LIBERATE MEDICAL, LLC

Clinical Research Protocol

BREATH SYNCHRONIZED ABDOMINAL MUSCLE STIMULATION TO FACILITATE VENTILATOR WEANING: A PILOT STUDY

Protocol Number:	VF-KINDRED-01
Version Date:	8 August 2016
Investigational Product:	VentFree
IDE Number:	Non-significant risk device
Sponsor:	Liberate Medical, LLC 6400 Westwind Way, Suite A Crestwood, KY, 40014
Funding Organization:	Liberate Medical, LLC
Principal Investigator:	Name: Dr. Lucas Abraham Telephone: (502) 587-8000 Fax: (502) 583-8001
Medical Monitor:	Name: Dr. Franco Laghi Telephone: (708) 528-1807 Email: Franco.Laghi@vs.gov

Approval:

Amadeo Abraham M.D. — *PI or Sponsor Signature (Name and Title)*

9/22/16 — *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing Liberate Medical, LLC with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: VF-KINDRED-01

Protocol Title: Breath synchronized Abdominal Muscle Stimulation to Facilitate Ventilator Weaning: A Pilot Study

Protocol Date: 8th August 2016

Investigator Signature *Date* 9/22/16

Amadeo

Dr. Lucas Abraham, Pulmonary Physician

Print Name and Title

Site Name Kindred Hospital – Louisville

Address 1313 St. Anthony Place

Louisville, KY, 40204

Phone Number (502) 587-8000

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Investigator Signature	*Date*
Dr. Lucas Abraham, Pulmonary Physician	
Print Name and Title	
Site Name	Kindred Hospital – Louisville
Address	1313 St. Anthony Place
	Louisville, KY, 40204
Phone Number	(502) 587-8000

Table of Contents

1 List of Abbreviations

AE	Adverse event
APACHE II	Acute Physiology and Chronic Health Evaluation II
BMI	Body Mass Index
CFR	Code of Federal Regulations
COPD	Chronic obstructive pulmonary disease
CPF	Cough Peak Flow
CRF	Case report form
ETCO2	End-tidal carbon dioxide
FDA	Food and Drug Administration
FEV1	Forced Exhaled Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAUDE	Manufacturer and User Facility Device Experience
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MV	Mechanical ventilation
NMES	Neuromuscular electrical stimulation
PEF	Peak expiratory flow
PI	Principal Investigator
PTPdi	Pressure-time products of the diaphragm
PTPga	Pressure-time products of the gastric space
SAE	Serious adverse experience
SBT	Spontaneous breathing trial
SCI	Spinal Cord Injury
SPO2	Peripheral capillary oxygen saturation
VAP	Ventilator acquired pneumonia

2 Protocol Synopsis

TITLE	Breath synchronized Abdominal Muscle Stimulation to Facilitate Ventilator Weaning: A Pilot Study
SPONSOR	Liberate Medical, LLC
FUNDING ORGANIZATION	Liberate Medical, LLC
NUMBER OF SITES	1
RATIONALE	In the U.S. over 500,000 patients have difficulty weaning from mechanical ventilation every year. These patients cost the health care system $16 billion annually and have an increased risk of medical complications and morbidity. A major factor responsible for weaning failure is the imbalance between decreased respiratory muscle strength and excessive respiratory load. VentFree (Liberate Medical, LLC) is an investigational device that applies electrical stimulation to the abdominal muscles in synchrony with exhalation. This is hypothesized to improve the strength of the respiratory muscles. The long term goal of this project is to determine whether this approach can reduce the number of days taken for patients to wean from mechanical ventilation.
STUDY DESIGN	This is a single center, participant blinded randomized placebo controlled pilot trial.
PRIMARY OBJECTIVE	The primary objective of this study is to determine whether NMES applied to the abdominal wall muscles in synchrony with exhalation can increase the strength of the respiratory muscles in prolonged mechanical ventilation patients
SECONDARY OBJECTIVES	The secondary objectives of the study is to evaluate whether this intervention also affects: (1) the thickness of the abdominal wall muscles and the diaphragm, (2) functional respiratory measurements, and (3) weaning outcome
NUMBER OF PARTICIPANTS	Twenty six: 13 in the treatment arm and 13 in the control arm.
PARTICIPANT SELECTION CRITERIA	Inclusion Criteria: • Patients who have been mechanically ventilated for at least fourteen days. • Clinically stable: oxygen saturation > 90% with a fractional inspired oxygen ≤ 0.40, external PEEP ≤ 5 cm H_2O, temperature ranging from 35.5 to 38.5C°, no intravenous administration of vasoactive agents. Exclusion Criteria:

	• Patients in whom Neuromuscular Electrical Stimulation (NMES) does not elicit a palpable contraction of the abdominal muscles. • Patients with broken or irritated skin on the abdominal wall • Patients with a history of neuromuscular disease • Body Mass Index (BMI) > 35 kg/m^2 • Patients who are not medically stable • Patients with a pacemaker • Female patients who are pregnant • Patients under the age of 18 • Patients who are expected to die within four weeks • Patients who are unable to follow verbal instructions • Patients with epilepsy • Patients with an abdominal wall hernia • Patients with anoxic encephalopathy • Patients with history of, or active, substance abuse
ACTIVE DEVICE	VentFree prototype (VF03) that delivers electrical stimulation pulses to the abdominal muscles during exhalation with a frequency of 30 Hz, a pulse width of 350 µs and 90% of the maximum current that the participant can tolerate. These stimulation parameters were selected to cause a tetanic (continuous) contraction of the abdominal muscles, without pain for the patient. Stimulation will be administered for 30 minutes 2 times per day, 5 days per week, for 6 weeks; or until the patient is weaned from mechanical ventilation.
CONTROL DEVICE	Modified VentFree prototype (VF03) that delivers stimulation pulses to the abdominal muscles during exhalation with a frequency of 10 Hz, a pulse width of 100 µs and current set to 10 mA. These stimulation parameters were chosen to cause a twitch contraction of the abdominal wall muscles. Stimulation will be administered for 30 minutes, 2 times per day, 5 days per week, for 6 weeks; or until the patient is weaned from mechanical ventilation.
DURATION OF PARTICIPANT PARTICIPATION AND DURATION OF STUDY	Participants will participate in the study for up to 45 days. The total duration of the study is expected to be 6 months (4.5 months for participant recruitment and 1.5 months for final participant follow-up).
CONCOMMITANT MEDICATIONS	No medications will be restricted as part of this study.
EFFICACY EVALUATIONS	• Sensation of stimulation experienced by the patient • Number of days taken to wean

