Beaumont Hospital
Consent to Participate in a Research Study

Consent Form Version Date: 30 November 2018

Title of Study: **Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study**

Principal Investigator: Dr. James O'Rourke

Department: Department of Anaesthesia and Intensive Care Medicine, Beaumont Hospital, Dublin 9.

Phone Number: (01) 809 2015 Mon-Fri Office
(01) 8092494 24 hours/day

Co-Investigators: Professor Gerard Curley

Sponsor: Stimdia Medical, Inc.

Dear Patient,

You are being asked to take part in a research study. The investigators listed above are in charge of the study; other professional personnel may help them or act for them.

What are some general things you should know about research studies?

Research studies are designed to gain scientific knowledge that may help other people in the future. You may not receive any direct benefit from participating. There may also be risks associated with being in research studies.

Participation is voluntary, meaning it is your decision if you want to be part of the study. You may refuse to participate, or may withdraw your consent to be in any study at any time, and for any reason, without risking your future care at this site or your relationship with your doctor. If you are a patient with an illness, you do not have to participate in research to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have

about this study at any time and should make sure that your questions have been answered to your satisfaction.

What is the purpose of this study?

The purpose of this study is to assess the safety and performance of the Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System in patients who need to be on a breathing machine (ventilator) in the Intensive Care Unit (ICU). The PEPNS device will be used on you the patient for a period of up to 48 hours in the ICU.

The diaphragm muscle is the muscle that allows the lungs to suck in air. It is responsible for our ability to breathe and it is electrically driven by a nerve called the phrenic nerve which runs between your brain and diaphragm. Weakness of the diaphragm is known to be a big factor in patients who have problems coming off the breathing machine.

The research question is whether electrically pacing the diaphragm will decrease the time patients need to be on ventilators.

During your or your family member's stay in the ICU, the time to come off the ventilator (known as weaning) after receiving electrical stimulation in harmony with ventilation will be recorded. Once weaning is complete, or a total of 48 hours on electrical stimulation, whichever is shorter, the pacing leads used to provide electrical stimulation will be removed.

You are being asked to be in the study because you or your family member has been deemed a suitable candidate for this therapy and it may reduce your weaning time, the time to come off ventilation.

How many patients will participate in this study?

10 patients at this site will take part in this study. There may be a total of up to 20 patients in the study in up to 2 sites.

Candidates for this study will be excluded if ANY of the following conditions are present:

1. The patient's heart has significant difficulties pumping blood (a low cardiac output), has had a recent heart attack (within 72 hours) or the patient is on high doses of medicines which change the heart's force of contraction.
2. Patient unlikely to survive 72 hours.
3. Patient has an implanted pulse generator or implanted electronic device.
4. Patient has or is at risk of significant bleeding problems or is receiving full dose systemic blood-thinning medicines.

5. Patient has known or suspected phrenic nerve damage, sometime evident in patients as an elevated diaphragm muscle, or neuromuscular or inflammatory muscle diseases where the diaphragm itself may not be functional.
6. Patient has an active systemic infection or local infection at or around the insertion site. Patient has low white blood cell counts or has signs of a largely compromised immune system.
7. Patient is known or suspected to be pregnant or making breast milk.
8. Patient will be unavailable for, or is unwilling to comply with protocol follow up.
9. Patient has enrolled in a clinical study within the past 30 days.
10. Patient has undergone a surgery or interventional procedure within the neck region aside from placement of an internal jugular (IJ) vein catheter.
11. Patient has and has been treated for neck cancer within the past 5 years.
12. Patient has intra cardiac thrombus on heart ultrasound.
13. Patient has an uncontrolled thyroid gland, high blood pressure.
14. Patient has had a stroke or a temporary block of blood flow within the past 6 months.
15. Patient has progressive nerve disorder.

How long will your participation last?

The overall time you are being screened and treated in this study may extend up to 3 to 4 days. The time of electrical stimulation will last up to 48 hours or shorter, depending on the time it takes you to wean from ventilation. A follow-up study visit will occur at 30 days +7 days from the end of your stimulation period and will be approximately 30 minutes in duration. Thus, your total study participation period may be up to 41 days.

What will happen if you take part in the study?

