COVER PAGE

Randomized Study of the pdSTIM™ System (phrenic nerve to diaphragm STIMulation) in Failure to Wean Mechanically Ventilated Patients

(ReInvigorate Study)

Document: Clinical Investigation Plan (CIP)

Document Date: 15 May 2025

CLINICAL INVESTIGATION PLAN (CIP)

Randomized Study of the pdSTIM™ System

(phrenic nerve to diaphragm STIMulation)

in Failure to Wean

Mechanically Ventilated Patients

(ReInvigorate Study)

Protocol Number: CIP0002

[redacted]

Sponsor:

Stimdia Medical Inc.

[redacted]

**********IMPORTANT NOTICE**********

****

The ReInvigorate study is designed to establish the safety and efficacy of use of the pdSTIM System to improve weaning success in patients who are on mechanical ventilation for 96 hours or more and who have not weaned as compared to standard of care. [redacted]

The [redacted] Feasibility Cohort has completed enrollment and is closed for further recruitment. [redacted]

This document contains confidential information for use by the investigators and their designated representatives participating in the clinical trial presented herein. It must be held confidential and maintained in a secure location. It must not be copied or made available for review by any unauthorized person or company.

Stimdia

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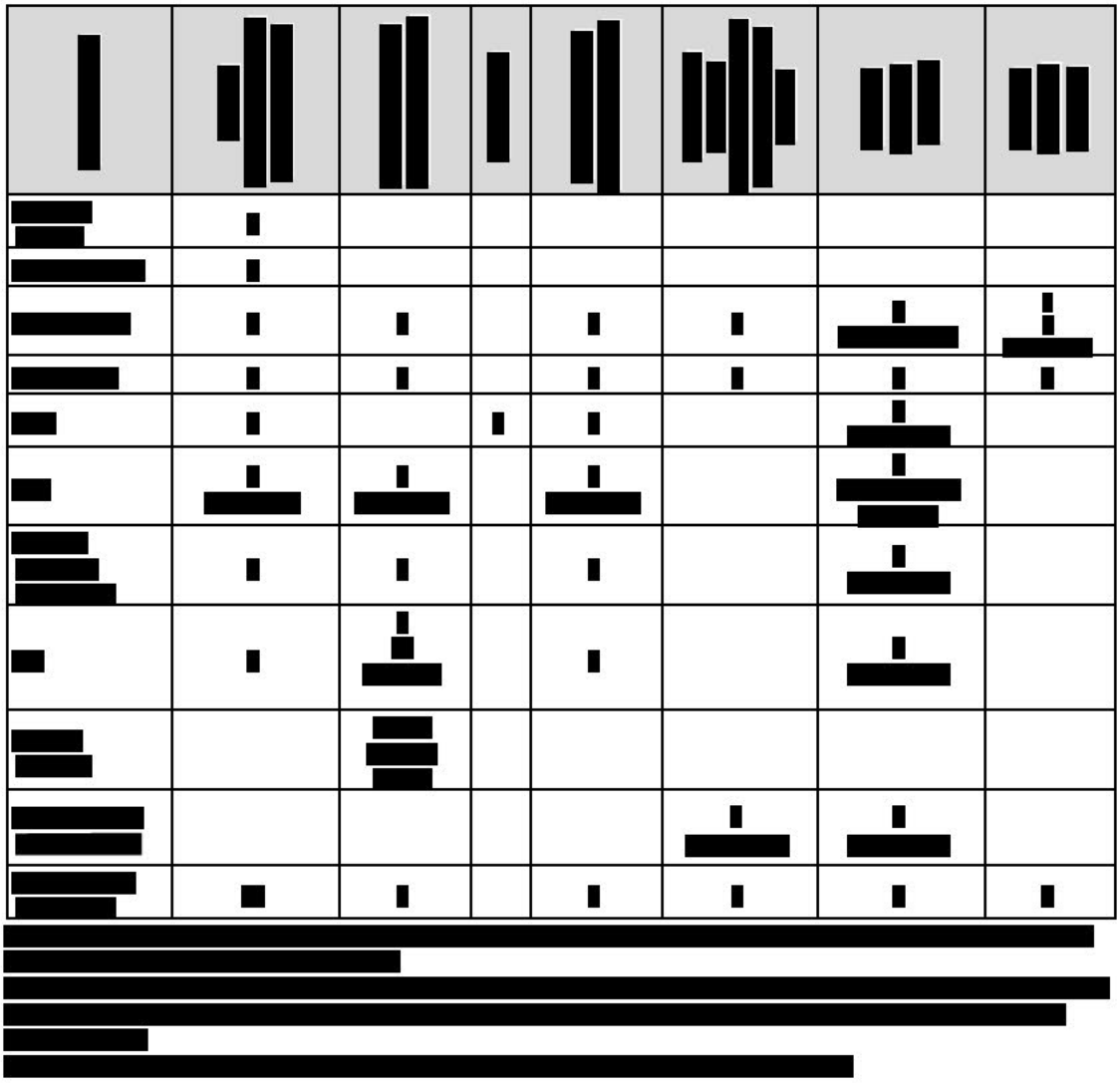
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1. STUDY OVERVIEW

Protocol Synopsis [redacted] This document outlines the procedures for the [redacted] Feasibility Cohort only. [redacted]	
Title	Randomized Study of the pdSTIM™ System (phrenic nerve to diaphragm STIMulation) in Failure to Wean Mechanically Ventilated Patients (ReInvigorate Study)
Sponsor	Stimdia Medical, Inc. [redacted]
[redacted]	[redacted]
Indications for Use	The pdSTIM System is indicated for mechanically ventilated adults at least 18 years old suffering from diaphragmatic dysfunction who have been on mechanical ventilation for ≥ 96 hours and have failed at least one weaning attempt.
Intended Use	The pdSTIM System is intended to facilitate weaning via temporary stimulation of the phrenic nerve.
Study Design	The pdSTIM [redacted] Study is a prospective, multicenter, randomized, controlled clinical study to evaluate the safety and efficacy of the pdSTIM System to facilitate weaning from mechanical ventilation through phrenic nerve stimulation. Potential subjects who are on mechanical ventilation for at least four days and have failed at least one weaning attempt will be considered for the study. Those enrolled will be randomized in a 1:1 manner between a Treatment group that is standard of care with the pdSTIM System and a Control group that is standard of care.
Study Purpose	The objective of this study is to evaluate the safety and efficacy of use of the pdSTIM System to increase diaphragm strength and improve weaning for subjects on mechanical ventilation when compared to standard of care.
[redacted]	[redacted]
Follow-up	[redacted] Randomized subjects will be followed out to 60 (± 7) days post randomization. Total subject participation will be no longer than 67 days.
Primary Endpoints	The primary endpoints will be assessed following completion of the 30-day follow-up by all available randomized subjects. 1. Time to successful weaning from mechanical ventilation for the subjects randomized to Treatment as compared to subjects randomized to Control. 2. Assessment of Serious Adverse Events (SAEs) for the subjects randomized to Treatment as compared to subjects randomized to Control.
Secondary Endpoints	The secondary endpoints will be assessed following completion of the 30-day follow-up by all available randomized subjects.

Protocol Synopsis [redacted] This document outlines the procedures for the [redacted] Feasibility Cohort only. [redacted]	
	1. Compare 30-day mortality rates of Treatment and Control subjects. [redacted]
[redacted]	[redacted]
Study Population	Subjects will be recruited sequentially and screened for the study from each investigator's population of patients on mechanical ventilation. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be included in the study. <u>Inclusion Criteria:</u> 1. Subject is 18 years or older. 2. Subject, or subject's Legally Authorized Representative, understands study requirements, study visits, and is willing and able to provide written informed consent prior to study specific procedures or testing. 3. Subject has been on mechanical ventilation for ≥ 96 hours prior to randomization (intubation or tracheostomy). 4. Subject has failed at least 1 weaning attempt (E.g., site directed spontaneous breathing trial(s) did not result in liberation). 5. At the time of enrollment, the subject is likely to be ventilated for an additional 48 hours, at minimum, in the opinion of the investigator. <u>Exclusion Criteria:</u> 1. Subject has been on invasive mechanical ventilation for > 45 days. 2. Subject failed to wean due to pre-existing neurological or neuromuscular issues affecting the respiratory muscles (e.g., ALS, phrenic nerve paralysis, inflammatory muscle disease, underlying myopathy, myasthenia gravis, cervical spinal injury). 3. Subject's medical history, known anatomy or investigator's inability to visualize necessary anatomical landmarks that could prevent the safe placement of the pdSTIM leads. 4. Subject is at risk of significant hemorrhage or is currently receiving a full dose of systemic anticoagulation (e.g., IV heparin, high dose of subcutaneous heparin. Subjects on prophylactic anticoagulation or daily aspirin regimen on their own are not excluded unless other exclusion criteria apply). 5. Subject has an implant or external electrical device that may interact or interfere with the pdSTIM System (examples may include cardiac pacemaker, implantable defibrillator, vagal nerve stimulator, spinal cord stimulator, gastric stimulator, diaphragmatic stimulator). 6. Subject has been diagnosed and has been treated for neck cancer within the past 5 years or subject had any prior radiation treatment to the neck.

Protocol Synopsis [redacted] This document outlines the procedures for the [redacted] Feasibility Cohort only. See CIP0002 [redacted]	
	7. Subject currently has hemodynamic instability due to any cause (e.g., severe sepsis, hemorrhagic shock, or septic shock) with vasopressor support > 0.1 mg/kg/min of norepinephrine or epinephrine, or equivalent, or is actively being titrated. 8. Subject has a local infection at or around the proposed pdSTIM Lead insertion site. 9. Subject is neutropenic or has signs of significant immunocompromise. (Subjects intubated for respiratory failure due to COVID-19 are not excluded unless other exclusion criteria apply). 10. Subject has severe COPD as indicated by evidence of significant expiratory obstruction on the ventilator flow waveform or, where ventilator flow waveforms are not utilized, has a FEV1 ≤ 30%. 11. Subject has pre-existing severe chronic pulmonary fibrosis. 12. Subject has pleural effusion occupying greater than 1/3 of the pleural space on either side. 13. Subject is currently on or expected to begin neuromuscular blockades. 14. Subject is anticipating withdrawal of life support and/or shift to palliation as the goal of care with less than 6-months life expectancy. 15. Subject is known or suspected to be pregnant or lactating. 16. Subject is currently enrolled in or exited early from *a)* any investigational drug study or *b)* an investigational device study that may impact the ability to wean or is directly related to the lungs or diaphragm.

Protocol Synopsis	
[redacted] This document outlines the procedures for the [redacted] Feasibility Cohort only. [redacted]	
[redacted]	
Study Sponsor	Stimdia Medical Inc.
[redacted]	[redacted]
[redacted]	[redacted]

2. INTRODUCTION

This document is the Clinical Investigational Plan for a human pivotal clinical study of the pdSTIM™ System. This study will be conducted in the US and in accordance with the

Declaration of Helsinki and relevant parts of the Code of Federal Regulations. This protocol outlines the procedures for the [redacted] Feasibility Cohort (Cohort 1). [redacted]

2.1. Background

In the United States in 2017, there were an estimated 903,745 hospitalizations involving mechanical ventilation.[1] Complications from ventilation can result in longer hospital stays, increased risk of disability and increased healthcare costs. According to the American Association for the Surgery of Trauma, estimated national costs were 27 billion USD representing 12% of all hospital costs.[2] Over a third of time in the ICU is spent on mechanical ventilation, and approximately 40% of time on mechanical ventilation may be spent weaning from ventilation.[3] Additionally, those with prolonged mechanical ventilation are 50% more likely to be discharged to skilled nursing facilities for further care.[4]

Multiple studies have suggested that mechanical ventilation has an unloading effect on the respiratory muscles that leads to diaphragmatic atrophy and dysfunction. Sonographic assessments of diaphragm thickness and diaphragm biopsies have shown the rapid rate of diaphragm atrophy during mechanical ventilation.[5] After 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 and animal models have shown a reduction of diaphragmatic force generating capacity proportional to the duration of mechanical ventilation.[6] The findings showed increased diaphragmatic proteolysis during inactivity in as little as 18 hours of disuse. Studies have