	• Time spent breathing without mechanical ventilation support • Respiratory muscle strength • Peak expiratory flow • Resting breathing parameters
PRIMARY ENDPOINT	• Maximum inspiratory and expiratory pressure
SECONDARY ENDPOINTS	• Thickness of the abdominal wall muscles • Thickness of the diaphragm • Weaning success • Number of days taken to wean • Time spent breathing without mechanical ventilation support • Cough peak flow • Resting breathing parameters • Adherence to the study protocol • Sensation of stimulation experienced by the patient • Adverse events
STATISTICS Analysis Plan	Only participants who fulfil the protocol in terms of eligibility, interventions and outcome assessment will be included in the statistical analysis. Study results will first undergo descriptive level statistical analyses. In the second level of analysis, we will quantify the magnitude to which abdominal NMES exhibits a protective effect using regression models. Weaning success will be compared between the study groups using Poisson regression. Kaplan Meier survival analysis will be used to compare the time to wean in both study groups. Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study treatment.
Rationale for Number of Participants	This study is intended to be a pilot study that will be used to obtain initial data on the feasibility and safety of VentFree to assist in the process of ventilator weaning. The primary outcome of this study is the effect of abdominal NMES on respiratory muscle strength over time. There is currently no data in the literature to support a sample size calculation for this study. Given this constraint, in this pilot study a total of 24 participants was deemed adequate and is consistent with sample size recommendations in the literature.[1] Allowing for a 10% drop out rate, a total of 26 participants will be recruited for this study. The data collected on the secondary endpoints will be used to

	determine the participants needed for a future randomized controlled trial of the device on weaning outcome.

3 Background

Approximately one million patients in the US are estimated to undergo mechanical ventilation from respiratory failure (MV) every year, resulting in an annual cost of $27 billion.[2] Approximately seven hundred thousand of these patients have difficulty weaning from MV, with many requiring prolonged MV.[3] In the US, the overall health-care cost of this latter group of patients is estimated to be more than $16 billion per year.[4] Furthermore, patients requiring prolonged MV are susceptible to a wide range of secondary complications and have excess mortality.[5,6] The current standard of care to wean patients requiring prolonged MV is to have them undergo daily spontaneous breathing trials (SBTs).[7,8] These trials are carried out using a variety of strategies intended to progressively reduce the extent of MV support,[7,8] while encouraging the patient to breathe on their own. These SBTs, which can last anywhere between days[5] and months,[7,8] aim to recondition the respiratory muscles, which are weakened during MV.[9] However, in the most severe cases, patients may never wean from MV.[10] There are currently only a limited number of interventions that can accelerate the process of weaning from MV.

3.1 The Healthcare Problem

The most common indications for MV, as derived from a study of more than 5000 patients in 20 countries,[11] are acute respiratory failure (69%), coma (17%), acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD; 10%), asthma (2%), and neuromuscular disorders (2%). The objectives of MV are to improve gas exchange, relieve respiratory distress and permit lung and airway healing while avoiding complications. [12] Though potentially life-saving, MV can also cause life-threatening complications including barotrauma, ventilator associated pneumonia (VAP), respiratory muscle atrophy, ventilator-associated lung injury and psychological complications such as depression. [12] Accordingly, it is imperative to wean patients from MV in the fastest time possible.[12]

3.2 Why Do Patients Fail To Wean?

In most patients, the primary pathophysiologic mechanism of weaning failure is an imbalance between an excessive respiratory load and reduced respiratory muscle strength (see Figure 1).[13] Increased respiratory load can be caused by an increase in the stiffness and/or resistance of the respiratory system. [12] Increased stiffness can be the result of VAP, pulmonary edema and pulmonary fibrosis and increased resistance can be the result of endobronchial neoplastic pathologies, asthma and COPD, or by the process of weaning itself (either by the presence of the endotracheal tube or due to increased secretions following extubation).[13] Reduced respiratory muscle strength can result from a combination of disuse atrophy/dysfunction, sepsis, polyneuropathy, as well as poor nutrition and medications.[13] Strikingly, recent evidence has shown a 50% decrease in diaphragm muscle fiber cross sectional area after just 18 to 72 hours of controlled MV.[14]

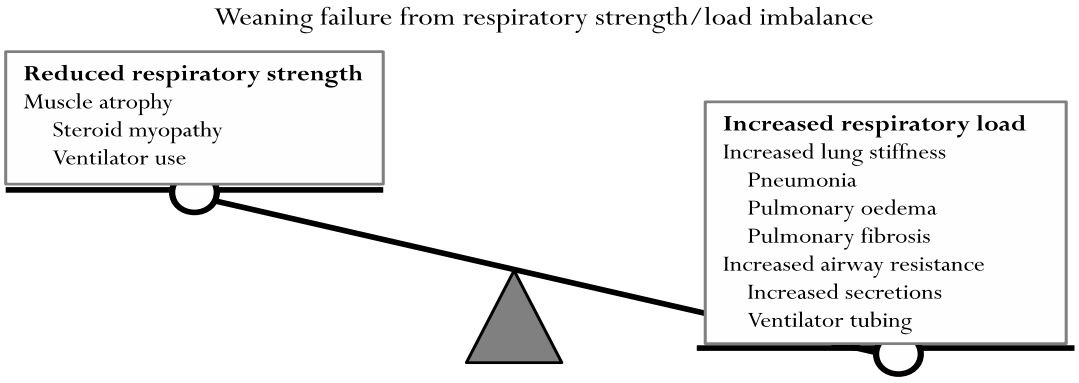

Figure 1 Illustration of the imbalance between an excessive respiratory load and reduced respiratory muscle strength

3.3 Current Standard of Care

A recent international symposium generated guidelines for weaning from MV. These guidelines state that active weaning from MV should commence when the pathology responsible for the institution of MV has been resolved and when the patients are clinically stable. [13] A weaning trial commonly consists of a period of completely unsupported breathing (e.g., T-tube trial) or a period of minimal ventilator support (e.g., pressure support ventilation). If the patient does well during the weaning trial (i.e. is able to comfortably breathe unassisted) he/she is extubated; otherwise, the patient resumes MV. [13]

When patients do not pass the first weaning trial, the potential mechanisms for weaning failure must be identified and addressed.[13] In addition, the aforementioned guidelines suggest implementing daily SBTs, during which the work of breathing accomplished by the ventilator is progressively reduced, and thus, the respiratory muscles weakened during the preceding pre-weaning period of MV are reconditioned.[9,15]

3.4 Unmet Medical Need

To date, a daily SBT is the only intervention used in the weaning of prolonged MV patients. Unfortunately, this process can last anywhere between days[5] and months.[7,8] In the most severe cases, patients never wean from MV.[10] Therefore, novel interventions designed to hasten the weaning process are sorely needed. This is particularly true for patients requiring long-term MV due to their significant healthcare costs and increased risk of morbidity and mortality.[4–6].

4 VentFree

VentFree (Liberate Medical, LLC) is a neuromuscular electrical stimulation (NMES) device that applies transcutaneous electrical stimulation to the abdominal wall muscles (primarily rectus abdominis and external oblique) in synchrony with a patient's voluntary exhalation.

NMES elicits muscle contractions through the delivery of small electrical pulses to motor nerves that supply a given muscle.[16] When NMES is applied to the abdominal wall muscles in synchrony with exhalation, the effect on ventilation is similar to a physiological contraction of the muscles.[17] An important advantage of VentFree, however, is that it can be used to recruit the abdominal wall muscles in the absence of patients' voluntary or automatic recruitment of these muscles (i.e. severe atrophy or paralysis). Accordingly, the VentFree technology provides a convenient and consistent method of producing contractions of the abdominal wall muscles for training/strengthening purposes.

4.1 Study Device

This study will use the VentFree prototype (model number: VF03-K) that consists of a commercially available and FDA cleared neuro muscular electrical stimulator (Continuum, Empi, USA) and a stimulation trigger (designed by Liberate Medical). The disposable components of the device are single patient use and include two sets of 4 cm by 5 cm rectangular stimulation electrodes (PALS Platinum) and a variable orifice pneumotachograph (Braebon). A picture of the device is shown in **Error!**

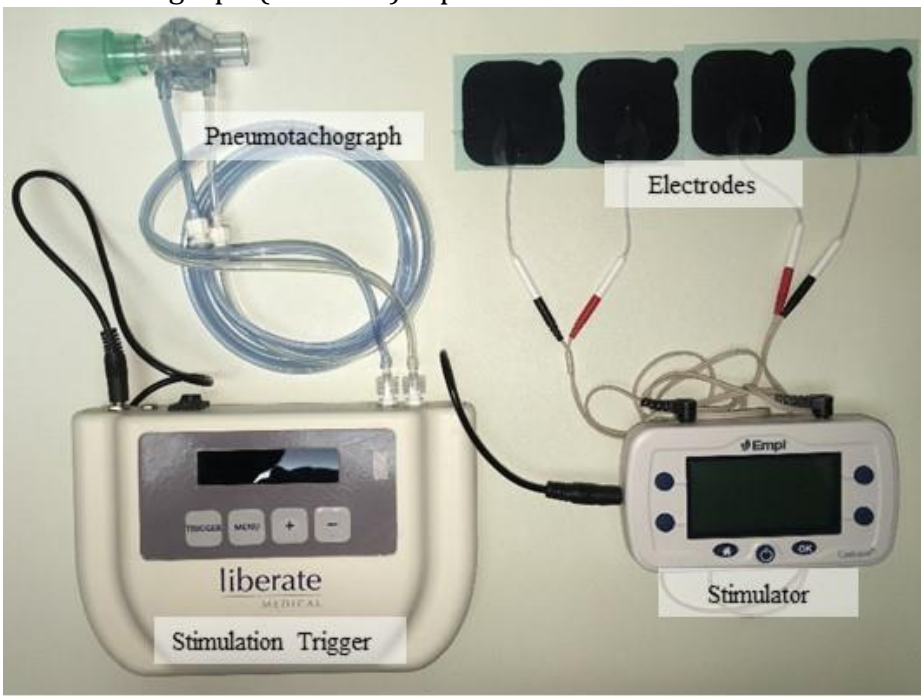

Figure 2 VentFree picture

Reference source not found..

The main features of the device are:

- **Exhalation synchronized stimulation to the abdominal wall muscles** – the device allows the timing and duration of the stimulation burst as well as the parameters of the stimulation pulses to be modified by the user.

- **Expiratory flow limitation test** – this mode of the device records the output of the respiratory sensor for the purposes of conducting an expiratory flow limitation test (see Section 11.8).
- **Compliance monitoring** – the time, date and the duration of each stimulation session is recorded by the device.

4.2 Overview of Clinical Studies

A detailed description of the clinical effects of VentFree is included in the Investigators Brochure. This includes the results from: (1) a structured literature review that evaluated the safety and performance of the effect of abdominal muscle stimulation on respiratory function; (2) four prospective clinical trials of VentFree, which collectively included a total of 52 subjects; and (3) a structured review of muscle stimulation adverse events reported to the Food and Drug Administration, Manufacturer and User Facility Device Experience (MAUDE) database. The main findings from this work includes:

1. AFES in synchrony with exhalation can be used to both acutely improve respiratory function, whereby the user's respiratory function is temporarily improved when they are using the device, and to chronically improve respiratory function, whereby a training intervention of the device results in an improvement in the patient's unassisted respiratory function.
2. Fourteen articles, two Ph.D. theses and all four of Liberate Medical's prospective clinical trials supported the acute effects of AFES. This research showed that during AFES-assisted, compared with unassisted, resting breathing tidal volume and minute ventilation were augmented in healthy subjects, patients with COPD, and patients receiving prolonged MV. In addition, Liberate Medical's trials demonstrated that the AFES-induced augmentation in minute ventilation during resting breathing was associated with a reduction in the inspiratory work of breathing. Lastly, studies in the literature demonstrated that AFES could be used to augment cough peak flow in patients with spinal cord injury.
3. Six articles and two Ph.D. theses investigated the chronic (training) effect of AFES. The majority of these studies included patients with spinal cord injury and they all found that FVC, FEV1 and PEF increased in response to AFES training. Three studies included a follow up period, which ranged from 3 months to 6 months. While these studies indicated that the improvement in respiratory function was maintained after training ceased, the long-term effect of AFES remains to be established.

A small number of adverse events were reported in the literature. These were minor, infrequent and transient in nature. No adverse events have been reported in Liberate Medical clinical studies conducted to date. The FDA MAUDE database included reports of injuries and malfunctions resulting from electrical stimulation devices. The reported adverse events were minor in nature, and no further complications were reported. Based on the available safety information, AFES offers an acceptable safety profile.

The combined results from the prospective clinical trials conducted by Liberate Medical and the literature included in the structured literature review have demonstrated that abdominal stimulation applied in synchrony with exhalation can be used to acutely improve breathing volumes in a range of different patient groups. In addition the studies cited in the literature review indicate that abdominal muscle training using electrical stimulation can be used to improve unassisted respiratory function in SCI and that this improvement is sustained after the cessation of stimulation training. Finally, two studies indicate that abdominal stimulation may be able to be used to assist ventilator weaning. However, additional studies are required to verify the abdominal muscle training results in additional patient groups and to determine the functional benefit of abdominal stimulation for patients.

5 Objectives of the Clinical Investigation

The primary objective of this study is to determine whether NMES applied to the abdominal wall muscles in synchrony with exhalation can increase the strength of the respiratory muscles in prolonged mechanical ventilation patients. If feasible it will be used to design a follow up trial on clinically relevant endpoints.

The secondary objectives of the study is to evaluate whether this intervention also affects: (1) the thickness of the abdominal wall muscles and the diaphragm, (2) functional respiratory measurements, and (3) weaning outcome.

6 Study Design

This is a single center, participant blinded randomized placebo-controlled pilot trial that includes 12 patients in the intervention arm and 12 patients in the placebo arm.

Screening data will be reviewed to determine participant eligibility. Patients who meet all of the inclusion criteria and none of the exclusion criteria and who are willing to participate in the study will be entered into the investigation.

Each participant will receive either active or placebo electrical muscle stimulation to the abdominal wall during exhalation for sixty minutes per day, five days per week for the shorter of six weeks or until the patient is weaned from mechanical ventilation. Participants will be assigned to active or placebo stimulation in random order (using a random number generator). Evaluations will be performed at baseline, after three weeks of treatment and at the end of treatment. A flow diagram of the study protocol is shown in Figure 3.

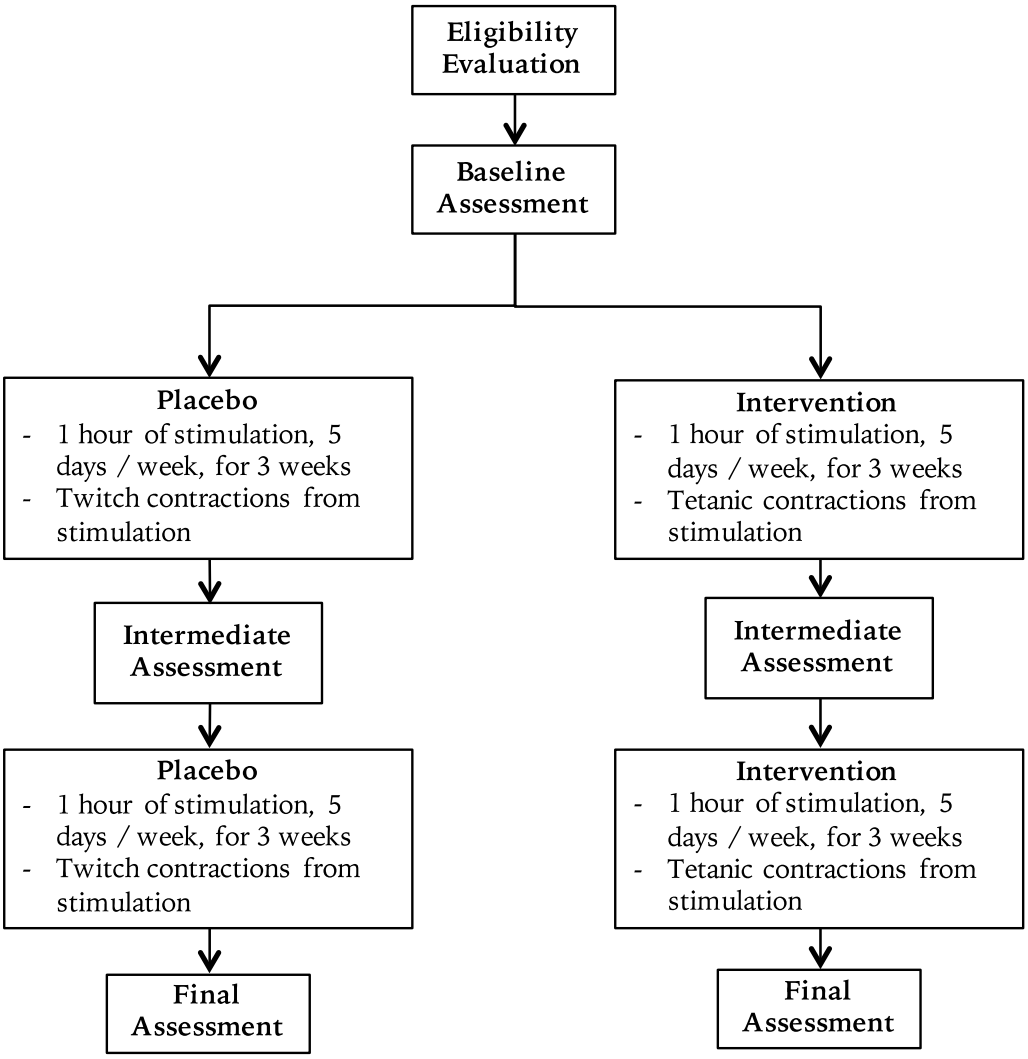

Figure 3 Study Flow Diagram

The maximum duration of participant participation is 45 days. The total duration of the study is expected to be 6 months.

