Electrically Evoked Compound Action Potentials Human Observation Medtronic Algorithm Comparison Study (ECHO MAC)

Statistical Analysis Plan V1.0, 25-MAY-2021

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Electrically evoked compound action potentials human observation Medtronic Algorithm Comparison study (ECHO-MAC)
Clinical Investigation Plan Identifier	MDT19024
Clinical Investigation Plan Version	Version 2.0
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Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigational Plan
CL	Closed-Loop
DD	Device Deficiency
DMC	Data Monitoring Committee
ECAP	Evoked Compound Action Potential
ECHO-MAC	Electrically evoked compound action potentials human observation Medtronic Algorithm Comparison study
ECAP	Evoked Compound Action Potential
IDE	Investigation Device Exemption
ITT	Intent-to-treat
IRB	Institutional Review Board
MI	Multiple Imputation
MedDRA	Medical Dictionary for Regulatory Affairs
OL	Open-Loop
PASS	Power Analysis & Sample Size
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCS	Spinal Cord Stimulation

3. Introduction

This Statistical Analysis Plan (SAP) is based on the Electronically evoked compound action potentials human observation Medtronic Algorithm Comparison (ECHO-MAC) Study Clinical Investigational Plan (CIP). The SAP presents the details of the methods to be used to analyze and report the study results of the ECHO-MAC study, protocol number MDT19024.

4. Study Objectives

4.1 Primary Objective

To demonstrate that the proportion of subjects with a reduction in overstimulation[a] sensation with spinal cord stimulation (SCS) using a closed-loop (CL) algorithm compared with SCS in open-loop (OL) exceeds a performance goal of 50%.

[a] Overstimulation is defined as an uncomfortable sensation of stimulation (intense tingling, shocking, jolting) brought about by protocol-prescribed activities (i.e. coughing, back arch, performing Valsalva maneuver). This overstimulation sensation is transient and reversed by the subject's returning to a neutral position.

[redacted]

- [redacted]
- [redacted]

4.3 Safety Assessment

All device-related, therapy-related, and procedure-related adverse events and device deficiencies will be characterized from the start of the in-clinic testing until study exit.

5. Investigation Plan

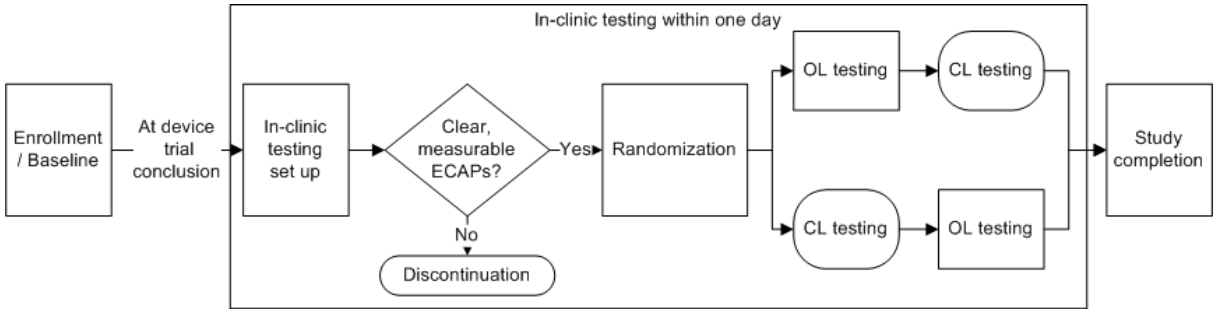
This is a prospective, multi-center, randomized, single-blind, cross-over, non-significant risk Investigation Device Exemption (IDE) study. This study will be conducted in the United States with up to 15 sites; each site will contribute up to 10 enrolled subjects. Up to 60 subjects are expected to be enrolled in the study to allow for at least 42 subjects for analysis.

The expected total study duration is approximately 6 months. The duration of a subject's participation is approximately 2 weeks from enrollment, although this may vary depending on when enrollment occurs relative to the SCS device trial.

Figure 5-1 is a flow diagram of how subjects will complete the study. Subjects will be required to come into the clinic for 2 study visits, although they could occur on the same day:

- Enrollment
- In-clinic Testing Visit

Figure 5-1: Study Visit Diagram



Subject randomization will occur after a clear, measurable ECAP [redacted] is verified and the algorithm is setup. Subjects will be randomized to the sequence of receiving OL and CL in-clinic testing. Subjects will be blinded to the settings tested. The In-clinic Testing Visit is expected to last up to 3 hours and subjects will be discontinued at the end of the visit.

