Revised Statistical Analysis Plan for Randomized Clinical Trial in Cranial Nerve Non-Invasive Neuromodulation Using PoNS™ for Treatment of Symptoms Due to Mild to Moderate Traumatic Brain Injury

Prepared for

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1.0 BACKGROUND

This is a randomized clinical trial (RCT) in cranial nerve non-invasive neuromodulation (CN-NINM) using PoNS™ for treatment of symptoms due to mild to moderate traumatic brain injury (mTBI), post-concussive sequelae, (PCS) and post-traumatic stress (PTS). The study will involve training of both balance and gait, with assessments using standardized and relevant metrics to monitor changes in these indications, as well as cognitive function, sleep, headache, anxiety, mood, and eye-movement control.

1.1 Study Objective

The primary objective of this study is to demonstrate that CN-NINM training using the PoNS™ device with normal stimulation is more efficacious than training using a very low but perceivable stimulation device (Control) in subjects with symptoms due to the mild to moderate traumatic brain injury (TBI).

In this experimental investigation, data will be generated to describe the mean changes in balance and gait behavior from baseline for two treatment groups. The results will help to design and power the subsequent, incremental studies investigating the clinical efficacy of this intervention. Standardized clinical assessment mechanisms will measure changes in balance, gait, cognition, emotional function, headache, eye movement, and sleep in individuals with post-concussive and post-traumatic stress complaints in a 14-week rehabilitation program and after a 12-week withdrawal period.

1.2 Study Design

This is a randomized double blind study that will enroll up to 44 subjects (males and females) with identified balance deficits that will be equally distributed (1:1) into 2 subgroups: an "Active" CN-NINM device (PoNS™) group, and a "Control" (very low stimulation) device group.

The study will be run for a total of 26 weeks, consisting of three stages:

a) The first stage consists of twice-daily in-lab training (ITP) for 2-weeks (with at-home training during the intervening weekend). The intensive CN-NINM training program will focus on balance and gait.

b) The second stage will consist of subjects performing the same training for 12 weeks during Stage 2 – the Home Training Program (HTP). During this second stage, subjects will return to the lab 1 time per week for a training session.

c) After completion of the second stage, subjects continue in the third stage, the withdrawal stage, where they no longer use the PoNS™ device for 12 weeks.

2.0 STUDY POPULATION

Subjects presenting with a chronic balance deficit due to mTBI. Subjects who also present with other symptoms, such as gait disturbance, mild to moderate recurrent headaches, sleep, memory, attention, or cognitive deficits, will be considered for participation. All candidates will have had a closed-head, non-penetrating, blunt, whiplash, or explosive blast-induced brain injury. Subjects will be required to provide their most recent neuroradiologic report and evidence of having completed a prescribed therapeutic regiment for their symptoms.

3.0 STATISTICAL CONSIDERATIONS

3.1 Sample Size Calculations

This study is an investigation to discover changes in the Composite SOT scores of subjects from baseline at the end of Week 2 and Week 14visits in Active and Control groups.

The sample size for the study is based on the primary endpoint of change in mean SOT score from baseline at the end of Week 2 and Week 14 visits. The following assumptions are made:

- Control group response is half of that of the Active group
- Two-sided Test
- Equal variances in both groups
- Alpha Level= 0.05
- Power = 80%
- μ_{A1} = Mean change in SOT score from baseline to the end of Week 2 visit in Active group
- μ_{A2} = Mean change in SOT score from baseline to the end of Week 14 visit in Active group.
- μ_{C1} = Mean change in SOT score from baseline to the end of Week 2 visit in Control group
- μ_{C2} = Mean change in SOT score from baseline to the end of Week 14 visit in Control group.