7 Outcome Measures

7.1 Primary Outcome Measures

The primary outcome measure in this study is:

- **Maximum Expiratory and Inspiratory Pressure –** The strength of the inspiratory and expiratory muscles will be assessed using the maximum inspiratory pressure and maximum expiratory pressure test respectively.

7.2 Secondary Outcome Measures

The secondary outcome measures in this study are:

- **Thickness of the Abdominal Wall Muscles** – The end inspiratory and end expiratory thickness of the external oblique, internal oblique and transversus abdominis muscles will be measured using ultrasound.
- **Thickness of the Diaphragm** - The end inspiratory and end expiratory thickness of the diaphragm will be measured using ultrasound.
- **Weaning Success –** Defined as 72 hours of spontaneous respiration without any mechanical ventilation support.
- **Number of Days Taken to Wean** – Defined as the time from the patient's original admission to the point of weaning success.
- **Time spent breathing without mechanical ventilation support** - The time spent breathing without MV support will be recorded on a daily basis throughout the study.
- **Cough Peak Flow –** The peak flow during a voluntary cough will be recorded.
- **Resting Breathing –** This outcome will be assessed using measurements of tidal volume, respiratory rate and minute ventilation during a one-minute period of resting breathing.
- **Adherence to the Weaning Protocol –** The number and duration of the weaning sessions supported by electrical stimulation during the study period will be recorded for each participant.
- **Sensation of Stimulation Experienced by the Patient –** Surface electrical muscle stimulation stimulates sensory nerves in addition to motor nerves and can cause pain at high intensities. The degree of discomfort experienced by participants during stimulation will be quantified using the behavioral pain scale.[18]
- **Adverse Events** – All medical complications experienced by the study participants during the study will be assessed for severity and relationship to the study device and recorded.

8 Participant Selection

8.1 Participant Population

Participants who meet the inclusion and exclusion criteria will be eligible for participation in this study.

8.2 Inclusion Criteria

- Patients who have been mechanically ventilated for more than fourteen days.
- Clinically stable: oxygen saturation > 90% with a fractional inspired oxygen ≤ 0.40, external PEEP ≤ 5 cm H_2O, temperature ranging from 35.5 to 38.5C^o, no intravenous administration of vasoactive agents.

8.3 Exclusion Criteria

- Patients in whom NMES does not elicit a palpable contraction of the abdominal muscles.
- Participants with broken or irritated skin on the abdominal wall.

- History of neuromuscular disease
- Body mass index > 35 kg/m^2
- Patients who are note medically stable
- Participants with a pacemaker
- Female participants who are pregnant
- Patients under the age of 18
- Patients who are expected to die within four weeks
- Patients who are unable to follow verbal instructions
- Patients with epilepsy
- Patients with an abdominal wall hernia
- Patients with anoxic encephalopathy
- Patients with history of, or active, substance abuse

8.4 Patient Recruitment

The research team, including research nurses, principle investigator, and the associate investigators will be responsible for recruitment. Eligible participants will be informed of their eligibility by their clinician. Patients who are interested in taking part will be provided with an information sheet (attached) and advised to discuss the study in further detail with the investigators after taking adequate time to digest the information in the information sheet. Written informed consent will then be obtained from each participant before they take part in the study. However, because MV is a requirement for eligibility, participants will frequently be incapable of informed consent at the time of inclusion. In such cases, we will obtain informed consent from a legally authorized representative making decisions for eligible patients. As the participants recover, they will be evaluated for the capacity by their clinician and when they are deemed to have regained capacity they will be asked to provide informed consent to continue in the study.

Participation is entirely voluntary, with participation in no way affecting the care received. Patients will not be financially compensated in any way for participating in this study.

9 Study Treatments

9.1 Method of Assigning Participants to Treatment Groups

Up to 26 eligible patients will be randomly assigned to either active or placebo stimulation treatment groups in a 1:1 ratio using a computer generated random sequence.

9.2 Blinding

The difference between active and placebo stimulation can be distinguished visually as active stimulation causes a tetanic muscle contraction whereas placebo stimulation causes a sub-tetanic muscle contraction. Therefore study personnel who apply the treatment to subject will not be blinded to study patients' treatment group assignment.

The following procedures will be used to ensure that patients are blinded to the treatment group that they have been assigned to:

- Study personnel will be instructed not to inform patients as to whether a tetanic or twitch contraction is the active or placebo treatment arm of the study.
- The appearance of the active and placebo stimulation devices will be identical.

In addition, all clinical staff not involved in the study and all study personnel who do not apply stimulation to patients will be blinded to the treatment group assignment of participants. This measure will help ensure that decisions to attempt weaning are unrelated to the study and are only based on clinical care.

9.3 Active and Placebo Study Devices

The VentFree prototype (model: VF03-K) will be used for both the active and placebo devices. The active stimulation device's stimulation parameters will be set to cause a tetanic contraction of the abdominal muscles, whereas the placebo stimulation device's stimulation parameters will be set to cause a twitch contraction of the abdominal muscles. All other device parameters will be identical between the two types of devices. The relevant stimulation parameters will be locked on each device so that it is not possible to accidentally change the parameters that distinguish the active devices from the placebo devices.