If you agree to be in the study, a screening form will be completed to ensure that you are able to be treated that will ask questions about your medical history and whether or not you are pregnant or producing breast milk. The sponsor will also collect the following information: sex (male or female), ethnicity/race, the reason you are on a ventilator and for how long, the number of attempts to wean you from a ventilator, mode of ventilation, sedatives that are being used, data on your lung function, date of birth, height, weight, body mass index, neck diameter and blood pressure. If you do not want to share any of this data you should not take part in the study.

Then you will have chest x-rays, electrocardiograms (ECGs) and ultrasound measurements of your neck and diaphragm taken during the study which are all standard tests. Ultrasound does not pose any risk to you. The ECG consists of a 12-lead device placed on skin surface to record the electrical activity of the heart. Then the stimulation lead(s) will be temporarily placed under

the skin and will be used to electrically stimulate your lung muscle (diaphragm) during mechanical ventilation. The leads will be removed after the stimulation period and/or weaning is complete (not to exceed 48 hours). Your doctor will explain the details about the procedure to place the stimulation lead(s) under your skin as well as what to expect during the recovery period. This procedure is performed using intravenous sedation or general anaesthesia (if required). During the procedure the following data will also be collected: all ventilation data, blood gases, pH, hematocrit, temperature, heart and breathing rate, blood pressure, muscle twitching, visual pain and agitation assessments and repositioning. If you do not want to share any of this data you should not take part in the study.

You may also have a nerve conduction study performed which will test the function of your phrenic nerves and diaphragm before and after the study. This is a non-invasive surface tests where the strength and speed of your muscles and nerves related to breathing are examined.

The PEPNS system is designed to help weaning by stimulating the diaphragm during ventilation in patients who have been on mechanical ventilation for 24 hours or more and who are at risk of having problems in weaning. The stimulation causes the diaphragm to work during ventilation and it is believed that this will prevent weakening of your diaphragm muscle.

Two stimulation leads will be placed over the phrenic nerves in your neck or in the neck of your relative. These are the nerves that your body uses to drive your lung muscle known as the diaphragm. Your doctor will use ultrasound to help see and aid in the guidance of these leads as they are placed under the skin. The PEPNS technology consists of two disposable stimulation leads, a flow sensor and an external electrical function generator designed to stimulate the phrenic nerve in synchrony with the inspiratory cycle of the ventilator. Prior to and during the stimulation period, you will be watched using standard tools to determine the treatment is suitable for you and is not causing you any distress.

If you are one of the first two patients in the study you will only be stimulated on the left phrenic nerve and will also have a phrenic nerve conduction test done prior to the stimulation and at or before the 30 day follow up on both phrenic nerves to try and to see if the left one was changed by the stimulation. If the treating physician sees a difference in the stimulated nerve, fluoroscopy, meaning an x-ray video of the diaphragmatic movement may be done.

You or your relative will be followed up for a period of 30 days and be visited at that time or before that time if you are scheduled for hospital discharge.

After that visit, your participation in the study will be complete. You will be followed on a routine basis by your physician in a manner which is customary.

The data collected during the study will be processed and analyzed by the study sponsor or its statisticians. It will also be retained by the sponsor and the site for at least 10 years.

What are the possible risks or discomforts?

The potential risks related to the PEPNS System and procedure may include but are not limited to the following:

1. Cardiac pacing – This lead is a pacemaker and it is possible that it could temporarily pacer the heart muscle, again should this occur it will be immediately recognized and treated as appropriate.
2. Infection – This lead is a potential source of infection, it is placed under conditions of strict sterility but we will monitor the entrance site closely for any evidence of infection. Local infections are the most likely type of infection from this device.
3. Local bleeding - Although your relative bleeding status will be closely measured, there still remains a small chance of local bleeding.
4. Local Burn – The voltages used for pacing are very small but a local burn is a theoretical complication.
5. Nerve damage – Caused by over stimulation of the nerve or device misuse but stimulation will be closely monitored and all device users will be trained.
6. Pain – The treated patients will be closely observed to ensure the pacing lead does not result in significant pain or discomfort. If it is determined that it is likely uncomfortable any pain issues will be addressed, should these pain issues persist after treatment the leads will be removed.
7. Pneumothorax (punctured lung) - This lead is placed under ultrasound guidance so the incidence of lung damage will be extremely rare.
8. Procedure failure – Operator unable to insert leads into appropriate position.
9. Vagus nerve stimulation - Stimulation of wrong nerve, this could potentially cause a temporary slowing (bradycardia) or stopping (asystole) of the heart, should this occur it will be immediately recognized and treated as appropriate.