6. Determination of Sample Size

The primary endpoint is to demonstrate that the proportion of subjects with a reduction in overstimulation sensation with SCS using a CL algorithm compared with SCS in OL exceeds 50%. PASS 2020 Group-Sequential Tests for One Proportion in a Fleming Design module was used to calculate the sample size. With a null proportion of 50%, an alternative proportion of 75%, and one interim analysis at 70% of the total sample size, 42 subjects are needed to achieve more than 90% power with a one-sided alpha = 0.025 test.

[redacted]

To account for a 30% attrition between enrollment and randomization, up to 60 subjects may be enrolled into the study. A 30% attrition rate was based on historical attrition rates from similar studies, as well as to account for the subjects who don't have a clear, measurable ECAP.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized by study visit in a flow diagram. Discontinuation will be summarized by visit and discontinuation reasons will be provided.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All CIP deviations will be summarized by the type of deviation. Details of CIP deviations that affect scientific integrity and subject safety may be presented.

7.1.3 Analysis Sets

Enrolled Analysis Set: includes all consented subjects.

Intent-to-treat (ITT) Analysis Set: includes all subjects who are randomized.

Completer Analysis Set: includes subjects who are randomized and provide assessment for overstimulation sensation at both the OL and CL in-clinic testing periods.

7.2 General Methodology

Two formal analyses are planned for this study: one interim analysis will occur [redacted] and one final analysis will occur after all subjects complete the study. The Interim Analysis is described in 7.8. A final report will be prepared once all data collection has ended and all subjects have completed the study and have been exited.

General descriptive statistics for categorical and continuous variables will be used. Categorical variables will be summarized as counts and percentages; continuous variables will be presented using counts, mean, standard deviation, median, quartiles and range as applicable.

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.4 or higher) will be used to analyze the study results.

7.3 Center Pooling

There is no a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 10 subjects will be enrolled at each site. The per-study site enrollment cap may be increased upon Sponsor approval.

A poolability analysis to test for a treatment difference among sites is described in the supporting analyses of the primary objective in 7.9.1.7.1.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Missing data are a potential source of bias when analyzing study data. Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects' in-clinic testing sequences are randomized with stratification at each site. This is to ensure subjects get equal opportunities to start with either OL or CL testing.
- Subjects are blinded to the OL or CL testing settings. This is to ensure that the knowledge of testing settings is not going to influence the subjects' assessment of overstimulation sensation.
- Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring. All efforts will be made to ensure subject follow-ups are completed with limited attrition to ensure interpretability of study results.
- To reduce the possibility of atypical results from a site overly influencing the combined results, the maximum number of subjects to be enrolled at a single study site is limited to 10 and cannot be increased without prior sponsor approval.

The primary analysis of the primary objective will include subjects who are randomized (ITT Analysis Set) and if, across all subjects, more than 5% of the average intensity scores for either the OL or CL period are missing[1], will utilize the Multiple Imputation (MI) methodology for missing data. MI will only be used for the analysis of the primary objective and is not planned to be utilized for any other analyses.

Prior to the use of MI, the distributions of the continuous average stimulation intensity variables will be assessed for normality (using the Shapiro-Wilk test) to determine if transformation of non-normal variables ($p \leq 0.05$) may be considered, or if a different imputation specification that is more appropriate for non-normal data may be used.

[redacted] Following imputation, the objective will be evaluated using MI analysis method.

7.5 Adjustments for Multiple Comparisons

As there is one primary objective, adjustment for multiple endpoints is not required.

7.6 Demographic and Other Baseline Characteristics

Demographics and Baseline characteristics will be summarized for the Enrolled Analysis Set and the ITT Analysis Set separately, and may include:

- Age, sex, and race
- Primary Indication
- Medical history

- Medication information
- History of treatments

7.7 Treatment Characteristics

Relevant characteristics from the in-clinic test will be summarized and described.

7.8 Interim Analyses

One planned interim analysis will be conducted under the auspices of the data monitoring committee (DMC) assigned to this study. The DMC will disseminate interim results only if necessary. Any such dissemination will be documented and described in the final study report. Study sites will not receive information about interim results unless they need to know for the safety of their subjects.

[redacted]

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The primary objective is to demonstrate that the proportion of subjects with a reduction in overstimulation sensation with SCS using a CL algorithm compared with SCS in OL exceeds a performance goal of 50%.

7.9.1.1 Hypothesis

It is hypothesized that the proportion of subjects with a reduction in overstimulation sensation during CL compared to the OL period exceeds a performance goal of 50%. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $p \leq 50\%$

H_A: $p > 50\%$

Where p is the proportion of subjects with a reduction in overstimulation sensation during CL compared to the OL period.