9.3.1 Active Stimulation Device

The active devices will use the stimulation parameters that were used during Liberate's previous prospective clinical trials. Specifically:

- Stimulation frequency = 30 Hz
- Stimulation pulse width = 350 µs
- Stimulation current = 90 % of the participants tolerated maximum (see Administration Instructions, Section 9.6).
- Stimulation delay = 0.1 seconds after the start of exhalation.
- Stimulation ratio – The stimulation ratio, which determines the duration of stimulation during exhalation as a fraction of the duration of the proceeding inhalation, will initially be set to 0.8. If the study researcher observes that stimulation does not last for the duration of exhalation, then he or she will increase the stimulation ratio. Similarly, if the study researcher believes that the duration of stimulation is too short then he or she will reduce the stimulation ratio.

9.3.2 Placebo Stimulation Device

The placebo devices will use a stimulation frequency of 10 Hz, a stimulation pulse width of 100 µs and a stimulation current of 10mA. The stimulation ratio will be set to 0.8 for all subjects. All other parameters will be set according to the active stimulation device.

9.4 Number of Study Devices

Four stimulation timing controllers (manufactured by Liberate Medical, LLC) will be used for the study. Two devices will be used for the active stimulation group and two devices will be used for the placebo stimulation group. This will allow one operational device and one back up device per treatment group

Four Empi Continuum stimulators will be used for the study. Two devices will be set to deliver active stimulation and two devices will be set to deliver placebo stimulation. This will allow one operational device and one back up device per treatment group. The Empi Continuum is an FDA cleared stimulator for multiple patient use.

Six sets of electrodes will be provided per participant enrolled in the study to enable a new set of electrodes to be used every week that a patient is enrolled in the study. The PALS Platinum electrodes are FDA cleared electrodes that can be used multiple times with a single patient. 132 sets of electrodes will be used in total.

One variable orifice pneumotachograph will be provided per patient enrolled in the study (26 provided in total). The Braebon variable orifice pneumotachographs are FDA cleared and can be used multiple times with a single patient.

9.5 Packaging and Labeling of the Study Devices

Placebo and active stimulators will be able to be distinguished using a colored sticker, placed on the bottom of the device, with the meaning of each color identifiable only to the research team.

9.6 Device Administration

In both of the study arms (active and placebo stimulation), stimulation will be administered for thirty minutes, twice per day, 5 days per week for the shorter of six weeks or until the patient is weaned from mechanical ventilation by one of the two trained study researchers.

9.6.1 Electrode Placement

Adhesive surface electrodes (Pals Platinum, Axelgard, CA) will be placed bilaterally over the posterolateral aspect of the abdominal wall as described by Lim et al.[19] Specifically, one pair of electrodes will be placed from the midline, angled diagonally downward, 2 cm below and parallel to the costal margin, toward the anterior superior iliac spine on each side of the abdomen[19]. A second pair of electrodes (cathodes) will directed from the midaxillary line at the eight thoracic vertebral body level obliquely down toward the posterior superior iliac spine. [19] (The electrodes will be positioned symmetrically on both sides of the abdomen.) [19]

9.6.2 Device Setup

Complete instructions for use will be provided with each study device. In addition, each study researcher will be fully trained by the PI prior to the start of the study. Briefly the following steps will be taken to setup the device:

1. Place the electrodes on the participant's abdomen (described in Section 9.6.1)
2. Connect the electrodes to the stimulator.
3. Connect the variable orifice pneumotachograph to the patient's endotracheal tube.
4. Connect the pneumotachograph's pressure hoses to the stimulation timing controller.
5. Turn on the stimulation timing controller and verify that the timing settings are correct.

9.6.3 Stimulation Session

At the start of the session the study researcher will apply 0.5 second bursts of stimulation starting from stimulation current of 5 mA and progressing in increments of 5 mA for each side of the abdomen until the participant reports that the sensation of stimulation is painful or until a maximum amplitude of 60 mA is reached. This upper limit in stimulation amplitude was based on the maximum tolerated stimulation amplitude found in our preliminary studies. A behavioral pain scale > 4 will be used to determine painful stimulation in patients who are unable to verbally communicate.[18] The researcher will set the stimulation current to 90% of this maximum tolerable level (deemed acceptable in previous clinical studies performed by Liberate) and begin the session by turning on the exhalation synchronized stimulation mode of VentFree.

Throughout the session, heart rate, blood pressure, oxygen saturation and skin irritation will continuously be monitored. Every ten minutes, participants will be asked whether the intensity of abdominal wall muscle stimulation can be increased or should be decreased. During these 10-minute intervals, the investigator will quantify pain using the behavioral pain scale. If signs of distress develop, the investigator will stop the session and the attending physicians will provide immediate medical treatment, as appropriate. Criteria for distress include: a mean arterial blood pressure < 60 mmHg or > 110 mm Hg, heart rate < 40 beats per minute or > 130 beats per minute; respiratory rate > 40 breaths per minute, SpO2 < 90%, score of > 4 on behavioral pain scale[18], agitation or patient request to stop.

9.7 Device Deficiency/Failure

A log will be kept by the research team of any device deficiencies or failures. Such events will be discussed with the sponsor and, where appropriate, a defective device will be repaired and or replaced.

10 Apparatus

The specific apparatus that will be used for the study is described below.

10.1 Mouth Pressure Meter

MIP and MEP will be assessed using a hand-held respiratory pressure meter (MicroRPM, CareFusion, USA or similar). A disposable antimicrobial air filter will be used for each patient at each assessment session.

10.2 Peak Expiratory Flow Meter
PEF will be assessed using a hand-held mechanical peak flow meter. Each patient will be assigned an individual meter. The meter will be disinfected between uses.

11 Study Procedures

11.1 Concomitant Medications
Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured during the Baseline Visit, Intermediate Visit and Final Visit. No medications will be restricted as part of this study.

11.2 Demographics
Demographic information (date of birth, gender, race) will be recorded during the Baseline Visit.

11.3 Medical History
Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded during the Baseline Visit.

11.4 Physical Examination
A complete physical examination will be performed at the Baseline Visit.

11.5 Vital Signs
Body temperature, blood pressure, pulse and respiratory rate will be recorded after resting for 5 minutes at the Baseline Visit, Intermediate Visit, and Final Visit.

11.6 Oximetry
Oximetry will be measured on fraction of inspired oxygen set by the treating physician with the participant at rest at the Baseline Visit, Intermediate Visit, and Final Visit.

11.7 Acute Physiology and Chronic Health Evaluation
The Acute Physiology and Chronic Health Evaluation II (APACHE II) score will be calculated by a study investigator at the Baseline Visit.

11.8 Expiratory Flow Limitation
The presence of expiratory flow limitation will be evaluated at the Baseline Visit using manual compression of the abdominal wall as described by Ninane et al. [20] During this maneuver, subjects will be asked to breathe through the VentFree pneumotachograph while the device is in expiratory flow limitation mode. The gentle manual compressions of the abdomen tests will be performed when subjects show regular breathing. For this purpose, the investigator will put one hand gently on the abdominal wall of the subject with the palm on the umbilicus oriented perpendicular to the axis between the xiphoid process and the pubis. Gentle palpation of the abdomen during two or three breathing cycles will easily allow recognition of the expiratory phase. The investigator will then inform the subject that he/she was soon going to push

on the abdominal wall. The gentle compression will be maintained throughout expiration and afterwards the investigator will remove his/her hand. If expiratory flow limitation is present, the gentle manual compressions of the abdomen will not increase expiratory flow either during the whole tidal exhalation or during part of it. On the other hand, if expiratory flow is absent, the gentle manual compressions of the abdomen will increase expiratory flow during exhalation. Gentle manual compressions of the abdomen are known to be well tolerated without untoward effects.

11.9 Maximum Expiratory Pressure and Maximum Inspiratory Pressure

Maximum Expiratory Pressure (MEP) and Maximum Inspiratory Pressure (MIP) will be measured at the Baseline Visit, Intermediate Visit, and Final Visit using a cuff inflated cannula as described by Vitacca et al. [21]

11.10 Thickness of the Abdominal Wall Muscles

The end inspiratory and the end expiratory thickness of the external oblique, internal oblique and transversus abdominis muscles will be measured using ultrasound[22] at the Baseline Visit, Intermediate Visit and Final Visit.

11.11 Thickness of the Diaphragm

The end inspiratory and the end expiratory thickness of the diaphragm will be measured using ultrasound[22] at the Baseline Visit, Intermediate Visit and Final Visit.

11.12 Cough Peak Flow

CPF will be measured at the Baseline Visit, Intermediate Visit, and Final Visit through a deflated cuff as described by Winck et al.[23]

11.13 Sensation of Stimulation

The participant's sensation of stimulation will be measured using the behavioral pain scale every five minutes while receiving electrical muscle stimulation.

11.14 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study device will be recorded on the case report form (CRF).

11.15 Measures of Treatment Compliance

The study treatment devices will automatically record the date, time and duration of stimulation for an individual patient to a memory card.

12 Study Schedule

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1. A description of each procedure is provided in Section 11.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the participant.

12.1 Baseline Visit - Day 1

On day 1 the investigators will review the study with the participant and obtain written informed consent and HIPAA authorization. After consent has been obtained they will record the patient's demographic data, medical history and concomitant medications.

The investigators will determine if the patient meets the study inclusion and exclusion criteria. If the patient does not meet the criteria then no further procedures will be performed and they will be withdrawn from the study. If the patient does meet the criteria then the investigator will randomize the patient to a treatment group.

The study researcher will record their vital signs, oximetry, expiratory flow limitation, APACHE II score, MIP, MEP, thickness of the abdominal wall muscles and diaphragm, CPF and resting breathing parameters.

12.2 Stimulation Visits – Days 2 - 22

Patients will participate in Stimulation Visits two 2 per day in 5 days every week. Specifically, patients will participate in morning and afternoon Stimulation Visits 5 times between days 2 and 8, 5 times between days 9 and 15 and 5 times between days 15 and 22.

The investigators will administer sixty minutes of stimulation to the participant as described in Section 9.6. In addition, the investigators will record adverse events related to stimulation or otherwise.

12.3 Intermediate Visit – Day 23

The Intermediate Visit will ideally take place on day 21. However, if necessary the Intermediate Visit may be conducted no earlier than day 20 and no later than day 25, providing that it occurs after 15 Stimulation Visits.

At the start of the visit the investigators will measure MEP, MIP, CPF, thickness of the abdominal wall muscles and diaphragm, resting breathing parameters, changes to medications and adverse events related to stimulation or otherwise.

12.4 Stimulation Visits – Days 24 – 44

Patients will participate in a Stimulation Visits 2 times per day in 5 days every week. Specifically, patients will participate in morning and afternoon Stimulation Visits 5 times between days 24 and 30, 5 times between days 31 and 37 and 5 times between days 38 and 44.

The stimulation session will then continue as described in Section 9.6. In addition, the investigators will record adverse events related to stimulation or otherwise.

12.5 Final Visit – Day 45

The Final Visit will ideally take place on day 45. However, if necessary the Final Visit may be moved no earlier than day 43, providing that it occurs 15 Stimulation Visits after the Intermediate Visit, and no later than day 47.

During this visit the investigators will record the participant's MEP, MIP, thickness of the abdominal wall muscles and diaphragm, CPF, resting breathing parameters and adverse events related to stimulation or otherwise.

12.6 Early Withdrawal Visit

In the case that the patient withdraws or is withdrawn from the protocol (see Section 14) before the end of the intervention period, and providing the patient consents, then the investigators will perform and record the participant's MEP, MIP, thickness of the abdominal wall muscles and diaphragm, CPF, resting breathing parameters and adverse events related to stimulation or otherwise.

If the participant is withdrawn from the study because they have successfully weaned from mechanical ventilation then the study researcher will also calculate and record the number of days taken to wean taken from the institution of mechanical ventilation.

13 Adverse Experience Reporting and Documentation

13.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered an investigational product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure (attached) or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the participant, for the occurrence of AEs during each participant visit and record the information in the site's source documents. AEs will be recorded in the patient CRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for AEs (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory

abnormalities judged to be clinically significant. The guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1 AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Device

The relationship of an AE to the study device should be assessed using the following the guidelines in Table 2.