The risks have been reduced to an acceptable level by design, fault detection, use of standards, training and labeling. There are also some potential risks due to the ventilation and underlying patient comorbidities that were not listed here since they are not related to the use of the

PEPNS System. The use of this device is considered to be fairly benign and testing performed so far in pre-clinical studies has confirmed this.

What are the possible benefits?

The duration of time that a patient requires ventilation may be reduced by this technology, or it may not have this effect and you or your relative may not benefit at all from participation in the study.

If you choose not to participate, what other options do you have?

You may choose to not be in this study. Participation or non-participation will have no bearing whatsoever on the treatment your relative receives. Your alternative to being in this trial is to receive ventilation free of stimulation of the diaphragm.

What if we learn about new risks during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue to participate.

If the results reviewed during this study show any harm from placement and use of the stimulation lead, the study will be stopped and you will be informed of the findings. The clinical information obtained during the course of the trial might uncover certain medical conditions for which specific treatment is needed. Any findings of this type will be brought to the attention of your consultant and General Practitioner for appropriate medical care.

How will your privacy be protected?

The data provided to the sponsor will contain no patient identifying information. No patients will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure were required, Beaumont Hospital will take all steps allowable by law to protect the privacy of personal information.

Information from this study will be monitored and may be submitted to other ethics committees or regulatory agencies. While we make every effort to maintain your confidentiality, it cannot be absolutely guaranteed. Medical records which identify you and the consent form you signed may be inspected by Stimdia Medical, Inc., its monitor or a regulatory agency. The results of this research may be reviewed by the sponsor's clinical advisors and statisticians. The results of this research may also be presented at meetings or in publications; however, your identity will not be disclosed in those presentations.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow doctors caring for you to obtain information about procedures you have received during the study and treat you appropriately if you have health problems or needs during the study.

Will you be paid for participating?

You will receive no money for participation in this study. You may get reimbursed travel fees related to study visits.

Will it cost you anything to participate?

There will be no extra hospital or doctors' fees for you for being in this study.

What will happen if you are injured by this research?

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. Despite all precautions, you might develop medical problems from being in this study. If such problems arise, the researchers will assist you in finding appropriate medical treatment. You do not waive any liability rights for personal injury by signing this form. You will have insurance coverage during the study since the sponsor will have clinical trial insurance.

What if you want to stop before your part in the study is complete?

Your being in this study is voluntary and your consent may be withdrawn at any time by your legal representative notifying the study physician on your behalf since you will be under anaesthetic throughout the study. Your withdrawal would be without penalty, prejudice, or loss of benefits to which you are entitled and will not affect your current or future care.

If your legal representative decides to withdraw your participation in the research project, he/she should call your physician or the study coordinator. They will explain to him/her how to withdraw you from the study and any health consequences that might happen if he/she withdraws you. Dr. O'Rourke has a right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or the entire study has been stopped.

What if the sponsor or government agency stop the study?

The sponsor and government agencies, based on an intermediate evaluation, have the right to stop enrollment of new patients in the study. If the study is ended before the planned date, your further medical treatment is guaranteed.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have further questions, or if a research-related injury occurs, you should contact Dr. O'Rourke at the numbers on page one. Should he not be available he will return your call as soon as possible.

What if you have questions about your rights as a patient?

This research has been reviewed and approved by the Ethics Committee (EC) at Beaumont Hospital. If you have any questions regarding your rights as a research patient, you may contact Ms. Gillian Vale or Ms. Phil Oglesby on 01 809 2680 or you may email beaumontethics@rcsi.ie.

Patient's Agreement:

I give permission for researchers to look at my medical records to get information. I have been assured that information about me will be kept private and confidential.

I voluntarily consent to take part in, and to be contacted by researchers in this research study having been fully informed of the risks, benefits and alternatives and have been allowed to ask questions that have been answered to my satisfaction.

I give informed explicit consent to have my data reviewed, processed and analyzed as part of this research study by the sponsor or its clinical and statistical consultants.

_____ _____

Signature of Research Patient Date

_____

Printed Name of Research Patient

_____ _____

Signature of Legal Representative Date

_____

Printed Name of Legal Representative

I, the undersigned, have taken the time to fully explain to the above patient and/or the patient's legal representative the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them and will provide them with a copy of this signed informed consent for their records.

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent