PEPNS Study Statistical Analysis Plan

REVISION HISTORY

Revision	CCO	Description	Originator	Date
1	C2019-003	Initial release of document	J. O'Mahony	19-Mar-2019

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1. INTRODUCTION

The purpose of the Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) Study Statistical Analysis Plan (SAP) SAP0001 is to describe the statistical techniques and data analysis for the CIP0001 PEPNS System Feasibility Study in detail. The SAP defines all the statistical output and data analysis which will be included in the corresponding clinical study report (CIR0001).

The objective of the PEPNS study is to test the safety, feasibility and impact of temporary bilateral Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) on user specified periodic breaths during mechanical ventilation. The ability to control work of breathing (WOB) and synchronize electrical stimulation to mobilize the diaphragm during inspiration will be examined.

DATA SOURCE

Data will be analyzed from two main sources:

1. The Labchart files that log data in real time at 1000Hz Qwye, Pwye, WOB, Stim Signal and Trig Signal.
2. Clinical Report Forms.

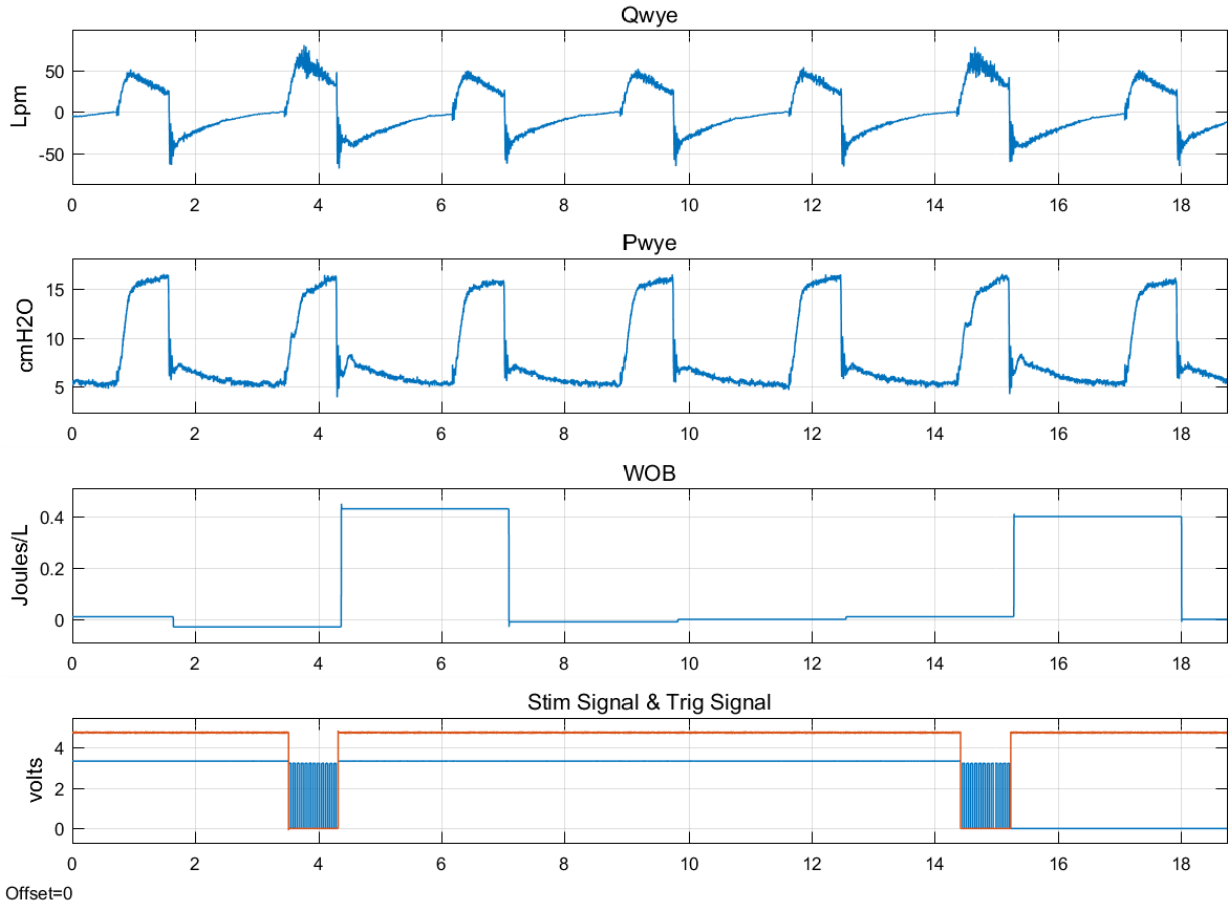

Figure 1: Shows the data acquired by ADInstruments Labchart at 1kHz sample rate. Trace 1 shows Qwye in Lpm, Trace 2 Pwye in cmH2O, Trace 3 WOB in Joules/L and Trace 4 the Stim Signal and Trig Signal in volts. This data is extracted from P07S02 in CPAP.

Table 1: Includes a Summary of All Patients Treated and Therapy Times

Patient	File name	Therapy Start Time	Therapy End Time	Diff Time
P01	P01Beaumont102209082018_Stim#1	2:22:15	4:22:15	2:00:00
	P01Beaumont182209082018_Stim#2	4:22:15	6:22:15	2:00:00
	P01Beaumont003709092018_Stim#3	0:37:05	2:37:05	2:00:00
	P01Beaumont085309092018_Stim#4	8:53:20	10:53:20	2:00:00
	P01Beaumont162809092018_Stim#5	16:28:00	18:46:00	2:18:00
	P01Beaumont024709102018_Stim#6	0:36:39	2:47:00	2:10:21
P02	P02Beaumont10062018 1013 stim1	10:13:00	12:17:00	2:04:00
	P02Beaumont10062018 1813 stim2	18:13:00	20:13:00	2:00:00
	P02Beaumont10072018 0220 stim3b	2:20:53	4:23:00	2:02:07
	P02Beaumont10072018 1050 stim 4th	10:53:16	12:50:55	1:57:39
	P02Beaumont10072018 2000 stim 5th	8:04:45	10:05:45	2:01:00
	P02Beaumont10082018 0500 stim 6th	5:17:40	7:21:00	2:03:20
P03	P03S01_7Nov2018_Stim Session1_1721_1922	10:21:00	12:22:00	2:01:00
	P03S01_7Nov2018_Stim Session2_0201_0407	7:01:00	9:07:20	2:06:20
	P03S01_8Nov2018_Stim Session3_0941_1144	2:41:09	4:43:52	2:02:43
	P03S01_8Nov2018_Stim Session4_1736_1936	10:36:40	12:37:02	2:00:22
	P03S01_9Nov2018_Stim Session5_0125_0328	18:25:28	20:28:44	2:03:16
	P03S01_9Nov2018_Stim Session6_0940_1142	2:40:21	4:41:20	2:00:59
P04	P04S01_11Nov2018_Stim Session1_1149_1350	4:49:00	6:50:00	2:01:00
	P04S01_11Nov2018_Stim Session2_1911_2111	13:11:00	15:11:00	2:00:00
	P04S01_11Nov2018_Stim Session3_0611_0811	23:11:00	1:11:00	2:00:00
	P04S01_11Nov2018_Stim Session4_1408_1608	7:08:20	9:08:46	2:00:26
	P04S01_11Nov2018_Stim Session5_2214_0014	15:14:20	17:14:13	1:59:53
	P04S01_11Nov2018_Stim Session6_0630_0833	23:31:10	1:33:51	2:02:41
P05	P05S02 Stim#1 0000_0200 16Nov18	0:00:00	2:00:24	2:00:24
	P05S02 Stim#2 1327_1528 16Nov18 Long due to recapture efforts	13:27:00	15:28:00	2:01:00
	P05S02 Stim#3 1633_1830 16Nov18	16:33:00	18:30:56	1:57:56
	P05S02 Stim#4 0041 0246 17Nov18	0:41:00	2:46:00	2:05:00
	P05S02 Stim#5 0844 1045 17Nov18	8:44:00	10:45:00	2:01:00
	P05S02 Stim#6 1628 1831 17Nov18	16:28:00	18:30:00	2:02:00
P06	P06S02 Stim#1 0156-0356	1:59:00	3:59:17	2:00:17
	P06S02 Stim#2 1155-1355	11:55:00	13:55:08	2:00:08
	P06S02 Stim#3 2054-2258	20:54:17	22:58:00	2:03:43
	P06S02 Stim#4 0552-0801	5:52:00	8:01:00	2:09:00
	P06S02 Stim#5 2136-2336	21:36	23:36:00	2:00:00
	P06S02 Stim#6 0243-0243	2:43:00	4:44:00	2:01:00
P07	P07S02 Stim#1 2345-0145	23:47:30	1:47:30	2:00:00

Patient	File name	Therapy Start Time	Therapy End Time	Diff Time
	P07S02 Stim#2 0544-0744	5:44:00	7:44:00	2:00:00
	P07S02 Stim#3 1311-1510	13:11:18	15:10:00	1:58:42
	P07S02 Stim#4 2208-0008	22:08:00	0:09:43	2:01:43
	P07S02 Stim#5 0540-0740	5:40:13	7:40:24	2:00:11
	P07S02 Stim#6 1347-1551	13:47:09	15:52:10	2:05:01
P08	P08S01 Stim#1 1836-2036	18:37:00	20:37:19	2:00:19
	P08S01 Stim#2 2212-0012	22:12:00	0:12:00	2:00:00
	P08S01 Stim#3 0817-1017	8:17:00	10:17:16	2:00:16
	P08S01 Stim#4 1511-1713	15:11:00	17:14:25	2:03:25
	P08S01 Stim#5 2212-0012	22:12:00	0:12:00	2:00:00
	P08S01 Stim#6 0811-1013	8:12:56	10:15:32	2:02:36
P09	P09S02 Stim#1 0348-0548 25Jan19	3:48:40	5:48:40	2:00:00
	P09S02 Stim#2 1353-1553 25Jan19	13:53:02	15:53:03	2:00:01
	P09S02 Stim#3 0111-0318 26Jan19	1:11:56	3:18:45	2:06:49
	P09S02 Stim#4 1007-1207 26Jan19	10:06:58	12:07:45	2:00:47
	P09S02 Stim#5 1905-2105 26Jan19	19:05:18	21:05:47	2:00:29
	P09S02 Stim#6 0135-0335 27Jan19	1:36:17	3:36:06	1:59:49
P10	P10S02 Stim#1 06Feb19 0126-0326	1:26:50	3:27:08	2:00:18
	P10S02 Stim#2 06Feb19 1230-1430	12:31:21	14:31:00	1:59:39
	P10S02 Stim#3 06Feb19 1820-2020	18:19:59	20:20:41	2:00:42
	P10S02 Stim#4 06-07Feb19 2230-0030	12:28:37	0:33:01	2:05:34
	P10S02 Stim#5 07Feb19 1159-1359	11:58:54	13:59:47	2:00:53
	P10S02 Stim#6 07Feb19 2140-2342	21:39:56	23:42:44	2:02:48
P11	P11S01 Stim#1 1817-2017	18:09:10	20:17:19	2:08:09
	P11S01 Stim#2 2221-0009	22:21:35	0:09:00	1:48:25
	P11S01 Stim#3 0820-1020 9Feb19	8:20:01	10:21:24	2:01:23
	P11S01 Stim#4 1458-1707 9Feb19	14:58:34	17:07:40	2:09:06
	P11S01 Stim#5 2211-0011 09-10Feb19	22:11:07	0:12:57	2:01:50
	P11S01 Stim#6 0822-1022 10Feb19	8:22:07	10:22:42	2:00:35
P12	P12S01 Stim#1 12Feb19 1135-1335	11:35:34	13:36:38	2:01:04
	P12S01 Stim#2 12Feb19 1920-2125	19:20:20	21:25:06	2:04:46
	P12S01 Stim#3 12-13Feb19 2210-0010	22:10:41	0:11:00	2:00:19
	P12S01 Stim#4 13Feb19 0755-0955	7:54:19	9:56:10	2:01:51
	P12S01 Stim#5 13Feb19 1423-1623	14:23:28	16:24:13	2:00:45
	P12S01 Stim#6 13-14Feb19 2205-0005	22:05:15	0:05:15	2:00:00

The following data forms will be transferred by Stimdia into an Excel data base which will be an electronic duplicate of the paper clinical research form. Scanned copies of the original data will be available for review alongside the electronic data entry forms. This data will be tested for transfer accuracy by both

quality and clinical personnel to ensure correctness. Only forms that were necessary to fill will be transferred and assessed. For instance, if an adverse event did not occur then this form will not be populated.

Table 2: Case Report Forms

Case Report Forms	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10	P11	P12
CRF0001	x	x	x	x	x	x	x	x	x	x	x	x
CRF0002	x	x	x	x	x	x	x	x	x	x	x	x
CRF0003	x	x	x	x	x	x	x	x	x	x	x	x
CRF0004	x	x	x	x	x	x	x	x	x	x	x	x
CRF0005	x	x	x	x	x	x	x	x	x	x	x	x
CRF0006	x	x	x	x	x	x	x	x	x	x	x	x
CRF0007	x	x	x	x	x	x	x	x	x	x	x	x
CRF0008	x	x	x	x	x	x	x	x	x	x	x	x
CRF0009	x	x	x	x	x	x	x	x	x	x	x	x
CRF0010	x	x	x	x	x	x	x	x	x	x	x	x
CRF0011	x	x	x	x	x	x	x	x	x	x	x	x
CRF0012	x	x	x	x	x	x	x	x	x	x	x	x
CRF0013	x	x	x	x	x	x	x	x	x	x	x	x
CRF0014	x	x	x	x	x	x	x	x	x	x	x	x
CRF0015	x	x	x	x	x	x	x	x	x	x	x	x
CRF0016	x	x	x	x	x	x	x	x	x	x	x	x
CRF0017	x	x	x	x	x	x	x	x	x	x	x	x

2. ANALYSIS OBJECTIVES

The company informed the FDA of plans to conduct a First in Human feasibility study within an OUS Tier I country (Canada, Europe or Australia) and stated:

As part of this study the following would be evaluated

a) Confirmation of the stimulation leads are easily deployed under ultrasound guidance
b) Confirmation that the diaphragm is easily stimulated without collateral stimulation similar to the Taira publication in references.
c) Confirmation of appropriate candidates for a pivotal study. Trending demonstrating that time to extubation is decreased when compared to historical data in similar patient population.

The first two patients enrolled in the trial will be analyzed specifically for safety of the procedure in terms of nerve damage which could result from electrical stimulation or mechanical damage due to lead insertion, patient movement or lead removal and any other adverse events. Compound motor action potential and nerve conduction time between the neck and diaphragm will be evaluated in the first two pilot patients. Since these patients are stimulated on the left phrenic nerve only, they will be included for the safety analysis only. The enrollment of subsequent patients was contingent upon these patients showing no damage to the phrenic nerve at ~30 days post stimulation in terms of the CMAP study, follow up x-ray and any reported adverse events deemed relevant to the procedure.

Primary and secondary endpoints for the study will be evaluated statistically in terms of per protocol (PP) and intent-to-treat (ITT) analysis. The clinical study protocol CIP0001 defined intent-to-treat as “All patients that were attempted to be treated with the PEPNS System but the procedure was aborted.” The

primary analysis will be per protocol and the secondary analysis will be intent-to-treat. Time of weaning from mechanical ventilation and diaphragm thickness from 0 to 48 hours will also be analyzed.

In addition, there may be additional analyses conducted and other tables and graphs created for the final clinical study report based on the outcomes of the initial analyses and additional data points of interest.

An interim analysis may be run and this was allowed in the protocol. See Statistical Methodology section for greater details.