Table 2 AE Relationship to Study Device

Relationship to Device	Comment
Definitely	Previously known adverse event; or an event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to the suspected device; that is confirmed by stopping administration of the device; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to the suspected device; that is confirmed by stopping the administration of the device; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to that suspected device; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study device.

13.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization

- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

13.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study device). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

13.3 Medical Monitoring

Dr Franco Laghi should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (708) 528-1807
Pager: (708) 216-8777 x :13312

14 Discontinuation And Replacement of participants

14.1 Withdrawal of Participants from the Study

A participant may be withdrawn from study treatment at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Successful weaning from mechanical ventilation
- Participant withdrawal of consent
- Participant is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the PI until the abnormal parameter or symptom has resolved or stabilized.

All participants who discontinue study treatment should come in for an early discontinuation visit as soon as possible.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. This will not affect the care they receive, now or in the future.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents.

12.3 Replacement of Participants

While it is estimated that 24 is a suitable sample size for this study, the actual study sample size of 26 allows for a 10% drop out rate. Therefore, up to two participants who withdraw from the study will be replaced.

15 Protocol Violations

A protocol violation occurs when the participant, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a participant.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

16 Protocol Amendments

Amendments to the clinical investigation plan must be submitted to the Sponsor for review before submitting to the appropriate IRB for approval.

17 Statistical Methods and Considerations

Only participants who fulfil the protocol in terms of eligibility, interventions and outcome assessment will be included in the statistical analysis. Patient variables will be presented using means and standard deviations for continuous normally distributed variables, medians and interquartile ranges for continuous non-normally distributed variables, and proportions and absolute numbers for categorical variables.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study treatment.

Study results will first undergo descriptive level statistical analyses. For continuous variables, Two-way, Student's t-tests will then be carried out using unequal variances where the variables are normally distributed. Tests for normality will be carried out using the Shapiro-Wilk method. Variables that are not normal in distribution that also cannot be log transformed to a normal distribution curve will be analysed using the Mann-Whitney U test or other non-parametric methods to be determined based on actual data distributions.

In the second level of analysis, we will quantify the magnitude to which abdominal NMES exhibits a protective effect. Crude and adjusted linear regression models will be carried out where the outcome variable is continuous and the covariates are normally distributed or categorical. Our prior experience with measures of respiratory function, which will be measured in this study, indicate that select covariates may need to be controlled for or otherwise do not always fit a normal distribution. Therefore, crude and adjusted generalized linear models are anticipated. These regression models will be carried out at the point of successful wean. All multiple regression covariates, linear or generalized, will be assessed for interaction, collinearity and confounding. For all unadjusted and adjusted multinomial models the overall model log likelihood ratio and Hosmer and Lameshow goodness-of-fit will be conducted to ensure models report significance and are not over fitted. Adjusted regression models will undergo sensitivity analysis and bootstrap analyses. Bootstrap analysis is a re-sampling strategy to estimate the population parameter of interest based on the observed, sample data.

The number of tries to successful wean will be quantified using Poisson regression. Crude and adjusted models will be carried out. Kaplan-Meier survival analysis will be carried out to quantify differences in the time to wean in the treatment abdominal NMES modality compared to the control. As the patients will be resident in hospital facilities, we do not anticipate significant methodological concerns with respect to censoring.

17.1 Sample Size

This study is intended to be a pilot study that will be used to obtain initial data on the feasibility and safety of VentFree to assist in the process of ventilator weaning. The primary outcome of this study is the effect of abdominal NMES on respiratory muscle strength over time. There is currently no data in the literature to support a sample size calculation for this study. Given this constraint, in this pilot study a total of 24 participants was deemed adequate and is consistent with sample size recommendations in the literature.[1] Allowing for a 10% drop out rate, up to 26 participants will be recruited for this study. The data collected on the secondary endpoints will be used to determine the participants needed for a future randomized controlled trial of the device on weaning outcome.

18 Data Collection, Retention and Monitoring

18.1 Data Collection Instruments

The PI and his research associates will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study treatment.

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific paper case report form (CRF) when the information corresponding to that visit is available. Participants will not be identified by name on any study documents to be collected by the Sponsor (or designee), but will be identified by a participant number and initials.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The PI and his research associates are responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

18.2 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following the completion of the study. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

18.3 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

18.4 Participant Confidentiality

Research personnel will have access to all study records, which may include patient identifiable information. In order to maintain participant confidentiality, only a

participant number and participant initials will identify all study participants on CRFs and other documentation submitted to the Sponsor.

Physical copies of study records will be kept in a locked office. Electronic versions of study records will be kept on a password protected computer.

Data collected during this study will not be used for any other purpose than that for which the subjects consented.

Additional participant confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

19 Statement of Compliance

This study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the ICH Guidelines for GCP (E6) and ISO 14155:2011 clinical investigations of medical devices for human subjects – good clinical practice.

20 Publication Policy

Data obtained from the current study will be submitted for publication to an international peer reviewed journal.

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22 APPENDIX A: SCHEDULE OF EVENTS

	Baseline Day 1	**Stimulation Visits** Days 2 - 22	**Intermediate Visit** Day 23	**Stimulation Visits** Days 24 - 44	**Final Visit** Day 45	**Early Withdrawal**
Informed Consent	X					
Randomization	X					
Medical History	X					
Concomitant Medications	X		X		X	X
Complete Physical Exam	X					
Height	X					
Weight	X					
Vital Signs	X					
Oximetry	X					
Expiratory Flow Limitation	X					
APACHE II	X					
Maximum Expiratory Pressure	X		X		X	X
Maximum Inspiratory Pressure	X		X		X	X
Abdominal Wall Thickness	X		X		X	
Diaphragm Thickness	X		X		X	
Cough Peak Flow	X		X		X	X
Tidal Volume	X		X		X	X
Respiratory Rate	X		X		X	X
Minute Ventilation	X		X		X	X
Administration of Stimulation		X		X		
Sensation of Stimulation		X		X		
Adverse Events	X	X	X	X	X	X
Time spent breathing without mechanical ventilation support	X	X	X	X	X	X
Number of Days Taken to Wean						X