[1] Kempker, JA, et al. The Epidemiology of Respiratory Failure in the United States 2002–2017: A Serial Cross-Sectional Study, Critical Care Explorations: June 2020 - Volume 2 - Issue 6 - p e0128 doi: 10.1097/CCE.0000000000000128.
[2] Aast.org. 2020. Mechanical Ventilation - The American Association For The Surgery Of Trauma. [online] Available at: <https://www.aast.org/GeneralInformation/mechanicalventilation.aspx> [Accessed 7 April 2020].
[3] Esteban A, et al. Modes of mechanical ventilation and weaning: a national survey of Spanish hospitals; the Spanish Lung Failure Collaborative Group. Chest 1994; 106:1188–1193.
[4] Zilberberg MD, Shorr AF. Prolonged acute mechanical ventilation and hospital bed utilization in 2020 in the United States: implications for budgets, plant and personnel planning. BMC Health Serv Res. 2008 Nov 25;8:242. doi: 10.1186/1472-6963-8-242. PubMed PMID: 19032766; PubMed Central PMCID: PMC2607272
[5] Grosu HB, et al. Diaphragm muscle thinning in patients who are mechanically ventilated. Chest. 2012 Dec;142(6):1455-1460. doi: 10.1378/chest.11-1638. PubMed PMID: 23364680.
[6] Levine S, et al. Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans. *N Engl J Med* 2008;358:1327-1335.

shown that 60% to 80% of mechanically ventilated patients manifest clinically significant diaphragm dysfunction.[7,8]

2.2. Unmet Clinical Need

It has been hypothesized that electrically pacing the diaphragm during mechanical ventilation may minimize or reverse diaphragm dysfunction resulting in faster weaning times.[9] The hypothesis that electrically pacing the diaphragm can prevent or reverse VIDD has been demonstrated in a spinal injury patient providing electrical stimulation for as little as 30 minutes per day.[10] Diaphragm pacing is used in conjunction with mechanical ventilation in patients that require extended diaphragm reconditioning which is common in spinal cord injury patients.

Stimdia developed a percutaneous electrical phrenic nerve stimulation (PEPNS) system used to temporarily stimulate the phrenic nerve in order to mobilize and recondition the diaphragm using a subcutaneous lead placed in the neck. [redacted]

2.2.1. Clinical Evidence

The PEPNS clinical Study was a prospective First In Human study with twelve patients enrolled at two centers in Europe, using the PEPNS System (https://clinicaltrials.gov/ct2/show/NCT03559933). The study was used to demonstrate the safety of electrical stimulation and lead deployment during a 48-hour period of use with 30-day follow-up. The first two patients enrolled underwent CMAP (Compound

---

[7] Dres M, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med. 2017;195(3):57-66.
[8] Demoule A, et al. Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: a prospective longitudinal study. Ann Intensive Care. 2016;6(1):75.
[9] Pavlovic D, Wendt M. Diaphragm pacing during prolonged mechanical ventilation of the lungs could prevent from respiratory muscle fatigue. Med Hypotheses 2003;60:398-403.
[10] Ayas NT, et al. Prevention of human diaphragm atrophy with short periods of electrical stimulation. Am J Respir Crit Care Med. 1999 Jun;159(6):2018-20. PubMed PMID: 10351955.
[11] Sassoon CS, Zhu E, Caiozzo VJ. Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med. 2004 Sep 15;170(6):626-32.
[12] Sassoon CS, Caiozzo VJ, Manka A, Sieck GC. Altered diaphragm contractile properties with controlled mechanical ventilation. J Appl Physiol (1985). 2002 Jun;92(6):2585-95.

Motor Action Potential) studies before lead insertion and at 30 days post study follow up and showed no degradation in nerve conduction or action potential amplitude. The study confirmed the feasibility of deploying leads in a patient neck while exercising the patient's diaphragm in synchrony with mechanical ventilation. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The pdSTIM system which will be used for this study is an evolution of the PEPNS System.

2.2.2. Risk Benefit Summary and Study Rationale

Early research has shown that stimulating the phrenic nerves to strengthen the diaphragm has potential to both strengthen the diaphragm and wean patients from mechanical ventilation more effectively than current standard of care. There are currently no FDA cleared/approved products on the market for this purpose. The pdSTIM System, a novel system used to stimulate a patient's diaphragm while on mechanical ventilation, may support earlier weaning by strengthening the diaphragm.

[redacted]

[redacted]

2.3. Device Description

2.3.1. The pdSTIM System

The pdSTIM System is a device used to stimulate the patient's diaphragm to exert effort when the patient is on a mechanical ventilator. [redacted]



Figure 2-1. The pdSTIM System Overview



Figure 2-2. pdSTIM Console, pdSTIM Leads and Flow and Pressure Sensor System

2.3.2. Indications for Use

The pdSTIM System is indicated for mechanically ventilated adults at least 18 years old suffering from diaphragmatic dysfunction who have been on mechanical ventilation for ≥ 96 hours and have failed at least one weaning attempt.

2.3.3. Intended Use

The pdSTIM™ System is intended to facilitate weaning via temporary stimulation of the phrenic nerve.

[redacted]

[redacted] the pdSTIM Console (“console”), the pdSTIM Lead (“lead”) and the pdSTIM Introducer Kit (“introducer kit” or “introducer”) will be labeled as investigational and tracked accordingly in this study. Each of these components will include on the label: “CAUTION Investigational device. Limited by Federal (or United States) law to investigational use”. [redacted]

3. STUDY DESIGN

3.1. Design

The ReInvigorate Study is a prospective, multicenter, randomized, controlled clinical study to evaluate the safety and efficacy of the pdSTIM System to facilitate weaning from mechanical ventilation through phrenic nerve stimulation. Potential subjects who are on mechanical ventilation for ≥ 96 hours and have failed at least one weaning attempt will be considered for the study. Those enrolled will be randomized in a 1:1 manner between a Treatment group that is standard of care with the pdSTIM System and a Control group that is standard of care.

[redacted]

3.2. Study Objectives

The objective of this study is to evaluate the safety and efficacy of use of the pdSTIM System to increase diaphragm strength and reduce weaning time of subjects on mechanical ventilation when compared to standard of care.

3.2.1. Primary Endpoints

The primary endpoints will be assessed following completion of the 30-day follow-up by all available randomized subjects.

1. Time to successful weaning from mechanical ventilation for the subjects randomized to Treatment as compared to subjects randomized to Control

2. Assessment of Serious Adverse Events (SAEs) for the subjects randomized to Treatment as compared to subjects randomized to Control

3.2.2. Secondary Endpoints

The secondary endpoints of the study are the following:

1. Compare 30-day mortality rates of Treatment and Control subjects.



3.3. Subject Selection Criteria

Subjects will be recruited sequentially and screened for the study from each investigator's population of patients on mechanical ventilation. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be included in the study.

3.3.1. Inclusion Criteria

Subjects must meet all the following inclusion criteria to participate in the study:

1. Subject is 18 years or older.
2. Subject, or subject's Legally Authorized Representative, understands study requirements, study visits, and is willing and able to provide written informed consent prior to study specific procedures or testing.

3. Subject has been on mechanical ventilation for at ≥ 96 hours prior to randomization (intubation or tracheostomy).
4. Subject has failed at least 1 weaning attempt (E.g., site directed spontaneous breathing trial(s) did not result in liberation).
5. At the time of enrollment, the subject is likely to be ventilated for an additional 48 hours, at minimum, in the opinion of the investigator.

3.3.2. Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

1. Subject has been on invasive mechanical ventilation for > 45 days.
2. Subject failed to wean due to pre-existing neurological or neuromuscular issues affecting the respiratory muscles (e.g., ALS, phrenic nerve paralysis, inflammatory muscle disease, underlying myopathy, myasthenia gravis, cervical spinal injury).
3. Subject's medical history or known anatomy or investigator's inability to visualize necessary anatomical landmarks that could prevent placement of the pdSTIM leads.
4. Subject is at risk of significant hemorrhage or is currently receiving a full dose of systemic anticoagulation (e.g., IV heparin, high dose of subcutaneous heparin. Subjects on prophylactic anticoagulation or daily aspirin regimen on their own are not excluded unless other exclusion criteria apply).[13]
5. Subject has an implant or external electrical device that may interact or interfere with the pdSTIM System (examples may include cardiac pacemaker, implantable defibrillator, vagal nerve stimulator, spinal cord stimulator, gastric stimulator, diaphragmatic stimulator).
6. Subject has been diagnosed and has been treated for neck cancer within the past 5 years or subject had any prior radiation treatment to the neck.

[redacted]

7. Subject currently has hemodynamic instability due to any cause (e.g., severe sepsis[14], hemorrhagic shock, or septic shock[15,16]) with vasopressor support > 0.1 mg/kg/min of norepinephrine or epinephrine, or equivalent, or is actively being titrated.
8. Subject has a local infection at or around the proposed pdSTIM Lead insertion site.
9. Subject is neutropenic or has signs of significant immunocompromise. (Subjects intubated for respiratory failure due to COVID-19 are not excluded unless other exclusion criteria apply).
10. Subject has severe COPD as indicated by evidence of significant expiratory obstruction on the ventilator flow waveform or, where ventilator flow waveforms are not utilized, has a FEV1 ≤ 30% has a FEV1 ≤ 30%[17].
11. Subject has pre-existing severe chronic pulmonary fibrosis.
12. Subject has pleural effusion occupying greater than 1/3 of the pleural space on either side.
13. Subject is currently on or anticipated to begin neuromuscular blockades.
14. Subject is anticipating withdrawal of life support and/or shift to palliation as the goal of care with less than 6-months life expectancy.
15. Subject is known or suspected to be pregnant or lactating.
16. Subject is currently enrolled in or exited early from a) any investigational drug study or b) an investigational device study that may impact the ability to wean or is directly related to the lungs or diaphragm.

4. METHODS

4.1. Informed Consent

Subjects participating in this study will be recruited sequentially from the Investigator's population of patients that have been on mechanical ventilation for ≥ 48 hours. To

[redacted]

determine eligibility of a subject, the investigator will implement the consent process and determine if the medical status of the subject meets the study selection criteria. Subjects or their representatives must be informed about the study and the potential benefits and risks prior to enrollment. Only those subjects who voluntarily provide written consent, or whose authorized representative provides written consent, to participate will be allowed to continue in the screening process.

The Institutional Review Board (IRB) approved consent document must be signed and dated by the subject or representative. An original, signed document is to be kept with the subject's file and the second original or a signed copy must be provided to the subject or their representative (if the representative signs the form). Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled, and also informed that withdrawal from the study will not jeopardize their future medical care.

The Sponsor will provide a template informed consent form (ICF) for IRB submission. This template may be modified to suit the requirements of each study site; however, the Sponsor or designee must pre-approve all changes to the ICF prior to submission to the site's IRB.

4.2. Screening

After the subject informed consent document has been signed, subject eligibility will be verified through evaluation of the inclusion and exclusion criteria. [redacted]

A subject is considered enrolled when *a)* the subject, or their legally authorized patient representative, has provided written informed consent and agrees to participate in the clinical investigation and *b)* the subject has met all study qualification criteria.

Subjects who provide informed consent but do not meet all the study entrance criteria or do not proceed to randomization will be considered screening failures; [redacted]

Following successful screening and enrollment, baseline assessments will be conducted. Randomization will occur and, when possible, pdSTIM System placement will take place on the day of randomization [redacted]

[redacted] Only those subjects who provide consent documentation and meet all the study entrance criteria (enrolled subjects) will be randomized and assigned a study subject identification number through the electronic database.

[redacted]

4.4. Study Assessment Methods

The following assessments will be conducted, data collected throughout the study duration and recorded in the study database.

4.4.1. Physical Exam and Medications

Relevant physical exam and vital signs will be documented in the study database at each visit, while the subject is hospitalized. Relevant medications will be documented at the baseline visit and changes to the medications will be noted at each visit.

4.4.2. Richmond Agitation and Sedation Scale[18] (RASS)

The RASS is a validated scale to evaluate a subject's level of sedation while in the setting of MV. RASS will be collected at baseline and every 3 days after randomization.

[redacted]

[redacted]

4.4.3. Rapid Shallow Breathing Index (RSBI)

RSBI is a standard measure of respiratory muscle fatigue defined as the ratio of respiratory frequency to tidal volume (f/VT). An RSBI value greater than 105 may predict a subject's inability to tolerate a Spontaneous Breathing Trial (SBT).

[redacted]

RSBI is required only for subjects that are able to initiate inspiratory effort.

4.4.4. Weaning Readiness Assessment

All subjects will be evaluated to determine readiness to wean criteria while on MV unless contraindicated. [redacted]

[redacted]

[redacted]

[

SBT. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.4.6. Liberation from Mechanical Ventilation

Subjects successfully meeting the SBT criteria and have had mechanical ventilation removed will be monitored for 48 hours then assessed to determine if liberation from mechanical ventilation has been successful. [redacted] Subjects that do not require re-intubation/or a return to mechanical ventilation or do not require MV within 48 hours are considered successfully liberated from MV. Subjects in the Treatment group will have their pdSTIM System leads removed after the subject has met the criteria for successful liberation from mechanical ventilation or no later than 30 days from time of lead insertion.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

4.5. Baseline Assessment

Baseline data includes subject demographics and medical status prior to randomization.

[redacted]

4.6. Randomization

[redacted] subjects that agree to participate and meet all entrance criteria and have had their baseline assessments completed will be randomized to the Control or Treatment Group.

[redacted]

[redacted]

[redacted]

4.7. pdSTIM Lead Placement Procedure – [redacted] Treatment Group Only

Site investigators will be trained on the pdSTIM System and procedure for bilateral lead placement according to the Instructions for Use. Detailed training for device handling and the placement technique will be provided by the Sponsor. The pdSTIM leads will be inserted and set up with the pdSTIM System according to the Instructions for Use.

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.8. Stimulation Therapy Sessions – [redacted] Treatment Group Only

During a stimulation session, the pdSTIM console will electrically stimulate the phrenic nerves [redacted] Subjects will be monitored throughout each session.

Stimulation therapy with pdSTIM will occur two times per day until the subject is successfully extubated/removal from mechanical ventilation or the 30-Day follow-up visit, whichever is first. [redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.9. Daily Follow-Up Assessments

Subjects in both groups will be assessed for weaning readiness at least once per day and subsequent SBT will be conducted when the readiness to wean criteria are met or, if in the opinion of the investigator, the subject is clinically able to attempt the SBT.[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

4.11.30-Day Follow-Up Assessment

Subjects will complete a 30 (±2) day follow-up visit post-randomization [redacted] unless prior early withdrawal has been documented. [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

The lead removal (if applicable) should be completed no later than 30 days after they were placed. The assessment for liberation from mechanical ventilation should be conducted per Section 4.4.6.

[redacted]

- [redacted]
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- [redacted]

4.12. 60-Day Follow-Up Assessment

Subjects will continue with the study until the 60 (±7) day follow-up visit post-randomization [redacted] unless prior early withdrawal has been documented. [redacted]

[redacted]

[redacted]

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4.13. Data Collection Methods

To ensure data quality and completeness, all required data will be reported via electronic case report forms. [redacted]

[redacted]



[redacted]

4.14. Adverse Event and Device Deficiency Reporting

Any reportable Adverse Events that occur following informed consent to the end of the subject's participation in the study will be reported to the Sponsor in the study database. [redacted]

4.14.1. AE Definitions

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

Adverse Device Effect (ADE): AE related to the use of an investigational device.

Serious Adverse Event (SAE): Any AE that led to death, led to a serious deterioration in the health of a subject that either resulted in a life-threatening illness or injury, permanent impairment of a body structure or a body function, 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, or any AE that led to fetal distress, fetal death or a congenital abnormality or birth defect.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.14.2. Reporting of Adverse Events

All reportable AEs that occur to any subject during the study must be documented on the AE eCRF including the following information: event description, treatments given, severity of the event, relationship with the study, and the outcome of the event.

When reporting an AE, the Investigator should report the diagnosis of the event with correlating signs and symptoms on the AE eCRF. Individual signs and symptoms and treatment/intervention/diagnostic testing should not be reported as separate adverse events, but instead be reported as supporting documentation on the AE eCRF (for example, heart failure decompensation should be reported rather than individual reports of fluid retention, shortness of breath, etc.).

Pre-existing conditions or planned procedures will not be reported as AEs unless the event increased in severity during the course of the study, and if at the determination of the Investigator, it is relevant to the study. For the purposes of the ReInvigorate study, occurrences or clinical signs considered not clinically significant by a study investigator and documented as such in the medical record will not be reported as adverse events.

[redacted]

The Investigator must comply with reporting requirements of the reviewing IRB. If the Investigator determines that an AE is a Serious Adverse Event as defined in this protocol, it is to be reported to the Sponsor as soon as possible but no later than 48 hours after the Investigator first learns of the event and to the IRB per their reporting requirements. The Sponsor will investigate any reported SAE to determine if the event type and severity was anticipated. [redacted]

4.14.3. Adverse Event Relatedness

The relatedness of the AE to the procedure and pdSTIM System will be determined by the Investigator using the following definitions:

- Definite**:** The AE follows a reasonable temporal sequence from the time of index procedure. This includes an AE that occurs during the index procedure and/or during the follow-up period.
- Possible: The AE follows a reasonable temporal sequence from the time of index procedure and the possibility of index procedure and/or pdSTIM System involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- Not related: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

4.14.4. Device Deficiencies

A device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labelling.

Malfunction is described as the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or clinical study protocol.

Use Error is described as an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Device deficiencies will be documented on CRFs and are reported to the Sponsor no later than 48 hours after the site becoming aware of the deficiency and to the IRB according to local regulations. Investigators must characterize device deficiencies according to whether they could have led to a serious adverse device effect (SADE).

[redacted]

5. STUDY MANAGEMENT

5.1. Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established for adverse event classification and adjudication. The proposed CEC will consist of a minimum of three physicians and/or respiratory therapists with expertise in the study population. A CEC

Charter will be developed to document the responsibilities, meeting logistics and other related information.