PRIMARY ENDPOINTS

The primary endpoints for the study relate to the ability of the therapy to mobilize the diaphragm and of the PEPNS system to stimulate specific levels of work of breathing.

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

The capture of the left and right phrenic nerve will be demonstrated during setup and by maintaining the WOB between 0.2 and 2 Joules/L. The stimulation voltage resultant from the tissue impedance and the user set current will be logged and evaluated to ensure it is less than 10.5 volts. Capture will also be evaluated in terms of synchrony.

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

Model:

capture = (timepoint) (subject)

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

Capture for this analysis is defined as synchrony of the stimulated breath with the output parameter < 10.5 volts and WOB between 0.2 and 2.0 Joules/L. Synchrony will be achieved if the lag time between start of inspiration and start of stimulation is less than 88 ms.

Hypothesis:

H_o: The proportion of capture is less than or equal to the performance goal (PG) of 80%. Note: This hypothesis used a 90% performance goal in the protocol for the purposes of sample size calculation to ensure that there would be sufficient data to achieve the 80% performance goal when taking into account lost to follow up due to death, etc.

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

H_A: The proportion of capture is greater than the performance goal of 80%.

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

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

Sample Size:

This sample size calculation reflects the use of a 90% performance goal as noted above in the hypothesis section and in the CIP. Again, this was done to ensure that there would be sufficient data to achieve the 80% performance goal when taking into account lost to follow up due to death, etc. The following

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

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

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

Methods:

The proportion of successful capture will be analyzed using a logistic regression model accounting for patient as a random effect. The null hypothesis will be tested comparing the lower bound of the 95% two-sided confidence interval for the estimated percent agreement to the performance goal of 80% (see note above). If the lower bound is greater than 80%, the null hypothesis will be rejected and the endpoint will be considered met.

If the logistic regression model does not converge (i.e. it does not provide reliable estimates of diaphragm capture), other methods will be used to characterize the capture rate. The method used will be dependent on the data and will be described in detail along with the reasons for using that method.

An interim analysis of the primary endpoints may be done on the first 10 patients that were stimulated on both phrenic nerves. If they are met the secondary and other remaining analyses will also be performed. If not, the study will continue to enroll patients and all study endpoints and additional analyses will be analyzed when enrollment has been completed. If an interim analysis is done, the significance level used for testing will be 0.0125. At the final analysis (if needed) the significance level used for testing will be 0.0194. These levels were derived using a power cumulative error spending function with the parameter (rho) set to 1.0. This setting produces Pocock type boundaries (i.e. approximately equal spending for the two tests).

If an interim analysis is not done, the final analysis will use a significance level of 0.025 for testing the primary endpoints.

SECONDARY ENDPOINTS

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

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

Safe and Successful Lead Placement

The percentage of patients who received safe and successful placement of the multipolar lead on the Left and right phrenic nerve utilizing ultrasound guidance will be evaluated in terms of the mean and standard deviation for preparation, placement, securement, removal and twitching. Twitching includes neck spasms, arm movement, shoulder movement on unwanted visible stimulation. This will be reviewed on a site basis, by neck circumference and BMI.

Adverse Events

The percentage of patients who experience one or more serious device/procedure-related adverse events during the study will be reported. The evaluation results for the follow-up x-ray will also be noted.

Stim and Vent Synchrony

The phrenic nerve stimulation in synchrony with Mechanical Ventilation (MV) breaths will be measured to verify that it occurs with inspiration over all of the stimulated breaths for each of the patients. The synchrony on the detection of inspiration and expiration will be compared against the user set trigger flow section and compared to a fast trigger time which has been reported as 88 msecs.

Related Evaluations

Critical Care Pain Observation Tool (CPOT) assessments are made on all patients enrolled and will be reported before during and after stimulation on all patients. The pain assessment tool, CPOT, is based on four domains: the patient's facial expressions, body movements, compliance with ventilator (or voice use for non-intubated patients), and muscle tension. Each domain has a possible score of 0 to 2. The total score can vary between 0 and 8, where 0 indicates no pain behavior and 8 indicates clear signs of pain behavior.