7.9.1.2 Endpoint definition and derivation

For every overstimulation sensation brought about by 3 to 5 protocol-prescribed activities, subjects will rate the intensity of the sensation in the following 5-point Likert scale:

- No overstimulation sensation (code=0)
- Weak overstimulation sensation (code=1)
- Moderate overstimulation sensation (code=2)
- Strong overstimulation sensation (code=3)

- Very strong overstimulation sensation (code=4)

The average of all non-missing intensity score s during the OL and CL period will be calculated for each individual subject. If there is at least one non-missing intensity score for a period, the subject's data will be used without imputing values. If a subject is missing all intensity scores for a period, then that subject has a missing average intensity score for that period. If, across all subjects, more than 5% of the average intensity scores for either the OL or CL period are missing, then MI will be utilized as specified in 7.4. If the average intensity score during the CL period is less than that from the OL period, the subject is considered as a subject with a reduction in overstimulation sensation during CL vs. the OL period. The proportion of subjects with a reduction in overstimulation sensation among subjects who have in-clinic testing is the primary endpoint.

7.9.1.3 Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 50% or, equivalently, if the p-value for the hypothesis test is less than 0.025.

[redacted]

7.9.1.5 Analysis Methods

The proportion of subjects with a reduction in overstimulation sensation during CL compared to the OL period will be calculated and evaluated with a one-sided 97.5% confidence lower bound. This proportion will be tested against 50% using a binomial exact test. The confidence lower bound needs to be greater than 50%, or equivalently, the p-value needs to be less than 0.025 to declare a study success. This implies that among the estimated total 42 randomized subjects, 28 subjects or more need to have a reduction in overstimulation sensation for the study to be considered a success.

Two sensitivity analyses will be performed if there is any missing primary endpoint data. One sensitivity analysis, a tipping point analysis, will be performed using the ITT Analysis Set. This analysis will be performed on the primary endpoint by displaying the full range of proportions on the potential impact of missing data by running an analysis assuming all missing values are a higher average stimulation intensity value for CL vs OL (worst case) to all missing values are a lower average stimulation intensity value for CL vs OL (best case).

Another sensitivity analysis will be performed on the primary endpoint by including only the subjects who finish the in-clinic testing and provided the scoring of overstimulation sensation for both OL and CL periods (Completer Analysis Set).

7.9.1.6 Determination of Subjects/Data for Analysis

The primary analysis for the primary objective will follow the ITT principle by including all the subjects randomized (ITT Analysis set). If more than 5% of the average intensity scores for either the OL or CL period are missing, then the subjects who were randomized but have missing average values for intensity scores during OL and/or CL period will have their data imputed using Multiple Imputation (MI), as described in 7.4.

[redacted]

[redacted]

7.10 Safety Evaluation

All serious, device-related, procedure-related and/or therapy-related adverse events (AEs) and all device deficiencies (DDs) will be considered reportable for this study and will be characterized from the start of the in-clinic testing until study exit. AEs and DDs will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Serious AEs will be summarized for all consented subjects (Enrolled Analysis Set), all subjects who are randomized (ITT Analysis Set), as well as for subjects who

provide overstimulation data (Completer Analysis Set). Device-related, procedure-related, and/or therapy-related AEs and DDs will be summarized for all subjects who underwent the OL and/or CL periods during the in-clinic visit (Completer Analysis Set). The severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the devices or procedure or therapy will be provided as listing. The number of events, the number of subjects who experience an event, and the percentage of subjects who experienced one or more events will be summarized. A listing of deaths and reasons for deaths will be provided if any deaths occur in the study.

7.11 Changes to Planned Analysis

Any changes to the data analysis methods described in the SAP will require an amendment only if it changes a principal feature of the SAP. Any other change to the data analysis methods described in the SAP, and the justification for making the change, will be described in the clinical study report.

8. Validation Requirements

Statistical programming code that affects the result of the main analysis for the primary objective shall be validated using Level I validation, which is defined as the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

Statistical programming code that affects the result of the main analysis for the additional measures shall be validated using Level II validation, which is defined as the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

In addition, the main statistical analyses that are planned for publication and have not been previously validated should be validated with at least Level II validation. The CIP deviation summary shall be validated using at least Level III validation and the high-level adverse event summary shall be validated using at least Level II validation. Additional measures where a p-value or confidence interval has been generated may need to be validated using at least Level II validation.

9. References

1) Buhi, Eric; Goodson, Patricia; Neilands, Torsten. Out of Sight, Not Out of Mind: Strategies for Handling Missing Data. American Journal of Health Behavior. 2008; 32(1):83-92

2) Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993; 2(2):121-45