CLINICAL INVESTIGATION PLAN (CIP)

Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study

Protocol Number: CIP0001
Version: 4

Date: November 30, 2018

Study Sponsor
Stimdia Medical, Inc.
P.O. Box 251, 5021 Vernon Road
Edina, MN 55436

CIP Approval Page - Sponsor

This Clinical Investigation Plan has been read and approved by:

Name	Patrick Wethington
Title	President & Chief Executive Officer
Company	Stimdia Medical, Inc.
Signature	
Date (DD/MMM/YYYY)	30 / Nov / 2018

Name	John O'Mahony
Title	Vice President of Research & Development
Company	Stimdia Medical, Inc.
Signature	
Date (DD/MMM/YYYY)	Nov 30th 2018

Name	Laurie E. Lynch, PhD
Title	Clinical Study Director
Company	Stimdia Medical, Inc.
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Date (DD/MMM/YYYY)	30 Nov 2018

Revision History

Version Number	Description of Change	Approval Date
1	Initial Release	April 7, 2017
2	Update to incorporate HPRA feedback as follows: specified at least 48 hours of mechanical ventilation, clarified that all patients will be followed up for 30 days, better defined difficulty weaning, revised exclusion criteria 6 to include patients with neuromuscular or inflammatory muscle diseases and specify that letter to general practitioner must be sent if patient is lost to follow up. Update to incorporate Czech Republic State Institute for Drug Control (SUKL) feedback as follows: add investigator and investigative site information, add information on the medical device manufacturer, total expected study duration, add information on premature termination of the study, refer to section 13.1 rather than 14.1 in section 13.4.9 since it was incorrect and add information on investigation of serious adverse incidents. Update to clarify indications for use by slightly rewording, add diaphragm thickness measurements and other minor clean up.	January 30, 2018
3	Update to add the potential risks of asystole and bradycardia due to vagus nerve stimulation based on feedback from HPRA.	July 26, 2018
4	Update primary endpoint #2 to WOB (Work of Breathing) kept between 0.2 joules/L and 2 joules/L for 80% of stimulated breaths. Remove references to patient initials. Change Declaration of Helsinki 2008 to 2013 and add General Data Protection Regulation (GDPR) and Data Protection Act 2018. Updated data retention to 10 years.	November 30, 2018

CIP Approval Page – Principal Investigators

I, the undersigned, have read and understood the Clinical Investigation Plan and agree on the contents. The Clinical Investigation Plan and the Clinical Investigation Agreement will serve as a basis for cooperation in the clinical investigation.

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CIP Approval Page – Principal Investigators

I, the undersigned, have read and understood the Clinical Investigation Plan and agree on the contents. The Clinical Investigation Plan and the Clinical Investigation Agreement will serve as a basis for cooperation in the clinical investigation.

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Table of Contents

STUDY SUMMARY

PEPNS System Feasibility Study Summary	
Title	Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study
Short Title	PEPNS System Feasibility Study
Study Sponsor	Stimdia Medical, Inc. Contacts: Patrick Wethington President and CEO +1 952-807-1371 pwethington@stimdia.com John O'Mahony Vice President of Research and Development +1 763-516-7605 jomahony@stimdia.com Laurie E. Lynch, PhD Clinical Study Director +1 952-221-2468 llynchassociates@gmail.com
Protocol Number & Version	CIP0001 Rev 4, November 30, 2018
Study Device	Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System
Purpose	The purpose of this study is to evaluate the safety and performance of the PEPNS System in patients that need to be mechanically ventilated for at least 48 hours and up to 7 days in the Intensive Care Unit (ICU).
Study Design	Prospective; Non-randomized; Open-label
Enrollment	Up to 2 sites and up to 10 subjects per site. The very first 2 subjects will be stimulated on the left phrenic nerve and followed for 30 days prior to enrolling additional patients. In addition, compound muscle action potential testing (CMAP) and nerve conduction studies, will be conducted on the first 2 subjects during the index procedure and at or before the 30 day follow up.
Follow Up	All subjects will be followed up for 30 days after their index procedure for a total participation period of up to 41 days.
Estimated Study Duration	It is expected that up to 10 subjects will be enrolled per site (up to two sites) during the course of 4 to 6 months for a total estimated study duration of up to 18 months once both sites start to enroll subjects.
Study Population	Patients that need to be mechanically ventilated for at least 48 hours and up to 7 days in the Intensive Care Unit (ICU).

PEPNS System Feasibility Study Summary	
Inclusion Criteria	Candidates for this study must meet all of the following inclusion criteria: 1. 18 years or older (Adult). 2. Male or Female. 3. Able and willing to give informed consent or whose legally authorized representative is able and willing to give informed consent. 4. Subject who in the opinion of the admitting consultant/intensivist is likely to be ventilated for > 48 hours from time of recruitment since study treatment will be for up to 48 hours.

PEPNS System Feasibility Study Summary	
Exclusion Criteria	Candidates for this study will be excluded if ANY of the following conditions are present: 1. Subject has a left ventricular ejection fraction (LVEF) < 20%. 2. Subject unlikely to survive 72 hours due to coexisting medical conditions. 3. Subject has an implanted pulse generator or implanted electronic device: Examples: Cardiac pacemaker, Defibrillator, ICD, Watchman, Vagal nerve stimulator, Spinal cord stimulator, Gastric stimulator or Diaphragmatic stimulator. 4. Subject has experienced an Acute Myocardial Infarction (AMI) within 72 hours prior to this screening or patient is on high dose inotropic support or subject is deemed to be in cardiogenic shock. 5. Subject has significant bleeding diathesis, or is at risk of significant haemorrhage, patient is receiving full dose systemic anticoagulation 6. Subject has a known or suspected phrenic nerve paralysis or neuromuscular or inflammatory muscle diseases where the diaphragm itself may not be functional. 7. Subject has an active systemic infection or local infection at or around the insertion site. Subject is neutropenic or has signs of significant immunocompromise. 8. Subject is known or suspected to be pregnant or is lactating. 9. Subject will be unavailable for, or is unwilling to comply with, follow up requirements of the protocol. 10. Subject is currently enrolled or is expected to be enrolled in any other study of an investigational drug or device who has received treatment under that protocol with the investigational product during the 30 days prior to screening. 11. Subject has undergone a surgery or interventional procedure within the neck region aside from placement of an internal jugular (IJ) vein catheter. 12. Subject has been diagnosed and has been treated for neck cancer within the past 5 years. 13. Subject is known to have a demonstrated intra cardiac thrombus on echocardiography. 14. Subject has uncontrolled hyperthyroidism, hypertension. 15. Subject has had any cerebral ischemic event (Stroke or Transient Ischemic Attack TIA) in the 6-month interval preceding the screening date. 16. Subject has degenerative nerve disorders such as amyotrophic laterals sclerosis (ALS). 17. Subject has an elevated hemidiaphragm on chest x-ray. 18. Subject written informed consent not obtained.

PEPNS System Feasibility Study Summary	
Primary Endpoints	1. Capture of the Left and/or Right Phrenic Nerve > 80% with an output parameter of < 10.5 volts. 2. WOB (Work of Breathing) kept between 0.2 joules/L and 2 joules/L for 80% of stimulated breaths.
Secondary Endpoints	1. The percentage of patients who receive safe and successful placement of the multipolar lead in the left and right phrenic nerve utilizing ultrasound guidance will be determined. 2. Phrenic nerve stimulation in synchrony with Mechanical Ventilation (MV) breaths will be measured to verify that is occurs with inspiration. 3. The percentage of patients who experience one or more serious device/procedure-related adverse events during the study will be reported.
Additional Study Data	1. Time to weaning from mechanical ventilation data will be collected. 2. Diaphragm thickness at 0, 24 and 48 hours.

1. INTRODUCTION

This document is the Clinical Investigational Plan for a human feasibility clinical study of the PEPNS System. This study is to be conducted according to ICH-GCP (International Conference on Harmonization - Good Clinical Practice, E6), EN ISO 14155:2011 (Clinical Investigation of medical devices for human subjects), General Data Protection Regulation (GDPR) and Data Protection Act 2018, Declaration of Helsinki - 2013 version, the European Union (EU) Medical Device Directive (MDD) (Council Directive 93/42/EEC 14 June 14 1993 and 2007/47/EC of 5 Sep 2007) and MEDDEV 2.7/3 revision 3, May 2015 - Guidelines on Medical Devices - Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/383/EE and 93/42/EEC, Ireland's Health Products Regulatory Authority (HPRA), Medical Device Regulatory Requirements for the Czech Republic, the State Institute for Drug Control (SUKL), the Czech Ministry of Health and requirements of other applicable government regulations in Ireland and the Czech Republic and institutional research committee policies and procedures, whichever accords greater protection to the human subjects.

1.1 General Information

1.1.1 Study Title

Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study

Study Number & Version: CIP0001 Rev 4, November 30, 2018.

1.1.2 Study Sponsor

Stimdia Medical, Inc.

Study Director	Name:	Laurie Lynch, PhD
	Address:	Stimdia Medical, Inc., P.O. Box 251, 5021 Vernon Avenue, Edina, MN 55436
	Cell Phone:	+1 952-221-2468
	Email:	llynchassociates@gmail.com
	Name:	Mr. John O'Mahony

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1.1.3 Study Monitor

Stimdia Medical Inc. study personnel and contract study monitors as applicable.

1.1.4 Participating Investigation Site(s) & Principal Investigator(s)

Investigative Site Information		
Investigative Site Name/ Address	Beaumont Hospital P.O. Box 1297 Beaumont Road Dublin 9, Ireland	Military University Hospital (ÚVN) U Vojenské nemocnice 1200, 169 02 Praha 6, Czech Republic
Principle Investigator	Dr. James O'Rourke, MB, BCH BAO, DIBICM, DCH, BSc Consultant in Intensive Care Medicine Anaesthesia and Intensive Care Medicine	MUDr. Michal Soták Department of Anaesthesiology, Resuscitation and Critical Care
Co-Principle Investigator	Professor Gerard Curley, MCR, PhD, MB, BCh, BAO Professor of Anaesthesia and Critical Care Anaesthesia and Intensive Care Medicine	None

2. BACKGROUND & RATIONALE

Ventilator-induced Diaphragm Dysfunction is a significant contributor to weaning difficulty in ventilated critically ill patients. It has been hypothesized that electrically pacing the diaphragm during mechanical ventilation may reduce diaphragm dysfunction resulting in faster weaning times.

Ventilator induced diaphragm dysfunction (VIDD) is considered a major determinant of the ability to successfully wean patients from mechanical ventilation[1]. After as little as 18-69 hours of mechanical ventilation, autopsy specimens from brain-dead organ donors showed greater than 50% reduction in the cross-sectional areas of diaphragm myofibers[2] and animal models have shown a reduction of diaphragmatic force generating capacity proportional to the duration of mechanical ventilation[3,4]. The hypothesis that electrically pacing the diaphragm could prevent VIDD has been previously proposed[5]. Surgically implanted systems for pacing the phrenic nerves and diaphragm have been used for the past 40 years in more than 2,500 adult and pediatric high-level spinal cord injury patients[6,7] and in late-stage Amyotrophic Lateral Sclerosis patients. Implanted systems are not suitable for critically ill patients due to the invasive and complex surgical procedure[8,9]. Brief transcutaneous stimulation of

phrenic nerves is often used for diagnostic purposes, but is not suitable for therapeutic purposes. Transvenous phrenic nerve stimulation (TPNS) has been periodically attempted over the past 50 years[10]. Stimdia has developed a novel percutaneous electrical phrenic nerve stimulation (PEPNS) system.

To evaluate the mitigating effect of phrenic nerve pacing on VIDD we have performed animal studies in canine, caprine and porcine models demonstrating that the operational parameters and insertion techniques chosen do not damage the surrounding tissue or nerves. Testing in animals has also demonstrated that the diaphragm strength is maintained in paced animals versus non-paced animals[11,12].

We hypothesize that beginning phrenic nerve pacing soon after initiation of deep sedation and mechanical ventilation will minimize the reduction in diaphragm strength over time in ventilated subjects and lead to faster weaning times. It has been shown that maintaining some level of work during sedation greatly reduces the deleterious decrease in diaphragm strength.

The PEPNS System Feasibility Study is being conducted to confirm the feasibility of phrenic nerve stimulation in the neck with PEPNS System to pace the diaphragm. The study will be used to confirm:

- The benefits of ultrasound imaging in guiding the deployment of the pacing leads across the phrenic nerve in the patient's neck;
- The ease of lead deployment in the neck;
- The current stimulation levels required to stimulate and contraction of the diaphragm in synchrony with the ventilators inspiratory breaths; and
- Stability of stimulation thresholds as patients are repositioned (supine, recumbent, lateral).

The PEPNS technology consists of two disposable multipolar stimulation leads and an external function generator designed to stimulate the phrenic nerve in synchrony with the inspiratory cycle of the ventilator. The purpose being to exercise the diaphragm during positive pressure ventilation to minimize the reduction in diaphragmatic strength.

Beyond testing the feasibility of the technology in humans the purpose of the study is to also:

- Demonstrate that the human experience is consistent with the preclinical trial results.
- Collect preliminary data that may refine the most suitable patient population for a pivotal study.
- Characterize diaphragm thickness observed on patients using mechanical ventilation and phrenic nerve electrical stimulation if feasible.

Diaphragm stimulation parameters in terms of currents, current profile waveforms, voltages and charge density are similar to those used in chronic diaphragm pacing patients where ventilatory support is replaced with pacing. Subjects will be treated per the standard of care for patients on ventilatory support, with weaning trials conducted up to 48 hours where weaning criteria are met. Time to weaning from mechanical ventilation will be collected. Adverse events will also be collected and analyzed.

The PEPNS System provides a minimally invasive alternative therapy to the standard of care for VIDD patients that may provide a reduction in mechanical ventilation weaning time. The target patient population for this study is the difficult to wean patients. The European Respiratory Society, American Thoracic Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine, and Societe ´de Re´animation de Langue Francaise convened an International Conference on weaning from mechanical ventilation as reported in 2011. The definition of difficult to wean patients is based off this panel's definition. Difficult to wean patients are

patients who required up to 7 days to be extubated from the first attempt of withdrawal from mechanical ventilation.[13] The study will confirm the protocol procedures to be used in the pivotal trial. In addition, the data from these subjects will provide evidence of the ability of stimulation to improve the time to weaning for subjects. This trial will not be powered to be statistically significant to demonstrate a reduction in weaning times.

Condition	Intervention
Patients who are having difficulty in weaning from mechanical ventilation	Device: Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System
Study Type:	Percutaneous placement of stimulation leads
Study Design:	Endpoint Classification: Safety Study Intervention Model: Single Group Assignment
Official Title:	Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study. Also, referred to as PEPNS System Feasibility Study.
Study Sponsor:	Stimdia Medical Inc.

3. SUMMARY OF PRE-CLINICAL TESTING

The PEPNS System has been evaluated extensively in a total of 26 animal studies. The main objective of these studies was to confirm the stimulation treatment could be delivered safely and effectively for the expected duration of use. These studies were also used to evaluate device reliability and usability as secondary objectives. See pre-clinical study table listed below.

Description	Name	Reference	Model	Duration	Start Date	End Date
	Pilot 1	16P10	Porcine	8 hrs	11/5/2015	11/5/2015
	Pilot 2	16G1	Caprine	8 hrs	12/29/2015	12/29/2015
	Pilot 3	16P97	Porcine	8 hrs	1/5/2016	1/6/2016
Evaluate Best Method of Sensing & Stimulation with Inhalation	Pilot 4	16G3	Caprine	10 hrs	3/1/2016	3/1/2016
	Pilot 5	16G4	Caprine	6 hrs	3/14/2016	3/14/2016
	Pilot 6	16G5	Caprine	24 hrs	3/15/2016	3/16/2016
	Pilot 7	16G6	Caprine	24 hrs	3/17/2016	3/18/2016
	Tech 1	16G8	Caprine	24 hrs	3/21/2016	3/22/2016
	Tech 2	16G9	Caprine	24 hrs	3/23/2016	3/24/2016
Select Best Animal Model - Durability to Complete 24 hrs. Studies	Tech 3	16D40	Canine	24 hrs	3/28/2016	3/29/2016
	Tech 4	16D41	Canine	24 hrs	3/30/2016	3/31/2016
	Tech 5	16P163	Porcine	24 hrs	4/13/2016	4/14/2016
	Tech 1	16P0241	Porcine	24 hrs	5/3/2017	5/4/2017
Evaluate Decline in Diaphragm Strength Overtime with and without Stim	Tech 2	16P0261	Porcine	24 hrs	5/5/2017	5/6/2017
	Tech 3	16P0252	Porcine	24 hrs	5/9/2017	5/10/2017
Evaluate Lead Types & Insertion Methods	Lead Pilot1	16P0344	Porcine	12 hrs	6/16/2017	6/16/2017
	Lead Pilot2	16P0433	Porcine	12 hrs	7/11/2017	7/11/2017
	pre-GLP Pilot1	16P0596	Porcine	24 hrs	8/30/2016	8/31/2016
	pre-GLP Pilot2	16P0684	Porcine	24 hrs	9/27/2016	9/28/2016
pre-GLP Pilot Studies	Needle Position Pilot	16P0671	Porcine	Acute	10/3/2016	10/3/2016
	pre-GLP Pilot3	16P0685	Porcine	24 hrs	10/6/2016	10/7/2016
	pre-GLP Pilot4	16P0687	Porcine	24 hrs.	10/6/2016	10/7/2016
	Revised pre-GLP Pilot1	16P0810	Porcine	30 hrs.	11/21/2016	11/22/2016
Nerve & Diaphragm Stim Integrity Test - 30 Day Chronic	Revised pre-GLP Pilot2	16P0847	Porcine	12 hrs.	12/1/2016	12/1/2016
	Revised pre-GLP Pilot3	16P0852	Porcine	12 hrs.	12/19/2016	12/19/2016
	Revised pre-GLP Pilot4	16P1000	Porcine	12 hrs.	12/22/2016	12/22/2016

The initial series of studies were completed to evaluate various:

a) animal models for durability and suitability,
b) modes of stimulation and
c) method of stimulation in synchrony with the inspiratory cycle.

The next series of studies were completed to evaluate the impact of stimulation of the diaphragm via the phrenic nerve at lessening the reduction of diaphragm strength in a prolonged mechanically ventilated porcine model when comparing the unstimulated control animal. Diaphragm strength was maintained from baseline in the animals receiving electrical stimulation while the control animals had a 20% decline in diaphragm strength from the start of the procedure (baseline).

The next series of studies were used to evaluate several stimulation electrode lead configurations and determine the best method to deploy the lead in the least invasive way possible. The lead configurations were evaluated for positionality, stability (acute and chronic), output/current requirements, durability of stimulation capture and size/accessibility criteria. The ideal stimulation electrode lead configuration was found to be the multipolar (4 electrode). The choice of a four-pole electrode for this application is further supported by the literature[14]; specifically, it has been demonstrated that use of multipole electrode facilitates optimization of the electrical stimulus after the lead is deployed percutaneously lying across the phrenic nerve. Crucially, four pole electrode leads have previously been used chronically to stimulate the diaphragm via the phrenic nerve in the neck to replace ventilator support in humans.

In addition to these assessments of multiple electrode lead configurations, another phase of studies also evaluated a percutaneous approach of placement of the lead. Previous phrenic nerve leads detailed in the published literature were surgically placed. Whereas the proposed insertion procedure uses a Through-the-Needle (TTN) deployment approach, minimizing trauma and scarring for the patient. Currently released medical devices or those in

development require some form of surgery to place the electrodes beside the phrenic nerve. These methodologies are thought to be too invasive and costly for short term use of phrenic nerve stimulation. The use of a percutaneous approach for placing a lead across the phrenic nerve was assessed in animal models. These lead insertion studies concluded that the ideal stimulation electrode lead configuration was found to be the multipolar (4 electrode) lead design inserted via percutaneous TTN approach in a cannula with a blunt needle design.

The final series of animal studies evaluated the impact of stimulation at maximum stimulation output parameters for extended periods of stimulation on the peripheral nerve and diaphragm (equating to nearly 7 days of stimulation). The results indicate the animals tolerated the stimulation during the procedure, had no abnormal clinical responses in a 30 day post stimulation procedure period. Gross necropsy and histopathology revealed no unusual findings post a 30 day period.

The PEPNS System pre-clinical testing demonstrated that the device was safe and effective for its intended use.

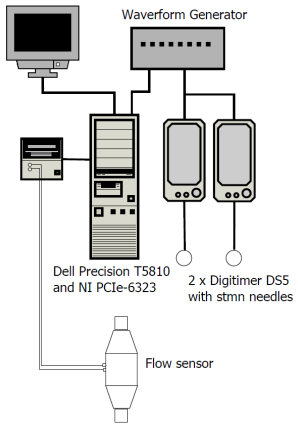
4. INVESTIGATIONAL DEVICE

4.1 Device Description

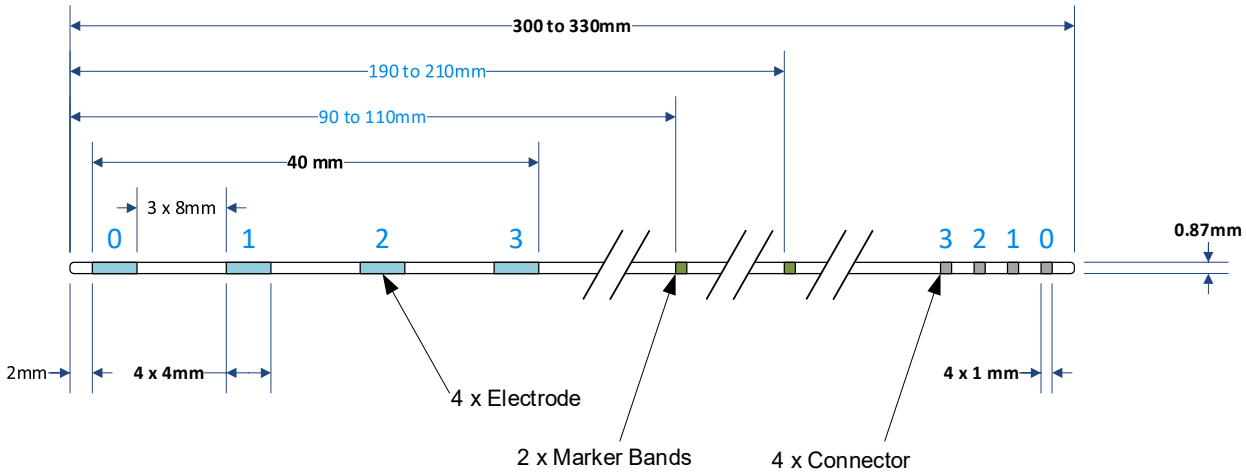
The Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System will be used in conjunction with a respiratory ventilator. The PEPNS System will stimulate the patient's diaphragm to contract in synchrony with the inspiratory cycle of the ventilator. As illustrated in Figure 1 the PEPNS System consists of a signal waveform generator, stimulator, flow sensor, two multipolar disposable leads and miscellaneous parts.

The PEPNS System is manufactured by Stimdia Medical, Inc., the study sponsor, which is located in Edina, MN. The PEPNS System device tradename is pdSTIM and this is reflected on some of the device labels.

Figure 1: The PEPNS System



The PEPNS Lead Electrode and Connector Configuration



4.2 Equipment and Accessories Used

The equipment used during the study may be divided in three categories:

1. **Stimulation System:** PEPNS Control system, used to stimulate the left and right phrenic nerve in concert with the inspired flow. This equipment, including the pacing leads, insertion kits and lead deployment device are provided by Stimdia.
2. **Data Acquisition:** PowerLab Data Acquisition System: used to log pressure, flow, WOB and Electrical Stimulation in experiments at 1000 Hz. This equipment, which is commercially available, is provided by Stimdia.

3. **Other Equipment:** Used to measure patient hemodynamics and vital signs during therapy as well as visualize and stimulate phrenic nerve during setup. This equipment is provided by clinical investigation site.

4.3 Indications For Use

The Stimdia Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System is intended to facilitate weaning from mechanical ventilation via temporary stimulation in patients who are on mechanical ventilation for 24 hours or more and who are at risk of having difficulty in weaning.

4.3.1 Frequency of Use

During this Feasibility Study, the PEPNS System is intended to be used for up to 2 days while the patient is on a mechanical ventilator in the ICU/CCU. During the study the PEPNS System will be used for up to 48 hours of continuous stimulation. The device is not intended for use outside of the hospital environment, such as a long-term care facility.

4.3.2 Body/Tissue Interacted With

The pacing leads are placed in close proximity to the phrenic nerves and surrounding muscle tissue in the patients' neck. Electrical stimulation is delivered to stimulate the phrenic nerve and activate the diaphragm.

5. STUDY OBJECTIVES

The primary aim of this feasibility study is to evaluate the preliminary safety and performance of the PEPNS System in patients that need to be mechanically ventilated in the Intensive Care Unit (ICU). Specific objectives are as follows:

(a) Determine whether pacing the diaphragm would be of benefit to the difficult to wean patient cohort in the ICU.

(b) Examine whether the placement of the phrenic nerve pacing leads between the anterior scalene and sternocleidomastoid muscles in the patients' neck would cause significant other muscular contraction (arm movements – brachial plexus transmission,) or local contractions (the muscles of the neck themselves - Sternocleidomastoid, Anterior scalene muscles).

(c) Determine stimulation levels necessary to elicit a change in the Work Of Breathing measurement as determined by the wye pneumotachograph and pressure sensor.

(d) Determine whether pacing the diaphragm will result in a progressive increase in tidal volume (or volume per breath) within the 48-hour period of the study.

(e) Determine if diaphragm thickness can be characterized over the 48 hours of electrical stimulation, if feasible.

5.1 Primary Endpoints

Primary Endpoints
1. Capture of the Left and/or Right Phrenic Nerve > 80% with an output parameter of < 10.5 volts.
2. WOB (Work of Breathing) kept between 0.2 joules/L and 2 joules/L for 80% of stimulated breaths.

5.2 Secondary Endpoints

Secondary Endpoints
1. The percentage of patients who receive safe and successful placement of the multipolar lead in the left and right phrenic nerve utilizing ultrasound guidance will be determined.
2. Phrenic nerve stimulation in synchrony with Mechanical Ventilation (MV) breaths will be measured to verify that is occurs with inspiration.
3. The percentage of patients who experience one or more serious device/procedure-related adverse events during the study will be reported.

5.3 Additional Study Data

- Time to weaning from mechanical ventilation data will be collected.
- Diaphragm thickness of electrically stimulated patients will be characterized using ultrasound at the discretion of the physician and based the ability of the site to make the measurement at 0 hours (before stimulation), at 24 ± 4 hours after stimulation, and at 48 ± 4 hours or at the end of the stimulation period during study. The repeatability of the measurement will be examined. This data collected may be characterized relative to the diaphragm thickness of unstimulated patients in the published literature.

6. STUDY DESIGN & METHODOLOGY

The study will examine performance and safety as defined in primary and secondary endpoints listed in Section 10. A maximum of up to 20 subjects will be enrolled in the study at up to 2 sites with up to 10 subjects per site. The final number of patients enrolled in the study will be based upon the time duration of the study and the rate of enrollment. In the first two patients, the investigator will stimulate the left phrenic nerve only and conduct CMAP tests and nerve conduction test on both phrenic nerves prior to and at least 3 weeks after the stimulation. These subjects will be examined 30 days' post study, to confirm safety of this method of stimulation of the phrenic nerve before enrolling the remaining patients up to a total of 20 subjects. After successfully demonstrating 30 day follow up on the initial two patients, stimulation will occur in both the left and right phrenic nerves simultaneously for the remainder of the trial. Typically, stimulation will occur once every 3 to 5 breaths and this decision will be left to the discretion of the attending physician. Figure 2 outlines the protocol for placement of the leads.

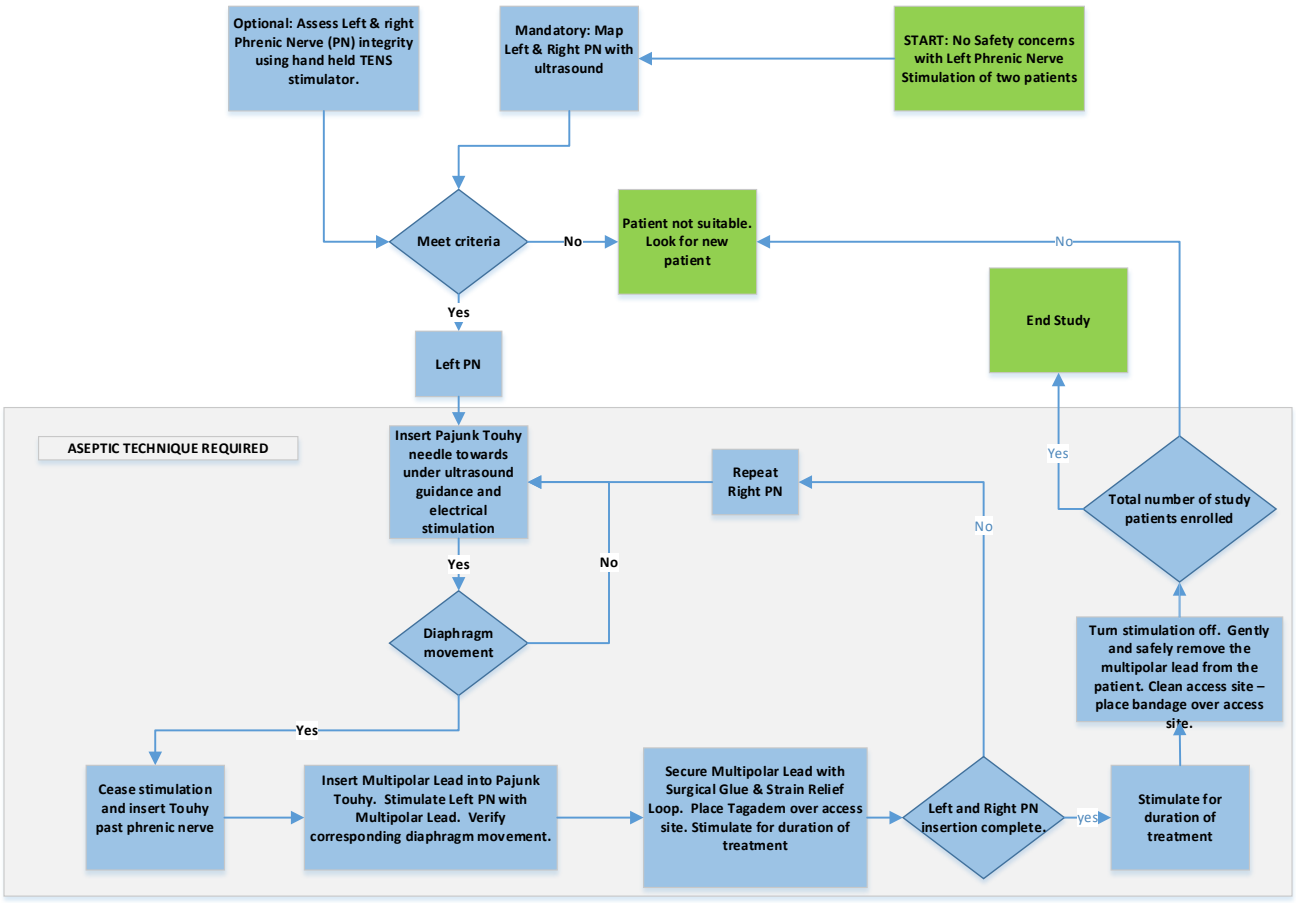


Figure 2. Study Left and Right Phrenic Nerve Pacing

Stimulation will occur for a maximum duration of 48 hours. A number of evaluations will also be conducted to measure the ease of placing and removing the stimulation leads as well as the ability of the lead to accommodate positional changes made by or to the patient.

6.1 Study Data Analysis and Statistical Methods

In general, summary statistics will include the mean, median, standard deviation, minimum and maximum for continuous measures and the number and frequency for categorical measures. All analyses will be conducted using SAS v9.3 or greater (SAS Institute Inc., Cary, NC, USA). Sample size calculations were conducted using

PASS v14 (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

6.2 Inclusion and Exclusion Criteria

Inclusion Criteria: Candidates for this study must meet all of the following inclusion criteria:
1. 18 years or older (Adult).
2. Male or Female.
3. Able and willing to give informed consent or whose legally authorized representative is able and willing to give informed consent.
4. Subject who in the opinion of the admitting consultant/intensivist is likely to be ventilated for > 48 hours from time of recruitment since study treatment will be for up to 48 hours.

Exclusion Criteria: Candidates for this study will be excluded if ANY of the following conditions are present:
1. Subject has a left ventricular ejection fraction (LVEF) < 20%.
2. Subject unlikely to survive 72 hours due to coexisting medical conditions.
3. Subject has an implanted pulse generator or implanted electronic device: Examples: Cardiac pacemaker, Defibrillator, ICD, Watchman, Vagal nerve stimulator, Spinal cord stimulator, Gastric stimulator or Diaphragmatic stimulator.
4. Subject has experienced an Acute Myocardial Infarction (AMI) within 72 hours prior to this screening or subject is on high dose inotropic support or patient is deemed to be in cardiogenic shock.
5. Subject has significant bleeding diathesis, or is at risk of significant haemorrhage, patient is receiving full dose systemic anticoagulation
6. Subject has a known or suspected phrenic nerve paralysis or neuromuscular or inflammatory muscle diseases where the diaphragm itself may not be functional.
7. Subject has an active systemic infection or local infection at or around the insertion site. Subject is neutropenic or has signs of significant immunocompromise.
8. Subject is known or suspected to be pregnant or is lactating.
9. Subject will be unavailable for, or is unwilling to comply with, follow up requirements of the protocol.
10. Subject is currently enrolled or is expected to be enrolled in any other study of an investigational drug or device who has received treatment under that protocol with the investigational product during the 30 days prior to screening.
11. Subject has undergone a surgery or interventional procedure within the neck region aside from placement of an internal jugular (IJ) vein catheter.
12. Subject has been diagnosed and has been treated for neck cancer within the past 5 years.
13. Subject is known to have a demonstrated intra cardiac thrombus on echocardiography.
14. Subject has uncontrolled hyperthyroidism, hypertension.
15. Subject has had any cerebral ischemic event (Stroke or Transient Ischemic Attack TIA) in the 6-month interval preceding the screening date.
16. Subject has degenerative nerve disorders such as amyotrophic laterals sclerosis (ALS).
17. Subject has an elevated hemidiaphragm on chest x-ray.
18. Subject written informed consent not obtained.

6.3 Enrollment

Subjects will be screened to determine eligibility i.e., who meet all inclusion and exclusion criteria. Those subjects that meet the eligibility criteria and who agree to participate in the study will sign an Informed Consent form. Subject is deemed to be enrolled into study when the subject provides written informed consent and agrees to participate in the clinical investigation.

All patients that were attempted to be treated with the PEPNS System (i.e., intent-to-treat patients) but the procedure was aborted will also be followed for 30 days (+7 days) post index procedure for safety (i.e., adverse event collection).

A screening log will be used to determine why patients were screened out of the study.

6.4 Subject Compliance

Subjects will be asked to return to the site for follow up visit at 30 days from the date of treatment to have a chest x-ray and to assess them for adverse events.

6.5 Withdrawal and Discontinuation

Subjects have the right to withdraw from the clinical investigation at any time and for any reason without prejudice to their future medical care by the investigation team or investigation site. Investigator will ask reason for their withdrawal. Investigator will record all information regarding the patient withdrawal and discontinuation.

A subject may be withdrawn from the clinical investigation for the following reasons:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and General Data Protection Regulation (GDPR) and Data Protection Act 2018 and their consent documentation without having to give a reason;
- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any illness(es), infection or condition(s) that might interfere with the protocol;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation; and
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

Subject withdrawal and discontinuation will not affect the standard of care the patient receives.

6.6 Early Termination or Suspension of Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time. After review of the clinical safety data and consultation with Principal Investigator, Sponsor will make a final determination on whether to terminate or suspend the study. In the event of premature termination or suspension of the study, the sponsor will promptly notify the investigational center and governing regulatory agencies and communicate a plan for orderly termination or suspension. Any subjects already enrolled in the study will still be followed up for 30 days.

6.7 Informed Consent Process

After a normal clinical assessment, the Principal Investigator may approach patients whom he or she feels may be suitable for entry into this clinical investigation. The Principal Investigator should introduce the patient or the patient's legally authorized representative to the clinical investigation by explaining the Clinical Investigation

Plan, procedures and objectives to the patient or his/her legally authorized representative. The Principal Investigator will then provide an information sheet describing the clinical investigation, potential discomforts, risks and benefits of participation. The patient or his/her legally authorized representative will have 24 hours to decide whether they wish to participate in this clinical investigation due to the criticality of the timing that the treatment is applied once the patient is on a mechanical ventilator.

Any queries that patients may have regarding this clinical investigation will be addressed appropriately by the Principal Investigator, or another member of the investigative team at the hospital. Patients or their legally authorized representatives will be instructed that they are free to obtain further information from the Principal Investigator at any time and that they are free to withdraw their consent and to discontinue their participation in the clinical investigation at any time without prejudice.

If the patient is willing to participate in the clinical investigation, he/she or his/her legally authorized representative must read, understand and sign the informed consent form. The Principal Investigator will also sign this at the same occasion. Two copies of the consent form will be made. The original signed consent form will be kept in the Investigation Site File. A copy will be kept in the subject's medical notes and a further copy provided to the subject or his/her legally authorized representative.

Since the subjects will be unconscious and mechanically ventilated at the time of the informed consent process should they regain consciousness they will be allowed to withdraw from the study if desired without any impact on their medical treatment. If subjects do regain consciousness during the treatment they will be asked to sign the informed consent form if they are able.

6.8 Study Design and Number of Observations

The study design includes a planned total of one to sites with up to 10 subjects per site. Defined data analysis will be conducted on enrolled and associated data.

6.9 Safety Endpoints

The secondary safety endpoints are the percentage of patients who receive safe and successful placement of the multipolar lead in the left and right phrenic nerve utilizing ultrasound guidance and the percentage of patients who experience one or more serious device/procedure-related adverse events during the study.

No formal hypothesis tests will be conducted; therefore, power and significance level are not relevant in this context. However, the sample size was chosen to provide sufficient data on the occurrence of adverse safety findings. According to Virzi (1992), 80% of all usability issues are detected with four or five subjects. With up to 10 to 16 humans, the percentage of problems detected is approximately 95% to 98% (with 30% probability of at least one event). (Ref: Virzi, RA. Refining the Test Phase of Usability Evaluation: How Many Subjects is Enough? Human Factors, 1992. 34(4), 457-468.).

6.10 Primary Performance Endpoint: Stimulation Pulse to Capture the Diaphragm

The ability of the stimulation pulse to capture the diaphragm will be assessed using WOB (Work of Breathing Measurements). A logistic regression model with successful capture as the outcome will be used. The model will include repeated measurements within a subject.

6.10.1 Model:

capture = (timepoint) (subject)

where subject is a random effect, and the outcome of capture is yes/no based on whether the stimulation captures the diaphragm.

6.10.2 Hypothesis:

H_o: The proportion of capture is less than or equal to the performance goal (*PG*) of 90%.

H_o: $\hat{p}_1 \leq PG$

H_A: The proportion of capture is greater than the performance goal of 90%.

H_A: $\hat{p}_1 > PG$,

where $\hat{p}_1$ is the estimated proportion of capture from the logistic model accounting for repeated measurements within a subject.

6.10.3 Sample Size:

The following assumptions were the basis for the sample size calculation for the performance endpoint evaluating stimulation capture of the diaphragm:

- Power: 80%
- 1-sided α: 0.025
- Performance goal: 90%
- Expected success rate: 97.5%

With an anticipated success rate of 97.5% and a performance goal of 90%, 80 observations would yield ≥80% power. Note that, for the purposes of sample size calculations, the observations are assumed to be independent. However, the primary analyses will account for within patient correlation, as described below. Increasing the number of observations will increase the statistical power.

6.10.4 Methods:

The proportion of successful capture will be analyzed using a logistic regression model accounting for patient as a random effect. The null hypothesis will be tested comparing the lower bound of the 95% two-sided confidence interval for the estimated percent agreement to the performance goal of 90%. If the lower bound is greater than 90%, the null hypothesis will be rejected and the endpoint will be considered met.

6.11 CMAP and Nerve Conduction Studies

Compound muscle action potential (CMAP) testing and nerve conduction studies will be conducted on the first two subjects during the index procedure and at or before the 30 day follow up. CMAP is a non-invasive test that causes minimal or no discomfort. A hand held electrical stimulator will be used to generate a bipolar electrical phrenic stimulation in the neck, while recording diaphragm electromyographic responses on the surface of the chest. These studies will be performed by an Electrophysiologist skilled in the performance of these tests who will make a clinical assessment regarding the effects of stimulation. The studies will measure the CMAP on both the left and right diaphragm as well as the conduction latency of the phrenic nerves before the initiation of treatment on the first two patients. This data will be compared to the measurement data generated at a follow up test performed post cessation of treatment. Electrical stimulation will only be performed on the left phrenic nerve (the smaller of the two lungs) on the first two patients, affording the opportunity to use the patient as their own control and assess any difference induced by the PEPNS therapy between the stimulation and unstimulating phrenic nerves and diaphragm of each patient using a comparison of the CMAP voltage amplitude and nerve conduction latency. Fluoroscopy may be done on first two patients if differences are seen in the CMAP and nerve conduction studies by the electrophysiologist for the treated phrenic nerve. The data will also be compared to the published literature for phrenic nerve conduction latency[15,16] and CMAP[17,18] voltage amplitudes.

6.12 Measurement of Diaphragm Thickness using Ultrasound

Diaphragm muscle thickness will be measured using a standardized technique described similar to that previously by Cohn et al[19] and Ueki et al[20] and later modified by Francis et al.[21] Imaging will be performed using the M-

Turbo ultrasound system (SonoSite, Inc) with a 7.5-10.0-mHz transducer probe or its equivalent in two-dimensional B-mode.

6.13 Electrocardiogram (ECG) and X-ray

The electrocardiogram testing will be conducted using 12 leads prior to the stimulation and during the stimulation approximately every 24 hours following standard hospital procedures for running this test so that a cardiologist can determine if there have been any ECG changes during or post stimulation.

A routine chest x-ray will be taken prior to the stimulation and at or before the 30 day follow up, to determine if there has been any obvious change in lung volume or degree of atelectasis (in comparison to the contralateral lung as a consequence of stimulation).

6.14 Secondary Performance Endpoint: Analyzing Phrenic Nerve Stimulation in Synchrony with MV Breaths

A breath by breath stim count analysis will be performed to determine the effectiveness of electrical stimulation on the inspiratory breaths stimulated. Effectiveness will be determined by measuring an effect on the work performed by the diaphragm and its ability to remain within normal physiological levels of work of breathing.

Figure 3. Sample Data Acquisition Data using Labchart for Qwye, Pwye, WOB and Stim Signals

The analysis will be performed for WOB as follows. A count will be performed to determine the number of stimulated breaths the measured WOB falls within a predetermined upper and lower control level for the stimulated breaths. This will be compared to the number of breaths electrically stimulated. These counts will be used to determine the effectiveness of electrical stimulation based upon percentage of electrical stimulation signals capturing breaths as intended.

6.15 Additional Study Data

Time to weaning from mechanical ventilation data will be collected and reported.

The effect of electrical stimulation on diaphragm thickness, blood gas parameters, vital signs, end tidal CO_2 and tidal volume may be characterized. To this end, stimulation will be stopped for a single period of 1 hour within the middle period of the 6 hour blood gas analysis collection period, when the patient has been deemed to be hemodynamically stable by the attending physician. Data will be collected on blood gasses, pulse rate, blood pressure, SpO_2, end tidal CO_2 and tidal volume at the end of the 1 hour period. This data will be used to characterize the effect of electrical stimulation on hemodynamics. The mode of ventilation will also be recorded because stimulation is predicted to have little effect on tidal volume in flow controlled modes whereas it is predicted to increase in pressure control modes of ventilation. Tidal volume may also be adjusted to be the same as when electrical stimulation was turned on to eliminate any confounding effects of decreased minute and tidal volumes when stimulation is turned off. All other parameters such as breath rate, PEEP, FIO2 etc. will be kept the same.

The diaphragm thickness may be measured prior to the stimulation, at 24 hours and at 48 hours or after the completion of all of the stimulation using ultrasound when clinically feasible, i.e., 0 hours, 24 hours and 48 hours or end of stimulation.

7. PROCEDURAL GUIDELINES (Treatment Procedure)

7.1 Operator's Manual

Detailed instructions are provided for the console and lead insertion and all participating investigators will be trained on how to use the PEPNS System. Refer to LM0001 PEPNS System Operator's Manual for detailed information.

8. SITE SELECTION CRITERIA

Site Selection Criteria
Number of ICU beds & state of the art status of ICUs and staffing (minimum of 10 ICU beds)
Number of Ventilation Patients – enrollment capacity (minimum of 300 mechanically ventilated patients on an annual basis)
• Critical Care Research (previous & existing and no competing studies, etc.)
• Outcomes (existing trials)
• Dedicated ICU/Critical Care Research Nurse
• Proficiency in mapping nerves with ultrasound and placing leads in the neck region within the ICU setting
• None of the investigators can be in the FDA disqualification proceedings database.

9. SITES AND ENROLLMENT

Sites and Enrollment
Up to 2 trained and enrolling sites
Up to 10 patients at each site

10. PROCEDURE DURATION AND FOLLOW-UP

Procedure Duration and Follow-up
Up to 48 hours of continuous stimulation time
Upon expiration of the 48 hour stimulation period the stimulation will be turned off and the PEPNS multipolar leads will be removed from the patient.

Patient Follow-up
Each patient will be followed for a total of 30 days after stimulation end to determine if he/she experienced any adverse events with a clinic follow-up visit and for a chest x-ray. This follow up may occur within +7 days of the 30-day follow-up period giving an allowable follow-up range of 30 to 37 days for AE's and 30 ± 7 days for the chest x-ray.

The total expected duration of the clinical trial is up to 18 months once both sites start to enroll subjects.

11. STUDY SCREENING AND STUDY PROCEDURES

11.1 Screening

Potential study candidates undergo a screening evaluation that includes:

- An evaluation of their suitability for enrollment in the study by the site Investigator including their current state of health, demographics and medical history;
- Height, weight and body mass index (BMI)
- Neck diameter at the cricoid cartilage
- Ventilation information
- Blood pressure
- Chest x-ray

11.2 Index Procedure

Once the study subject or authorized representative signs an ICF and his/her eligibility to participate in the study is confirmed, the PEPNS System procedure can be initiated. A primary operator will be performing the PEPNS System procedure, but an additional qualified operator may be present or assisting. A Stimdia representative may also be present during index procedure to provide technical guidance to the primary operator.

The Investigator will follow the procedure technique outlined in LM0001, PEPNS System Operator's Manual.

Prior to the start of electrical stimulation, the subject's diaphragm thickness may be measured using ultrasound and the subject will have a 12 lead ECG. In addition, baseline standard blood gasses such as pH and paO_2, $paCO_2$, SaO_2, HCO_3 etc. and exhaled gas analysis such as end-tidal CO_2 data will be garnered for up to 24 hours prior to stimulation.

A four pole pacing lead electrodes will be percutaneously placed beside the phrenic nerves using ultrasound guidance and the ultrasound screen shots will be captured if possible. The ease of gain pacing lead access and setup will be assessed and logged.

The subjects phrenic nerve(s) will then be electrically stimulated for up to 48 hours and device and procedure information, ventilation and PEPNS System stimulation will be recorded. In addition, patient vital signs including heart and respiratory rate, blood pressure, temperature, pH, $paCO_2$, paO_2, hematocrit, end-tidal CO_2, will be collected when available unless otherwise specified in table 1 below. If the patient is weaned from the mechanical ventilator during this time the time to weaning will also be recorded. Also, a chest x-ray will be obtained if the patients has not had one in the last 30 days. In addition, Critical Care Pain Observation Tool[22,23] (CPOT) and Richmond Agitation & Sedation Scale[24,25] (RASS) assessments will be administered prior to the electrical stimulation and every 6 hours during it. Patients will also be physically observed for any muscle twitching during the simulation period to try and determine if any other nerves were stimulated. Diaphragm thickness may be measured again at 24 and 48 hours or at the end of the stimulation period.

The ability of the pacing lead to accommodate neck movement and patient positional changes will also be assessed and logged during electrical stimulation.

The ease of removing the pacing leads from the patient's neck will also be assessed during lead extraction and logged.

Compound muscle action potential (CMAP) testing and nerve conduction studies will be conducted on the first 2 subjects during the index procedure and at or before the 30 day follow up.

11.3 Follow-Up Visits

All subjects will be followed up at 30 days to 37 days for adverse events and 30 ± 7 days for the chest x-ray. At this time hospital discharge and ventilation weaning time data will also be collected. Table 1 summarizes all required and optional test and procedures throughout the study including each visit's compliance windows.

Table 1: Study Procedures and Follow Up

Test / Evaluation	Screening (within 2 days pre-procedure)	Index procedure	30 day follow up
Signed Informed Consent	X		
Subject Demographics	X		
Medical History	X		
Height/Weight/BMI	X		
Blood Pressure	X		
Chest x-ray	X[1]		X
12 lead ECG		X	
Lead Insertion assessment		X	
1 hr. cessation of electrical stimulation		X	
Patient movement / repositioning assessment		X	
CMAP[2]		X	X
CPOT/RASS assessments		X	
Muscle twitching observation		X	
Ultrasound screen shots (optional) Ventilation settings and end-tidal CO_2 required Stimulation Data Vital Signs / pulse oximetry Standard Blood gases: pH, paO_2, $PaCO_2$ etc. Diaphragm thickness (optional)		X	
Lead Removal assessment		X	
Adverse Events		X	X
Device Malfunctions		X	

[1] It is acceptable if this has been taken up to 30 days prior to the screening visit.
[2] Only for the first 2 patients enrolled.

11.4 Unscheduled Visit

In addition to scheduled follow-up visits, the participants will be instructed and encouraged to contact the Investigator at any time during the follow-up period if he/she has questions or concerns relating to the PEPNS System therapy. If the patient is seen by the Investigator between scheduled follow-up visits (i.e., not a study required visit):

- No adverse events noted during unscheduled visit – no forms need to be completed.
- Adverse event noted – The Adverse Event (AE) Case Report Form (CRF) needs to be completed for each event.

The patient will still be required to return for the next scheduled follow-up visit if the unscheduled visit is out of the compliance with the follow-up window.

If the patient is treated by a health-care professional other than the Investigator for treatment-related complications, the Investigator must request copies of the medical records and, if necessary, complete an AE CRF.

11.5 Lost to Follow-up

If a patient is lost to follow-up, a Patient Deposition CRF must be completed. If a patient fails to comply with follow-up evaluations, the study center must make repeated attempts (at least three) to contact the patient. Each attempt to contact the patient and the method used (e.g., telephone contact, registered letter) must be documented in the patient's records. Also, a letter to the patient's general practitioner will be sent informing him/her that his/her patient was lost to follow-up.

11.6 Patient Withdrawal from the Study

11.6.1 Voluntary Withdrawal

A patient may voluntarily withdraw from the study at any time. The Patient Deposition CRF must be completed. If the patient has experienced an AE, where possible the patient should be followed until its resolution.

11.6.2 Withdrawal for Other Reasons OR Non-Treatment

If the patient has signed the ICF but was later found to not meet inclusion/exclusion criteria prior to enrollment or deemed not suitable for treatment by the physician the patient will not be considered enrolled in the study.

11.6.3 End of Study

Patients will exit the study at the time the study is closed or after the 30 day of follow up, whichever comes first. Patients may also exit the study by withdrawing his/her participation voluntarily. A Patient Disposition CRF is required at the time of study completion or discontinuation for all enrolled patients.

12. DATA RECORDING AND SUBMISSION REQUIREMENTS

Data
All aspects of the study will maintain patient privacy and be Declaration of Helsinki and General Data Protection Regulation (GDPR) and Data Protection Act 2018 compliant. All **raw data** will be entered into an Excel or validated spreadsheet format (with patient names excluded) and include all data collected on the patients up to the time the data is frozen including baseline, procedure, and all follow up data available. All data sets provided shall be clean with all queries resolved. The following are the types of data in the study: RAW DATA: 1. PEPNS System electronic archive – data recording by the PEPNS system will be electronically archived by Stimdia Medical. 2. Patient history file – this document will confirm patient meets inclusion and exclusion criteria while also documenting all demographic and physiology aspects of the enrolled patient. 3. PEPNS System procedure report – documentation of procedure related information, e.g., sedation, ventilation, stimulation, ultrasound, test article documentation, procedure step checklist and procedure related specifics noted. CASE REPORT FORMS (CRF): 1. Screening form 2. Index procedure form 3. Adverse event form 4. Patient disposition form 5. Protocol deviation form 6. Device malfunction form 7. Follow up form SPREADSHEET AND ANALYSES: 1. All data relevant to analysis will be maintained in a validated Excel spreadsheet until the completion of the study. The master spreadsheet will be validated and maintained by Stimdia Medical. All Excel files used for the data analysis must be password protected and only authorized study personnel can have access to the passwords. Interim analysis and results will be reviewed with the steering committee in a periodic manner.

13. RISK/BENEFIT ANALYSIS

An analysis of the risks associated with the intended use of the device was undertaken according to the guidelines laid down in the standard EN ISO 14971:2012, Medical Devices – application of Risk Management to Medical Device. A complete Risk Assessment has been documented and resides within the design history file.

13.1 Potential Risks

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

1. Blood loss > 10 mL
2. Burn
3. Cardiac pacing
4. Diaphragm fatigue
5. Infection
6. Inflammation
7. Nerve damage
8. Pain
9. Pneumothorax (punctured lung)
10. Procedure failure
11. Scar
12. Vagus nerve stimulation, potentially resulting in asystole or bradycardia

The risks were mitigated to an acceptable level by design, fault detection, use of standards, training and labeling. The use of this device is considered to be relatively benign and testing performed so far in animals has confirmed this.

There are also some potential risks due to the mechanical ventilation and underlying patient comorbidities such as the following:

1. Barotrauma / volutrauma
2. Hypercarbia
3. Hypoxia

There may also be other risks related to use of the PEPNS System and procedure that are not listed or that are not known at this time. This study will help characterize the risks associated with the PEPNS System.

13.2 Minimization of Risk

To minimize the risks, the PEPNS System has undergone extensive pre-clinical and bench testing. In addition, all Investigators will undergo training on the PEPNS System and procedure and subjects will be screened and evaluated for medical histories/conditions that may compromise successful performance of the PEPNS System.

13.3 Potential Benefits

Up to 40% of patients admitted to intensive care units (ICUs) may require mechanical ventilation (MV) due to acute respiratory failure (ARF) or acute on chronic respiratory failure (ACRF), and this need is increasing. Most ACRF patients and, to a lesser extent, some patients with *de novo* ARF, may be treated with noninvasive MV, whereas a minority of these patients in the ICU need invasive MV. There is evidence that 65–85% of these patients undergoing invasive MV, under appropriate clinical conditions, can be successfully extubated, whereas up to 20% of patients will need a prolonged ICU length of stay (LOS) due to difficult weaning. This therapy has the potential to reduce the LOS for these difficult to wean patient by accelerating the time to wean by maintain diaphragm strength during sedation.

The proposed study is a first in human study (FIH) which will help define a pivotal study which will be needed for the regulatory approval of this device. During use of this device patients will have their diaphragms exercised

and it is believed that diaphragm strength may be maintained or increased. The study will provide real world data for design and validation for the safety and operational use of the PEPNS system.

SAFETY REPORTING

13.4 Definitions In Line with EN ISO 14155 Unless Otherwise Denoted

13.4.1 Adverse events (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Notes:

- This definition includes events related to the investigational medical device.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational devices.

13.4.2 Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,
- Led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

13.4.3 Adverse device effect (ADE)

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

Notes:

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

13.4.4 Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

13.4.5 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 is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

13.4.6 Device Deficiency

A device deficiency is an inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

13.4.7 Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

13.4.8 Use error

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

Notes:

- Use error includes slips, lapses, and mistakes.
- An unexpected physiological response of the subject does not in itself constitute a use error.

13.4.9 List of Anticipated Adverse Events

See section 13.1 for a list of anticipated adverse events.

13.5 Adverse Event Classification

The severity of all adverse events and their relationship to the investigational device/study procedures will be classified by the investigator and reviewed by the steering committee or a clinical events committee. This review will include indication of any actions recommended be taken to protect patient safety and/or maintain data integrity.

13.5.1 Assessment of Adverse Event Relationship to Investigational Device

Investigators are required to assess whether there is a reasonable possibility that the Investigational Device caused or contributed to an SAE. Sponsor defines four degrees of relatedness: not related, unlikely, possible, probable, possible and causally related to the Investigational Device. The following definitions will be used to assess the relationship of the SAE to use of the Investigational Device per MEDEV 2.7/3 revisions 3 May 2015:

Not Related	The relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

	• harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/ procedures and the serious event.
Unlikely	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Possible	The temporal sequence between use of the Investigational Device and the effect is such that the relationship is not unlikely or Subject's condition or concomitant therapy could have caused the AE.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

If any Serious Adverse Event is considered to be either "possibly", "probably", or 'causally' related to the use of the Investigational Device, that event will be classed as an SADE.

13.6 Adverse Event Severity

The Investigator will also evaluate the severity in compliance with International Conference of Harmonization (ICH) – Good Clinical Practice (CGP) guidelines according to definitions from the Common Terminology Criteria for Adverse Events (CTCAE) from the department of U.S. Department of Health and Human Services.[26] See below for the applicable definitions

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

These definitions are for descriptive purposes only and are independent of the judgment of whether an event is classified as an AE or an SAE.

13.6.1 Handling and Reporting of Adverse Events

Investigator will report "to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports". Device malfunctions and use errors should also be reported without unjustified delay.

All Serious Adverse Events (SA(D)Es) and/or device deficiencies must be reported to the Sponsor by telephone within 3 calendar days of the principal investigator becoming aware of it using the contact information below:

Reporting all Serious Adverse Events (SA(D)Es), including all device deficiencies can also be done by completing the CRF (AE/SAE and Device Deficiency forms) within 3 calendar days of event knowledge.

Where possible, Investigator will return the device involved in the deficiency to Sponsor for analysis.

Investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome. The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. Investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality.

In the event of subject death, the investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. The investigator will determine the cause of death and its relationship to the investigational device; Investigator will record results on the Adverse Event Form. The investigator will include copies of an autopsy report, if available, and/or a death summary with this form.

It is the responsibility of each Investigator to report all Serious Adverse Events and/or Serious Adverse Device Effects to the Local Ethics Committee in a timely manner, according to national regulations and Ethics Committee requirements. A copy of the Ethics Committee report should be forwarded to Sponsor.

13.6.2 Regulatory Authority Notification (If applicable)

Sponsor is responsible for the classification and reporting of serious adverse events and ongoing safety evaluation of the study in line with ICH-GCP/EN ISO 14155:2011/MEDDEV 2.7/3, Ireland's HPRA, the Czech Ministry of Health and other applicable regulatory requirements.

The sponsor will assess, together with the investigator, any serious adverse incidents arising from the investigation of the medical device and inform other investigators, HPRA and SUKL and the ethics committees thereabout immediately after their occurrence.

It is the obligation and responsibility of the Sponsor to report to HPRA and SUKL all serious adverse events, serious adverse device effects and/or unexpected serious adverse device effects received from a Principal Investigator within 2 calendar days after learning of the event.

The Sponsor will also inform the other participating Principal Investigators and ethics committees of all serious adverse events, serious adverse device effects and/or unanticipated adverse device effects that are reported within 3 calendar days after learning of the event.

13.6.3 Follow-up of Unresolved Events

All serious adverse events, serious adverse device effects and/or unexpected adverse device effects will be followed until they are resolved or until the subject's participation in the clinical investigation ends.

14. DATA MANAGEMENT

14.1 Confidentiality

Confidentiality of subject data will be maintained at all times. Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. Subject anonymity will be guaranteed and all documentation relating to a subject will be kept in a secure location.

14.2 Subject Identification (ID)

A unique Subject Identifier (ID) will identify enrolled patients, which is a combination of a non-repeating, sequential number starting with P01, followed by the site ID. The site ID for UVN is S01 and the site ID for Beaumont Hospital is S02. In the advent of new sites being added, additional site numbers will be assigned sequentially.

14.3 Data Collection

The Paper based Case Report Form (CRF) is the primary data collection instrument for this study. Prior to the start of the clinical investigation, Sponsor will provide the Case Report Forms (CRF) for each individual subject. The recording of data on the visit specific Case Report Forms will be completed in full by Investigator/Study Coordinator for each individual subject. The sponsor or its designee will promptly address any data issues with the Investigator. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black or blue ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data, above it. All such changes must be initialed and dated by the individual making the correction. DO NOT ERASE OR WHITE OUT ERRORS.

The personal data recorded on all documents will be regarded as confidential.

Note: The site must record the subject's participation in this clinical investigation in the subject's medical records.

14.4 Review and Return of Completed Study Data

The investigator will maintain all source documents as required by the CIP, including laboratory results, supporting medical records, and signed Informed Consent forms. Sponsor and/or monitor will use source documents during the regular monitoring visits to verify data entered in the CRF. All CRFs will be reviewed for accuracy and the Principal Investigator will sign and date each completed CRF to document approval.

A copy of fully completed original CRFs will be made available to Sponsor.

Once all the subject data has been collected and verified, the analysis and reporting will be conducted. Any data existing for subjects who have not received treatment with PEPNS System will not be used in the analysis. Details of these subjects will, however, are referenced in the final report.

14.5 Study Final Report

The final report will be compiled by Stimdia Medical, Inc. and reviewed, approved and signed off by the Principal Investigator of participating site(s).

14.6 Study Material and Data Retention/Archiving

Data files used for statistical analyses will be retained by each investigational center and study sponsor for at least 10 years after the study has been completed.

15. TRAINING AND EXPERIENCE REQUIREMENTS

Sponsor will maintain records documenting all training.

15.1 Clinical Investigation Plan (CIP) Training

Prior to subject enrollment, Sponsor/CRO will conduct training that will include reviewing the CIP, study procedures and study administrative procedures. Sponsor or designee will provide periodic updates to review procedures changes, amendments to the CIP, or for any changes in investigative team members at the site.

15.2 Device and Procedure Training

To ensure familiarity with the instrumentation and treatment techniques, Sponsor will train each Investigator prior to enrolling their first subject in the clinical investigation and may attend some or all of the cases at each Investigation site to ensure proper device use.

16. ETHICAL, REGULATORY AND ADMINISTRATIVE REQUIREMENTS

16.1 Ethics Committee and Regulatory Approvals

Before study commencement, the Principal Investigator must submit the Clinical Investigation Plan, Investigator's Brochure, Essential Requirements Checklist, Patient information sheet and Informed consent form and any other documents as may be required to the appropriate Ethics Committee (EC) for review and approval. The Principal Investigator, and any other member of the investigative team, is a member of the Ethics Committee, must not participate in the decision-making. A signed and dated EC approval letter must be provided to Sponsor. The study will not start until written documentation of all required local and national regulatory approvals are obtained.

Any report of withdrawal of Ethics Committee approval will be submitted to the Sponsor within five (5) working days.

16.2 Informed Consent and Patient Information

A signed and dated informed consent must be obtained for all subjects enrolled. The Principal Investigator must explain to each subject or his/her legally authorized representative the nature of the clinical investigation, including any risks and benefits, its purpose and procedures, and expected duration of involvement in the clinical investigation. The subject or his/her legally authorized representative must have the opportunity to ask questions and must be informed that participation in the clinical investigation is voluntary and non-participation will not affect his / her right to the most appropriate standard treatment or affect the doctor/clinician-patient relationship. Subjects or their legally authorized representatives have full rights to withdraw from the clinical investigation at any time, irrespective of their initial consent.

Each subject must also give their permission for representatives of the Sponsor, auditor and regulatory authorities to review their hospital records for the purposes of source data verification. The informed consent form must also be signed and dated by the research team member obtaining consent. The signed informed consent form must remain in the subject's study file and be available for review by the study monitor.

16.3 Protocol Deviations

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement. The Investigator is not allowed to deviate from the Investigational Plan.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the Ethics Committee. Reports of any deviation from the protocol under emergency circumstances will be reported to the Sponsor and to the Ethics Committee as soon as possible after detection, but no later 5 working days from the time of the deviation.

Deviations shall be reported to the study sponsor regardless of whether medically justifiable, preapproved, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Case Report Form or Protocol Deviation Form. Non-subject specific deviations will be reported to the Sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their EC in accordance with their specific EC reporting policies and procedures.

Any deviations from the protocol must be documented in detail by the Investigator and reported to the study monitor as soon as possible.

