declaration

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs of priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected..
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country of countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable
or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researcher, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.