5.2. Data and Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established in accordance with FDA guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees" to oversee study progress and review clinical data and safety parameters. The proposed DSMB will consist of three medical experts, at least two of which are physicians and up to one of which may be a respiratory therapist, with expertise in the study population. An independent statistician will also be a member of the DSMB. A DSMB Charter will be developed to document the responsibilities, meeting logistics and other related information. [redacted]

[redacted]

5.3. Confidentiality

All information and data sent to the Sponsor or designee concerning subjects or their participation in this study will be considered confidential. Subjects' names or identifying information must not be used on any correspondence to the Sponsor. Subjects will be assigned an identification number instead, for their participation in the study.

Data used in the analysis and reporting of this study will be used in a manner without identifiable reference to a subject. The Investigator consents to the visits by the Sponsor and its representatives and the U.S. FDA or any other governmental body to review the study subjects' medical records.

5.4. Ethical Considerations

This study will be conducted in accordance with Good Clinical Practices, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements. The protocol and Investigator will comply with International Standards, country specific regulatory requirements, and the site's respective IRBs.

Procedures required for this protocol will not begin at a study site until the required approval from the IRB has been obtained. Any additional requirements imposed by the

IRB or regulatory authority shall be followed. The reviewing IRB will be an independent review panel responsible for ensuring the protection of the rights, safety and well-being of study subjects.

Investigators must submit the study protocol to their IRB and obtain the IRBs written approval before being allowed to conduct and participate in the study. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc. The Investigator will provide the Sponsor or designee with copies of such approvals and reports.

[redacted]

5.5. Subject Withdrawal from Study

Every effort should be made to retain subject participation for the duration of the study. During the informed consent process subjects/legal guardians should be fully informed of the follow-up schedule and procedures and should only be enrolled if willing to fully participate in the study. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any ongoing adverse events.

Subjects that did not meet the study criteria are screening failures and will not be counted toward the total enrollment for the study.

[redacted]

Subjects that are randomized but do not complete follow-up will not be replaced.

5.5.1. Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject withdraws from the study, the Investigator must ensure that there is documentation for the reason for the withdrawal (e.g., a signed note from either the subject or their authorized representative or the Investigator stating the reason for withdrawal) reported on the Study Exit CRF. The Investigator should attempt to determine the status of unresolved adverse events and the subject's medical status at the time of discontinuation.

The Investigator can decide to terminate a subject's participation due to safety reasons or if the relation between benefit and risk is no longer acceptable.

If the subject is being transferred to a facility outside of the area of supervision by the Principal Investigator and research team, the subject will need to be exited from the study. [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted] leads should be removed prior to the transfer.

If the subject had any unresolved AEs at the time of withdrawal, the Investigator should request continued communication with the subject until resolution of the AE(s), if possible.

5.5.2. Loss to Follow-up

Subjects that do not voluntarily withdraw and miss their 30-day or 60-day follow-up visit will be considered lost to follow-up. At least two attempts at reaching the subject, at least one in writing, must be documented in the subject's record.

5.6. Protocol Deviation Reporting

A Protocol Deviation CRF will be completed for each study protocol deviation (e.g., not performing required testing, missed follow-up window, etc.). The Investigator must notify the Sponsor and the reviewing IRB of any deviation from the protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five working days after the emergency occurred.

5.7. Device Accountability

Device accountability records will be maintained for all investigational product during the study. Upon receipt of devices at the clinical site, the lot and/or serial numbers (if applicable) will be recorded on the Device Accountability Log and devices will be maintained in a secured location with access only available to the investigational study team.

Once used, the subject ID number, date of use, and disposition of each device will be recorded on the Device Accountability Log.

At the conclusion of enrollment, all unused devices and kits will be returned to the Sponsor. Contact the Sponsor for handling instructions and return authorization of all investigational devices and kits.

5.8. Monitoring

The Sponsor or designee will monitor the progress of the study as required by GCP and as specified by a separate study monitoring plan. This will include routine, periodic visits to study sites to compare reported results with source documentation.

The Investigator and site personnel will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data as requested. Each enrolling site will be monitored at least once during the study. Monitoring will consist of reviewing of subject records, source documents, and other required documentation, including IRB approvals and correspondence. Site personnel must be available to meet with the monitor or other study Sponsor designee during site visits.

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

5.9. Sponsor Responsibilities

The Sponsor's or its designee's responsibilities in the study include:

- Provide training to Investigators and study site staff
- Select the Investigator, and other consultants (e.g., monitors) who participate in the study
- Provide financial support to each study site
- Ensure completion of site monitoring of clinical data at clinical study sites
- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes

The Sponsor or designee will maintain records of the name and address of the reviewing IRB, documentation of their decisions regarding the study, and approved consent document.

5.9.1. Site Selection

The clinical study sites will be selected based on the availability of the subject pool to be included in the study. The selected Investigators must be specialists in critical care of ICU subjects on mechanical ventilation.

Healthcare professionals or site staff that assist with the study-related data collection do not need to be trained in standard of care practices. [redacted]

Delegation of duties will be authorized by the Investigator and documented on a Delegation of Authority Log.

5.9.2. Amending the Protocol

[redacted] changes must be submitted to the IRB and applicable regulatory body for review and approval. Any change that would require alteration of the ICF must receive approval from the IRB prior to implementation. Following approval, the protocol amendment will be distributed to all protocol recipients at the site.

5.9.3. Early Study Termination

The sponsor will monitor the progress of the study. If warranted, the Sponsor may suspend or discontinue the study early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population. The Sponsor may terminate the Investigator's participation in the study for issues that include, but are not limited to, the following:

- Evidence of an Investigator's failure to maintain adequate clinical standards
- Evidence of an Investigator or staff's failure to comply with the protocol
- Inaccuracy or late submission of data forms
- Conditions of approval imposed by the reviewing IRB and/or regulatory agencies
- Evidence of safety concerns
- Change of staff at site that adversely impacts trial conduct

Any evidence or pattern of non-compliance with respect to these standards will be deemed to be "cause" for the site to be put on probation. If corrective actions are not promptly and subsequently undertaken, the clinical site will be terminated from the study and the Sponsor may replace their site.