Regulations (ICH-GCP/EN ISO 14155) require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

The following deviations are considered as major:

- ICF collection process not respected.
- Inclusion/Exclusion criteria not respected.

- Misuse of medical device.
- Lack in SAE reporting.
- Any protocol assessment in relation with the primary endpoints that is not respected.

If a Study Monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of ICH-GCP/EN ISO 14155 or other applicable regulations, or any conditions of approval imposed by the reviewing Ethics Committee, Sponsor will immediately either secure compliance or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation. The Investigator will be required to return all investigational devices, unless this action would jeopardize the rights, safety or welfare of a patient.

Protocol deviations will be analyzed by Sponsor for the impact to the overall integrity of the study. Disqualification is warranted when an investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur which do not warrant disqualification from a study, Sponsor will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

16.4 Amendments

The Clinical Investigational Plan, CRFs, Informed consent form and other subject information, or other clinical investigation documents will be amended as needed throughout the clinical investigation, and a justification statement will be included with each amended section of a document. Proposed amendments to the Protocol will be agreed upon between the sponsor and principal investigator(s).

The amendments to the Protocol and the subject's informed consent form will be submitted to obtain approval the EC and regulatory authorities, if required. The version number and date of amendments will be documented.

16.5 Investigational Device Accountability and Storage

The investigator must ensure that the device is used only in accordance with the protocol. Each individual PEPNS System that is used will be fully traced in the subjects' medical records and the Clinical Investigator File to ensure full accountability.

The investigator or designee is responsible for device accountability at the trial site i.e., to keep records documenting the receipt, use, return and disposal of the investigational devices. For that, a Device Accountability Log (DAL) will be provided to each investigational site. Such log shall record dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects, and date of procedure. A space will be provided for recording returned product and the reason for the return. The investigator should maintain records that adequately document that subjects were treated with the investigational device as specified by the protocol.

Upon receipt of an investigational device shipment, the Investigator or designee is required to reconcile inventory of the product received and verify the shipment by signing the packing list. All investigational devices must be stored in a locked storage facility to which only the investigator or designee will have access. The secure location should be a dry and ambient room temperature location.

16.6 Monitoring Plan

The study monitor will be responsible for securing the compliance of Principal Investigator(s) to the signed clinical trial agreement.

The study monitor appointed by the sponsor to oversee the conduct and progress of the study is the primary communication link between the sponsor and Investigator. Monitor responsibilities may include investigator selection and training, assurance of current Ethics Committee approvals, periodic on-site inspection and audit of site records to ensure continued compliance with the protocol, adequacy of the investigator and the facility to carry out the study, and verification that the device is being using in accordance with instructions for use. Functions that the monitor/sponsor will perform include:

- Pre-Investigation Screening to ensure sufficient staffing, cooperation, investigator training and adequate numbers of potential subjects.
- Review of study required documentation including signed agreements, protocol, required institutional approvals, Ethics Committee Approval.
- Study site initiation to review with site staff the protocol requirements, case report forms, data collection methods and any electronic data capturing system. Requirements for timely and accurate reporting of clinical data and unanticipated adverse events will be reviewed. During this visit the monitor will ensure training in proper use of the investigational device as well as ensuring safe and secure storage of study devices and device accountability.
- Investigational device accountability records will be reviewed including devices received, receipt dates, quantity, lot numbers, storage and signature of study personnel responsible for accountability.
- Personal contact with the investigator and staff throughout the study by telephone, mail and on-site visits, to continue until study is completed. This monitoring will ensure continued protocol compliance, adequate enrollment, accurate data reporting and query resolution and continued Ethics Committee approval of the study. A full record of monitoring activities will be maintained.
- Final on-site study close out visit at the completion of the investigation to collect outstanding documents and resolve outstanding queries, confirm site files are complete and accurate, review record retention requirements with the investigator and provide for return of unused study devices to sponsor.

16.7 Indemnity

Sponsor recognizes its liability in law to compensate for any injury sustained by a subject participating in this clinical investigation but only to the extent the study has been conducted in compliance with the protocol.

16.8 Insurance

All subjects enrolled in this study are covered by Clinical Trial Liability Insurance. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured is provided in the Investigator's Site File.

16.9 Investigators Responsibilities

- Sign and adhere to the Clinical Trail Agreement (CTA).
- Sign and adhere to all of the required elements of the Study Protocol.
- Resolve queries in a timely manner.
- Participate in Investigator meetings as required.
- Comply with the 2013 Declaration of Helsinki and the General Data Protection Regulation (GDPR) and Data Protection Act 2018.
- Obtain written Informed Consent from each study participant before any study specific procedures are performed.
- Complete all required case report forms (CRFs) for each subject.
- Comply with all applicable regulations and codes of approvals from Ethics Committees and other regulatory authorities.
- Notify Sponsor/CRO of any personnel changes at site that may affect the study protocol.
- Retain all records and study files until Sponsor/CRO notifies that files may be destroyed.
- Allow direct access to source data/documents, including subject records, in case of monitoring, auditing and/or inspection by the Ethics Committee and other regulatory authorities.

The investigator is responsible for the preparation and submission of the reports listed in table below:

Report	Submitted to	Description
All serious adverse events (SAE's), device deficiencies that may have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate and new findings/updates in relation to already reported events.	Sponsor & EC	The investigator's report on any SAEs must be submitted within 3 calendar days after the investigator first learns of the event.
Withdrawal of/EC approval	Sponsor	The investigator must report a withdrawal of reviewing EC approval within 5 working days.
Failure to obtain Informed Consent	Sponsor & EC	Notification must be made within 5 working days of use of the device.
Emergency deviations from the protocol	Sponsor and EC	Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a patient). If the deviation affects the rights, safety, or welfare of the patients (and is not an emergency), or the scientific soundness of the investigation, prior approval must be obtained from Stimdia Medical, the reviewing EC. All deviations must be documented on a Protocol Deviation Form
Progress Report	Sponsor & EC	The investigator must submit a progress report on an annual basis or as required by the governing regulatory agencies.
Final Report	Sponsor & EC	This report must be submitted within 3 months after termination or completion of the clinical study.

16.10 Sponsor Responsibilities

Stimdia Medical will maintain all records pertaining to the investigation including:

- EC approvals
- Signed Investigator Agreements and related materials
- Site monitoring reports
- Records concerning adverse device events
- All CRFs and received source documentation
- Financial Disclosure Forms
- Site Monitoring Visit Log
- All correspondence

Stimdia Medical or its approved representative is responsible for the preparation and submission of the reports listed below:

Report	Submitted to	Description
All serious adverse events (SAE's), device deficiencies that may have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate and new findings/updates in relation to already reported events. Reportable events occurring in Third Countries in which a clinical investigation is performed under the same clinical investigation plan. This includes events occurring in third Countries after European sites have closed.	National Competent Authority (NCA)	The sponsor or approved representative report on any SAEs must be submitted within 2 days after the sponsor or approved representative first learns of the event.
Any other reportable events such as: - any SAE, - any Device Deficiency that might have led to a SAE if: a) suitable action had not been taken or	NCA	Any other reportable events or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

Report	Submitted to	Description
b) intervention had not been made or c) if circumstances had been less fortunate - new findings/updates in relation to already reported events.		
Withdrawal of EC approval	EC, Investigators & approving regulatory agency(s)	Notification, when appropriate, will be made within 5 working days after Stimdia Medical receives notice of withdrawal of EC approval.
Withdrawal of regulatory agency approval (e.g. HPRA, SUKL)	EC & Investigators	Notification will be made within 5 working days after Stimdia Medical receives notice of withdrawal of regulatory agency approval.
Safety Reports	NCA	The EU requires that safety line listings and a cover letter that contains an assessment of the safety data and whether or not safety measures need to be taken and justification must be submitted quarterly. The EU requires and annual safety report that must include any new findings from the literature and the investigator's brochure must also be updated annually.
Progress Report	EC, Investigators & regulatory agencies	A progress report will be submitted at least yearly or as required by the EC or governing regulatory agencies.
Recall and Device Disposition	EC, Investigators & regulatory agencies	Notification will be made within 30 working days of Stimdia Medical's request that an investigator return, repair or otherwise dispose of any devices. Such notification will state why the request was made.
Notification of Termination or Completion	EC, Investigators & regulatory agencies	Notification will be made within 90 days.
Final Report	EC, Investigators & regulatory agencies	A final report will be submitted within 3 months after study completion or termination and be signed by the investigator.
Failure to Obtain Informed Consent	Regulatory agencies	Notification will be made within 5 working days of receipt of notice.

Report	Submitted to	Description
Emergency Deviations from Investigational Plan	EC	Notification will be made within 5 working days after Stimdia Medical learns of an emergency deviation from the Investigational Plan where the deviation was made to protect the life or physical well-being of a subject.

16.11 Statement of Compliance

- Sponsor and Investigator will conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki and General Data Protection Regulation (GDPR) and Data Protection Act 2018.
- Sponsor and Investigator will comply with EN ISO 14155:2011 and any regional or national regulations, as appropriate.
- Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the EC or regulatory authority, if appropriate.
- Investigator will follow any additional requirements imposed by the EC or regulatory authority, if appropriate.
- Sponsor will provide insurance for subjects.

16.12 Publication Policy

At the conclusion of the trial, a multi-center manuscript will be prepared for publication in a reputable scientific journal by the Sponsor, Stimdia Medical, Inc. The study will be registered in clinicaltrials.gov.

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