To calculate the sample size, the following two hypotheses, Null (H_0) and Alternative (H_A) are formulated:

$$H_0: \mu_A = 2\mu_C \quad \text{VS.} \quad H_A: \mu_A \neq 2\mu_C$$

Since there is very limited experience on PoNS^{TM} device and no data on control device, to calculate a sample size for this study, the mean change of 26.3 in composite SOT score at the end of Week 2 visit from baseline from the pilot study is used. Also it is assumed that the Control group response will be half of that of the Active group and equal variability in both groups with common standard deviation of 13.2, a 50% coefficient of variation in the Active group.

Based on the above assumptions, a sample size of 17 subjects in each group will have 80% power to detect a difference between the Treatment PoNS^{TM} group mean μ_A, of 26.3 and the Control group mean μ_C, of 13.2 assuming that the common standard deviation is 13.2 using a two group t-test with a 0.05 two-sided significance level.

Previous experience in two controlled pilot studies, a drop-out rate of not more than 25% is estimated. Therefore, using conservative approach, the sample size for this study is increased from 34 to 44 subjects with 22 subjects in each arm.

3.2 Randomization

Subjects will be randomly assigned to one of the two treatment groups by the Clinical Monitor as they are recruited using a rolling recruitment method. Cohort assignment will be made by serially selecting from a list of 44 randomly generated three-digit subject identification numbers, with 22 subjects in each Active and Control group, respectively.

3.3 Primary Endpoint and Observational Measures

The primary outcome measure is the Composite SOT score. Observational measures are the Neurobehavioral Symptom Inventory, California Verbal Learning Test, Brief Symptom Inventory, Wechsler Adult Intelligence Scale – Symbol Search and Coding, Pittsburgh Sleep Quality Index, Headache Disability Index, Physiologic Stress Response, Quantitative Gait Assessment using EMG, 6-minute walk test, Dynamic Gait Index, and Computerized Video Nystagmography. The observational measures will provide essential data for potential future studies investigating CN-NINM effects on a particular functional deficit.

4.0 STUDY OUTCOMES

4.1 Primary Outcome

NeuroCom CDP Sensory Organization Test (SOT) - Measures standing dynamic balance.

4.2 Secondary Outcomes

- 6-Minute Walk Test - over ground (6MWT) - Measures walking speed.
- Dynamic Gait Index (DGI) – assesses walking, walking with head turns, over and around obstacles, and stairs.
- Physiological Stress Test: resting & post exercise, heart rate, respiration, skin conductance, core temperature.
- Neurobehavioral Symptom Inventory (NSI) - Subjective inventory of TBI symptoms.
- California Verbal Learning Test (CVLT) – Assesses short- and long-term verbal memory.
- Brief Symptom Inventory 18 (BSI 18) – Assesses anxiety symptoms.
- Wechsler Adult Intelligence Scale – Symbol Search and Coding (WAIS-IV) – Assesses visual spatial abilities.
- Pittsburgh Sleep Quality Index (PSQI) - Subjective inventory of sleep habits, duration and quality.
- Headache Disability Index (HDI) – Assesses frequency & severity of headaches
- Quantitative Gait Assessment and EMG – to measure stride length and width, and muscle activation patterns during gait.
- Computerized video nystagmography (VNG) - Measures eye movement control.

4.3 Primary Efficacy Endpoints

The primary efficacy endpoint is the change in the SOT score from Baseline to the Week 2 and Week 14 visits. That is, if X_1 is the endpoint then:

X_1 = Composite SOT score at Week 2 visit – Composite SOT score at Baseline.

Similarly, X_2 is:

X_2 = Composite SOT score at Week 14 visit – Composite SOT score at Baseline.

4.4 Secondary Efficacy Endpoints

As stated above, there are multiple secondary efficacy endpoints.

4.5 Safety Endpoints

The primary safety endpoint is the frequency of falls, measured in daily activity logs. The secondary safety endpoint is the frequency of headaches as assessed by Headache Disability Index.

AEs and unanticipated (unexpected) AEs will be assessed and recorded.

5.0 PLANNED ANALYSIS

The following planned analyses will be performed by the unmasked study statistician, who will be communicating with the Data Safety Monitoring Committee (DSMC).