If the clinical study is terminated prematurely or suspended, the Sponsor will promptly inform the Investigator of such termination or suspension, and the reason(s) for this decision. The IRB will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator.

If the IRB suspends the study, the Investigator must inform the Sponsor within 48 hours of notification.

5.10. Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. Records are subject to inspection by the monitor and regulatory agencies. The Investigator should maintain the following records related to the study:

- Signed Clinical Trial Agreement
- Written copy of the IRB approval, informed consent document, recruiting materials and IRB correspondence
- Regulatory approval, if applicable
- Signed copy of the study protocol and amendments, if any
- All significant correspondence which pertains to the investigation
- Subjects' case history records, including signed subject informed consent form; all relevant observations; observations of adverse device events; medical history; completed worksheets; documentation of the dates and reasons for any deviation from the protocol
- Copy of the Delegation of Authority Log
- Current curricula vitae of the Investigator and sub-investigators
- Device Accountability Logs
- Signed financial disclosure forms

5.10.1. Archiving

The Investigator should retain the essential documents listed in Section 5.10 for a period of at least two (2) years (or longer if required per local regulations) after the study is terminated or the date that the records are no longer required for purposes of supporting publications or regulatory submissions.

5.10.2. Investigator Reports

A list of Investigator required reports is outlined in Table ***5-1***.

Table 5-1 Investigator Reports

Investigator Report	Submit To	Description
Withdrawal of IRB approval	Sponsor	Notification within five working days.
Serious AEs	Sponsor IRB	Immediately and no later than 48 hours As required
UADE	Sponsor IRB	Within 24 hours followed by written report within ten working days.
Device Deficiency	Sponsor IRB	Within 48 hours from occurrence Per IRB reporting requirements
Progress Report	IRB	The Investigator must submit this report at regular intervals, but not less than once per year per IRB requirements.
Deviations from protocol	Sponsor IRB	Report of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Notification within five working days. As required.
Investigator termination	Sponsor IRB	Within 24 hours

[redacted]

5.11. Good Clinical Practices

This study will be conducted in accordance with the current GCP guidelines as specified for medical devices in ISO 14155. Compliance to this guideline provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

[redacted]

6. RISKS AND BENEFITS

6.1. Risks

The potential risks related to the pdSTIM System and lead placement procedure may include, but are not limited to the following:

<u>PdSTIM Lead Placement Procedure and Lead Related Risks:</u>

- Lung damage
- Blood loss
- Extravasation
- Hematoma
- Infection
- Nerve damage
- Vessel Damage/Injury
- Pseudoaneurysm
- Pneumothorax
- Tissue damage
- Toxic or allergic response to the Lead
- Embolism
- Thrombus
- GI Symptoms from vagal nerve injury

Stimulation related risks:

- Cardiac pacing
- Unwanted stimulation of muscles other than the diaphragm
- Diaphragm myotrauma due to overwork
- Electric shock
- Inflammation
- Pain or discomfort from stimulation
- Tissue damage
- Nerve damage
- Arrhythmias
- Hoarseness
- Hypotension
- Cardiac arrest
- Stroke
- Barotrauma/volutrauma
- Gastroparesis

Other potential ventilation risks during use of the pdSTIM System

- Hypercarbia
- Hypocarbia
- Hyperoxia
- Hypoxia

Patients [redacted] may experience minor incisional pain, redness and a minor scar at the incision location. Minor discomfort during the therapy delivery is also possible. There will also be audible alarms from the pdSTIM console similar to standard alarms in an ICU setting. These are not reportable adverse events unless they present more moderately or if the PI determines that reporting is warranted. There may be other risks that are unknown at this time, including risks to pregnant or lactating mothers and unborn fetuses.

These risks are mitigated by design of the device using known materials and rigorous testing to ensure they are safe for use. Investigators will receive training on the pdSTIM System and lead placement procedure, and subjects will be screened and evaluated for medical conditions that may compromise successful performance of the pdSTIM System.

6.2. Benefits

Potential Benefits of the pdSTIM System may include the following:

- Reduced time on mechanical ventilation
- Reduced time in the Intensive Care Unit
- Increased respiratory muscle strength/endurance or reconditioning the diaphragm which may result in earlier weaning from mechanical ventilation

It is possible that some subjects may receive no benefit from the device.

Based on the risk assessment and potential benefits, Stimdia Medical believes that this system will be safe for use in subjects in this clinical study.

7. STATISTICAL METHODS

Planned statistical methods to be used for analysis and reporting of data for this study are described in the Statistical Analysis Plan. [redacted]

[redacted]

[redacted]

[redacted]

7.1. Sample Size Determination

A total of 350 randomized subjects were originally planned (see 7.8 Reporting and FDA Submissions below). However, only a total n = 32 randomized subjects were enrolled in the [redacted] Feasibility Cohort.

There was limited clinical experience on which to base the original design assumptions, [redacted]

7.1.1. Sample Size –Primary Efficacy Endpoint

Power calculations are based on a log-rank test for the second primary endpoint and calculated with PASS 2020 software.

