Medtronic Closed-Loop Spinal Cord Stimulation System

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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Evaluation of Long-Term Patient Experience with a Medtronic Closed-Loop SCS System (Closed-Loop SCS study)
Clinical Investigation Plan Identifier	MDT21017
Clinical Investigation Plan Version	4.0
Statistical Analysis Plan Version Date	27-JUL-2023
Sponsor/Local Sponsor	Medtronic Neuromodulation [redacted] Medtronic Australasia Pty Ltd [redacted]

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]
2.0	• Updated to CIP version 4.0 • Updated sample size from 90 to 140 calculation based on new expected attrition rate from Enrollment to Implant and implant to 3-month visit.	[redacted]
3.0	• Updated section 7.8 to mention the primary and secondary endpoint analysis • Updated section 7.9.3 to allow for analysis of some additional objectives in the PAS at 3-months • Updated sections 7.9.3.5, 7.9.3.6, 7.9.3.,7, 7.9.3.9, 7.9.3.10, 7.9.3.13, 7.9.3.14, 7.9.3.15, 7.9.3.16, 7.9.3.17, 7.9.3.18, 7.9.3.19, 7.9.3.20, 7.9.3.21, 7.9.3.22 to include potential analysis of objective in the PAS at 3-months.	[redacted]
4.0	• Version date on title page corrected from 13-JAN-2023 to 27-JUL-2023	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviations should be indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation	Definition
ACS	All Consented Set
AE	Adverse Event
CCS	Complete Case Set
CIP	Clinical Investigation Plan
CL	Closed Loop
ECAP	Evoked Compound Action Potential
[redacted]	[redacted]
FAS	Full Analysis Set
INS	Implanted Neurostimulator
ITT	Intention-to-treat
MCS	Mental Component Summary
MedDRA	Medical Dictionary and Regulatory Affairs
MI	Multiple Imputation
[redacted]	[redacted]
[redacted]	[redacted]
OL	Open Loop

Abbreviation	Definition
PAS	Primary Analysis Set
PCS	Physical Component Summary
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SCS	Spinal Cord Stimulation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
VAS	Visual Analogue Scale

3. Introduction

Spinal Cord Stimulation (SCS) is a therapy for the treatment of chronic pain that relies on the application of mild electrical stimulation delivered to the dorsal column fibers of the spinal cord via a lead or leads implanted in the epidural space. Several technologies have been developed for SCS, one of which is the closed-loop algorithm. The closed-loop algorithm uses the evoked compound action potential (ECAP), which is the spinal cord's physiological response to stimulation, to adjust the amplitude to stimulation, if required.

The purpose of the Closed Loop SCS Study is to further our understanding of closed-loop SCS in patients implanted with the Inceptiv INS. The Closed-Loop SCS study is a prospective, multi-center, randomized, single-blind, investigational, feasibility study. This is a first-in-man study since the fully implantable Inceptiv device has not been studied in humans.

This Statistical Analysis Plan (SAP) is based on the Evaluation of Evaluation of Long-Term Patient Experience with a Medtronic Closed-Loop SCS System (Closed-Loop SCS study) Clinical Investigation Plan (CIP). The SAP presents the details of the methods to be used to analyze and report the study results of the Closed-Loop SCS study, protocol number MDT21017.

4. Study Objectives

4.1 Primary Objective

To demonstrate that the proportion of low-back and leg pain subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense Off, at the randomization and in-clinic testing visit, exceeds a performance goal of 50%.

4.2 Secondary Objectives

1. To characterize the efficacy of spinal cord stimulation (SCS) therapy for the treatment of overall pain (for low-back and/or leg pain subjects) by evaluating the efficacy responder rate. The

efficacy responder rate is defined as the percentage of implanted subjects who experience at least a 50% improvement in overall pain, as measured by the Visual Analogue Scale (VAS), from Baseline to the 3-Month Visit.

2. To characterize the efficacy responder rate within in each type of pain (low-back or leg) for low-back and/or leg pain subjects, as measured by the pain-specific VAS, from Baseline to the 3-Month Visit.

[redacted]

5. Investigation Plan

The study is expected to be conducted at up to ten study sites located in Australia. Up to 90 subjects will be enrolled in the study to ensure up to 50 subjects with low-back and/or leg pain and up to 10 subjects with upper limb and neck pain are implanted with the study device. Up to 100 Inceptiv devices may be used in the study. Based on previous studies of this scope and magnitude, it is estimated that each study site will enroll approximately 9 subjects. To reduce the possibility of atypical results from a site overly influencing the study, no more than 20% of the total implanted population will be from each site unless the site gets pre-approval from Medtronic for additional enrollments.