Richmond Agitation and Sedation Scale (RASS) scores will be reported on all patients. The RASS measures agitation and sedation level, the score ranging from +4 to –5, where a score of 0 indicates an awake and adequate patient. Scores from –1 to –5 indicate an increasingly sedated patient, and scores from +1 to +4 indicate an increasingly irritable and agitated patient.

The CPOT and RASS scores will be evaluated to determine that the stimulation does not cause pain to the patient.

An assessment will be made to determine the sensitivity of the lead to patient position. Patient will be repositioned every 2 to 4hrs per hospital protocol and disease diagnosis requirements. Leads will be disconnected from the electrical stimulator using the extension lead during these non-stim periods. Reestablishing stimulation after reconnection will be evaluated along with the ability of the system to handle patient repositioning.

Vitals signs and blood gasses will be evaluated to determine if electrical stimulation does not have an untoward effect on patient. This will be evaluated by an expert in ICU ventilation / blood gas analysis.

ECG (electrocardiogram) will be reviewed before during and after electrical stimulation to ensure electrical stimulation is not adversely affecting the heart. This will be evaluated by an expert in the reading of ECGs.

Table 3: Patient Vitals and PEPNS Data

Patient ID	Age (yrs)	Weight (kg)	Height (cm)	Body Mass Index (BMI)	IJ Line (Y/N)	ET / Trach (E/T)	Neck circumfer-ence at the cricoid cartilage (cm)	Screening Blood Pressure	PEPNS System Lead Prepara-tion	PEPNS System Lead Place-ment	PEPNS System Lead Secure-ment	Lead Removal/ Skin Closure Assess-ment	Twitching?	Follow-up X-Ray Normal?	Adverse Events?	Device Malfunctions?
P03S01																
P04S01																
P05S02																
P06S02																
P07S02																
P08S01																
P09S02																
P10S02																
P11S01																
P12S02																
								Mean								
								Stdev								

ADDITIONAL EVALUATIONS

Briefly state the overall scientific objectives of the analyses, including the key unanswered questions that these analyses are designed to address. If necessary, provide additional detail to formulate the objectives in statistical terms. Include a brief summary of how each objective will be addressed in the analyses.

The clinical effect of electrical stimulation will also be examined for the following:

- Time to weaning from mechanical ventilation data.
- Diaphragm thickness at 0, 24 and 48 hours.

The period of time each patient was on ventilation before electrical stimulation and the time to wean will be reported. The number of attempts to wean the patient before and after electrical stimulation will also be reported, if available.

The trend in diaphragm thickness increase/decrease for each patient and the aggregation of patients will be evaluated over time. The trend in diaphragm thickness based upon its initial thickness will also be evaluated. Correlations in diaphragm thickness increase and neck circumference will also be reviewed.

3. ANALYSIS SETS/ POPULATIONS/SUBGROUPS

The only analysis populations that will be analyzed in this SAP are per protocol population as the primary analysis and intent-to-treat population as the secondary analysis. No other populations will be statistically analyzed since it is too small a data set to assess other subgroups.

There will be summary tables created for patient demographics. In general, summary statistics will include the mean, median, standard deviation, minimum and maximum for continuous measures and the number and frequency for categorical measures. This summary data will be reviewed to see if there are any trends that may have impacted study endpoints.

4. ENDPOINTS AND COVARIATES

There will be summary tables created for baseline and 30-day follow-up results. In general, summary statistics will include the mean, median, standard deviation, minimum and maximum for continuous measures and the number and frequency for categorical measures. This summary data will be reviewed to see if there are any trends that may have impacted study endpoints.

5. HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

The per protocol primary analysis will include all of the patients and all of the data garnered for them, as applicable. If there is sufficient data available, some additional analyses may be run that only includes patients that had no missing data or that were stimulated on both sides or that were stimulated only on one side to see if there was any impact on study results.

6. STATISTICAL METHODOLOGY

STATISTICAL PROCEDURES

The primary statistical methods used in this study will be descriptive where continuous variable will be summarized using means, medians, standard deviation, minimums and maximums and categorical variables will be summarized using frequencies and percent for each categorical level.

The primary endpoint will be analyzed using a logistic regression where diaphragm capture (yes/no) is the dependent variable and time point and subject are the independent fixed effect and random effect predictors. The point estimate of the diaphragm capture rate will be estimated from logistic regression model along with a two-sided 95% confidence interval. The lower bound of that confidence interval will be compared to the performance goal of 80%. If the lower bound is above 80%, then the endpoint will have been achieved.

Secondary endpoints will be summarized as noted in the secondary endpoints section. Each endpoint will be summarized descriptively.

Additional evaluations will also be summarized descriptively. In addition, diaphragm thickness over time will be modeled using regression analysis. The slope parameter and 95% confidence intervals will be presented. Additional diaphragm thickness analyses may be run.

If an interim analysis is performed, the database will be temporarily locked at the time of the interim analysis and the clinical study report will include the date that the data was transferred from the database to the statistician for the interim analysis. It will also specify whether or not the data had been monitored. The secondary end points and other remaining interim analyses will only be performed if the primary endpoints were met. If not, the study will continue to enroll patients and all study endpoints and additional analyses will be analyzed when enrollment has been completed. At the interim analysis the significance level used for testing will be 0.0125 which translates into calculating a 98.75% two-sided confidence interval on the capture rate and comparing the lower bound to 80%. At the final analysis (if needed) the significance level used for testing will be 0.0194 which translates into calculating a 98.06% two-sided confidence interval on the capture rate and comparing the lower bound to 80%. These levels were derived using a power cumulative error spending function with the parameter (rho) set to 1.0. This setting produces Pocock type boundaries (i.e. approximately equal spending for the two tests).

7. MEASURES TO ADJUST FOR MULTIPLICITY, CONFOUNDERS, HETEROGENEITY, ETC.

Since the study cohort was 9 Caucasian men and 1 Caucasian woman and study was very small no heterogeneity, multiplicity or confounder statistical analyses will be run. However, summary data may be presented for the different types of patients (neuro trauma, COPD etc.) to try and see if there were any trends or if therapy was more effective for one of the patient populations since this was one of the study objectives.

To see if the type of patient may have impacted the primary endpoint of diaphragm capture, the primary analysis will be rerun with type of patient added into the logistic regression as an independent predictor. A confidence interval will be constructed about the coefficient for type of patient and if that confidence interval overlaps zero then it will be assumed that the type of patient did not impact the primary endpoint.

8. SENSITIVITY ANALYSES

Since the study cohort was 9 Caucasian men and 1 Caucasian woman and study was very small no statistical sensitivity analyses will be run. However, summary data may be presented for different patient variables to see if there were any trends.

9. RATIONALE FOR ANY DEVIATION FROM PRE-SPECIFIED ANALYSIS PLAN PERFORMED BY STIMDIA

Not applicable.

10. QC PLANS

The accuracy of the study data entered into the database will be 100% verified by Stimdia Medical quality and clinical personnel. Any data or statistical analyses will have a 100% second person verification.

11. PROGRAMMING PLANS

Synchrony will be measured by first finding when inspiration starts using the trigger flows for each subject/stimulation combination. Next the start of stimulation will be found using the trigger signal. The difference in time between the start of inspiration and the start of stimulation will be the lag time. This will be calculated for all stimulated breaths.

Work of Breath (WOB) is calculated by finding the end of stimulation using the trigger signal, waiting 100 msec, and then capturing the next 50 observations for WOB. Each set of 50 observations is summarized using the mode of the 50 observations. This is also done for each stimulated breath.

If the lag time is less than 88 msec, and the WOB is between 0.2 and 2.0 Joules/L, and the output parameter is less than 10.5 volts then capture will have been achieved and a binary indicator variable will be set to 1.0. If capture is not achieved, that binary indicator variable will be set to 0.0. This binary indicator variable will be used for analyzing the primary endpoint.

12. REFERENCES

Taira T, Hori T. Diaphragm pacing with a spinal cord stimulator: current state and future directions. Acta Neurochir Suppl. 2007;97(Pt 1):289-92.