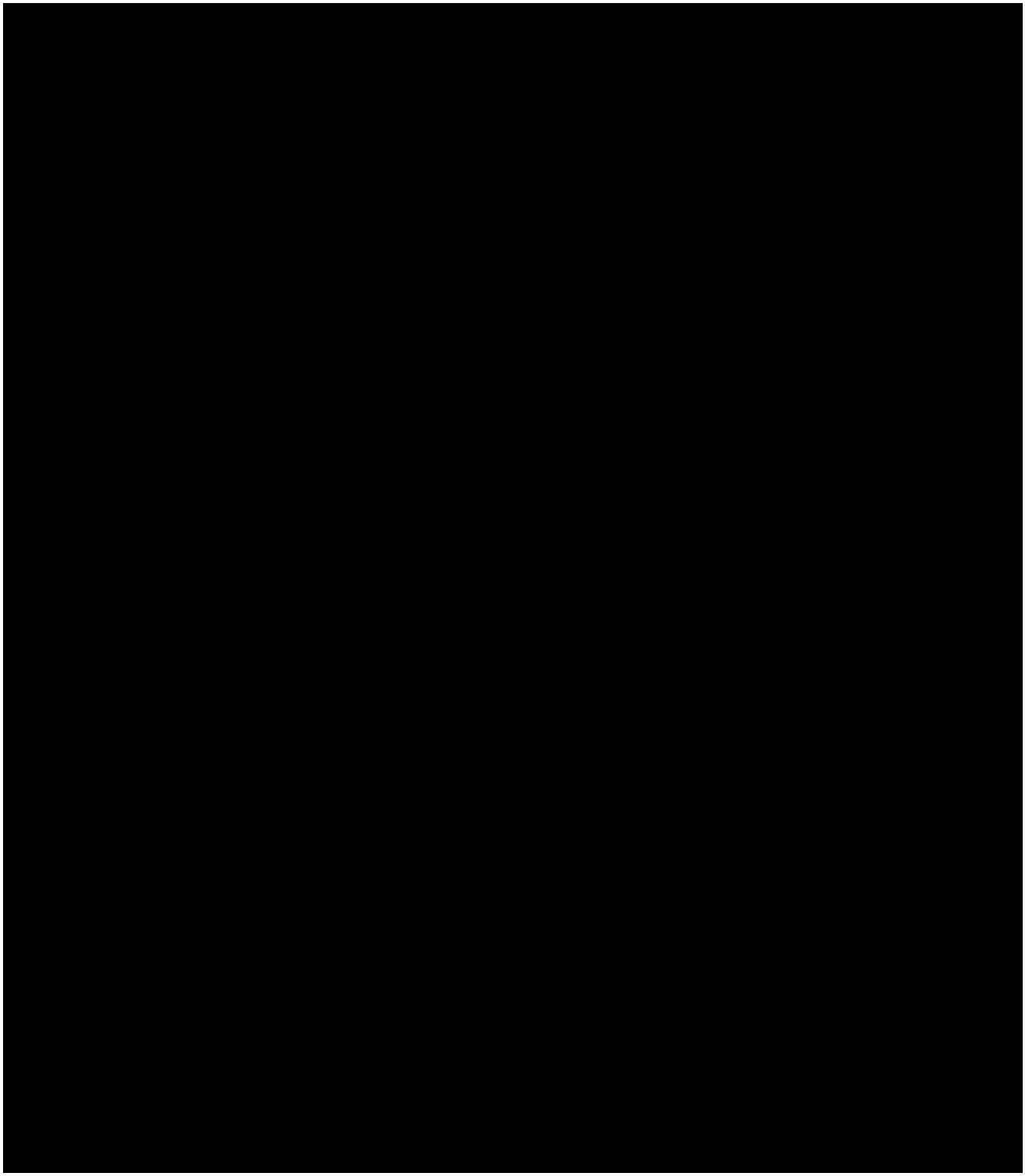
For the primary efficacy endpoint, for a one-sided 0.025 alpha (equivalently, a two-sided 0.05 alpha), assuming 50% for the population proportion of control subjects weaned by day 30, 90% power will be provided if the population proportion of treatment subjects successfully weaned by day 30 is approximately 65% (i.e., the hazard ratio for weaning events is 1.58). This degree of power is also maintained for approximate population proportions of 75% for controls and 87% for treatment (hazard ratio of 1.47), and for 25% for controls and 41% for treatment (hazard ratio 1.83).

Power should be maintained in the presence of competing risk. For example, with an assumed 50% for the population proportion of control subjects weaned prior to day 30, if the risk of competing events in each group is 20%, 90% power will be provided for a hazard ratio of 1.60 (instead of 1.58 for calculations without competing risk).

Finally, power should also be maintained in the presence of loss-to-follow-up. For example, with an assumed 50% for the population proportion of control subjects weaned prior to day 30, if the risk of loss-to-follow-up in each group is 10%, 90% power will be provided for a hazard ratio of 2.03 and 80% power will be provided for a hazard ratio of 1.87.

[redacted]

[redacted]



7.5. Analysis Populations

The following analysis populations are defined for analysis:

Intent-to-treat (ITT) analysis set: The ITT is defined as all randomized subjects. Analysis will be based on the randomized treatment assignment regardless of the actual treatment received.

[redacted]

Safety analysis set: The safety analysis set is defined as all randomized treatment subjects for whom treatment was attempted and all randomized control subjects who were not treated with the investigational device.

[redacted]

Unless otherwise specified, the primary analysis set for all endpoints and outcomes is the ITT analysis set. [redacted] Safety analyses will be based on the safety analysis set. [redacted]

7.6. Handling of Missing Data

All attempts will be made to limit the amount of missing data. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed.

Subjects lost to follow-up for the primary efficacy endpoint will be censored at their last known status date. Unless otherwise specified, analyses for other endpoints will be based on the available results without imputation for missing data.

Tipping point sensitivity analyses for the primary efficacy endpoint will be performed.

[redacted]

[redacted]

[redacted]

[redacted]

8. ABBREVIATIONS AND ACROYNMS

ADE	Adverse Device Effect
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
AMI	Acute Myocardial Infarction
BiPAP	Bilevel Positive Airway Pressure
BP	Blood Pressure
BPM	Beats Per Minute
CRF	Case Report Form
CPAP	Continuous Positive Airway Pressure
eCRF	Electronic Case Report Form
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practices
HR	Heart Rate
ICF	Informed Consent Form
IJ	Internal Jugular

IRB	Institutional Review Board
PaO_2	Partial Pressure of Oxygen
PEEP	Positive End Expiratory Pressure
PEPNS	Percutaneous Electrical Phrenic Nerve Stimulation
pdSTIM	Phrenic Nerve to Diaphragm Stimulation
PS	Pressure Support
RASS	Richmond Agitation & Sedation Scale
RSBI	Rapid Shallow Breathing Index
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SpO_2	Peripheral Capillary Oxygen Saturation
TTN	Through The Needle
UADE	Unanticipated Adverse Device Effect
US FDA	United States Food and Drug Administration
VIDD	Ventilator-Induced Diaphragmatic Dysfunction

REVISION HISTORY

Revision	Version Date	Description of Change and Reason for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

		[redacted]
[redacted]	[redacted]	[redacted]