5.1 Interim Analysis

Only one interim analysis is planned after first 22 subjects have completed their Week 14 visit. The interim analysis will be performed using the primary efficacy endpoint for the data of first 22 subjects that have completed the Week 2 and Week 14 visits. The two treatment groups will be listed as Group 1 and Group 2 to maintain the blinding of the treatments.

The number of subjects (most likely 11), and both the Mean and standard deviation (SD) for each group will be calculated by the study statistician. Student's *t*-test will be used to compare the two means. A *p*-value will be generated but no decision will be made at the interim analysis time, and the trial will continue to completion unless there are serious safety concerns.

The study statistician will present the interim analysis results (*n*, Mean and SD) by treatment group in unblinded fashion including the *p*-value to the DSMC.

Also, the statistician will present these results to the sponsor of the study but in the blinded fashion, by identifying the treatment groups only as Group 1 and Group 2.

5.2 Final Analysis

The study statistician will perform the final analysis using the primary efficacy endpoints when all 44 subjects have completed their Week 26 visit. Just like at interim analysis, mean and SD of each group will be calculated. Student's *t*-test will be used to compare the two groups and *p*-value will be reported.

Secondary analyses will consider group differences on measurements at a visit as well as change from baseline.

Descriptive statistics will be calculated for outcome and demographic variables. Mean and SD will be used for numeric variables and count (percent) will be used for categorical variables. The percentage of subjects compliant in each group will be calculated. Statistical comparisons between the groups will be made using Student's t-test for numeric data and chi-squared procedures for categorical data.

Data for comparison between the treatments are collected at baseline, week 2, week 5, week 8, week 11, week 14, week 17, week 20, week 23, and week 26 visits. Each subject has up to 10 data points collected for each of the outcome variables. Data at the end of each Stage (week 2, week 14, week 26) will be used for statistical comparison between the treatment groups. Statistical comparison between groups will be based on Student's t-test.

6.0 ANALYSIS POPULATION

6.1 Efficacy Population

Intent-to-Treat (ITT) Population: The ITT population consists of all subjects, who met the inclusion/exclusion criteria and were randomized to receive one of the two devices. Efficacy analysis based on ITT population dataset will be the primary analysis.

Per-Protocol (PP) Population: The PP population includes all subjects, who met the inclusion/exclusion criteria and were randomized to receive one of the two devices and who had no significant violations, such as not receiving the assigned device. Efficacy based on the PP population dataset will be the secondary analysis.

6.2 Safety Population

All subjects receiving at least one treatment of either device will be included in the safety population.

7.0 DATA SAFETY MONITORING COMMITTEE

A data safety monitoring committee will be formed to periodically review the accumulating study data. The primary responsibility of the DSMC is to monitor subject safety and conduct of study. The DSMC will have access to the safety data throughout the study, and will have the results of the efficacy analysis results by treatment device at the time of interim analysis. Again, it is emphasized that no decision will be made at the time of the interim analysis.

8.0 DATA COLLECTION

Data captured on all source documents from the study (demographics, Health Questionnaire, CRF's, ADE's, SAE's, assessments) will be entered into an OnCore database hosted at PI's institution.

8.1 Definition of Baseline and Change from Baseline

Subjects are scheduled to have one baseline/screening visit. At this visit subjects should have all baseline assessments obtained prior to being randomized. Values obtained at this visit and prior to randomization are considered baseline measurements. In the case a value is not obtained at the baseline visit, a value at a prior, post-screening visit, may be used. All baseline values must be obtained prior to randomization (i.e. a value obtained after randomization cannot be considered a baseline value).

9.0 STUDY DURATION

Each subject has the potential to be followed for up to 26 weeks of post-randomization.

9.0 BASELINE MEASURES

Baseline measures will be summarized by treatment group. No statistical comparisons are planned.

10.0 DATA SOURCES FOR STATISTICAL ANALYSIS

Data from OnCore databases will be extracted and maintained in SAS and R datasets for the statistical analysis.