Subjects will be enrolled, and baseline data will be collected. Those meeting all inclusion criteria and no exclusion criteria will undergo a device trial. Subjects with sufficient pain relief during the trial will be implanted with the study device and undergo Device Optimization for 1-Month. Approximately 1-Month post Device Activation, subjects will undergo in-clinic testing. Subjects will be randomized at the in-clinic visit to one of the two sequences: Neuro Sense On followed by Neuro Sense Off or Neuro Sense Off followed by Neuro Sense On. Subjects will be blinded to the settings tested. In each setting, subjects will perform a series of activities and asked to rate the intensity of the overstimulation sensation they experienced while performing the activity using a 5-point Likert scale. [redacted] It is recommended that the Neuro Sense feature be turned ON at the end of the in-clinic testing visit unless the patient prefers the Neuro Sense OFF setting. All subjects will then be followed for up to 24-months following device activation; scheduled study visits will occur at 3-, 6-, 12-, 18-, and 24-months post device activation.

Figure 5-1 is a flow diagram of how subjects will complete the study and Figure 5-2 is a flow diagram of how subjects will go through in-clinic testing.

Figure 5-1 Study Flow Diagram

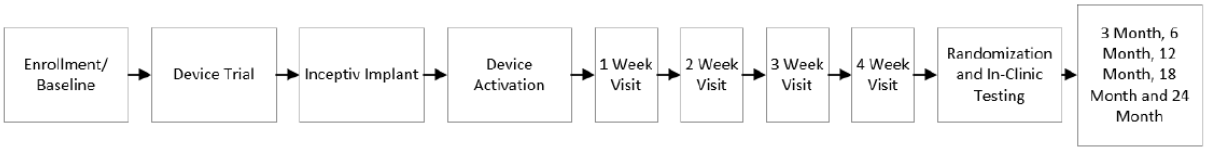
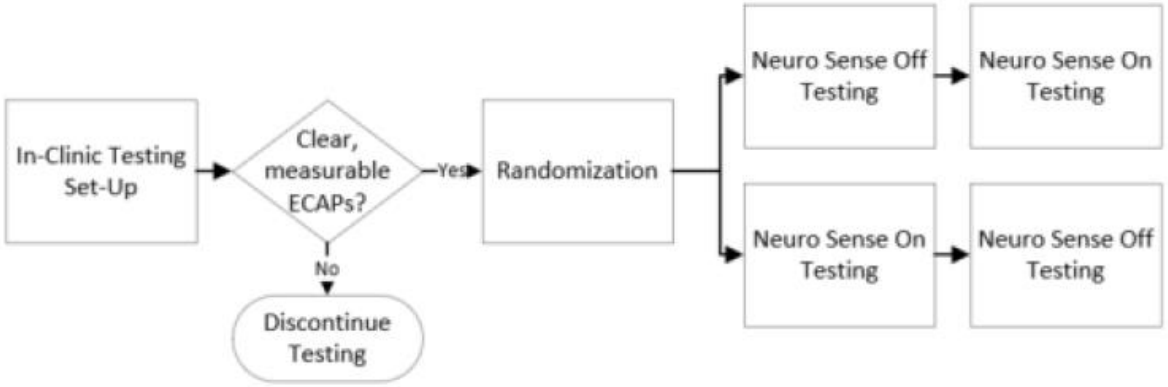


Figure 5-2 In-Clinic Testing Flow Diagram



6. Determination of Sample Size

[redacted]

[redacted]

[redacted]

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

For the primary objective, a subset (28) of the total device implanted low-back and/or leg pain subjects are needed to evaluate the endpoint. For the secondary objectives, up to 45 implanted subjects with low back and leg pain are desired to characterize the responder rates at the 3-Month Visit. Up to 9 implanted subjects with upper limb and neck pain are desired to characterize the population at the 3-Month Visit.

[redacted]

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated in a flow diagram. Subject visits will be tabulated and compliance to visit schedule will be summarized. Attrition will be identified and summarized.

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

- The **All Consented Set** (ACS) will include all subjects who signed the study specific ICF and enrolled in the study.
- The **Full Analysis Set** (FAS) will include all device-implanted subjects.
- The **Primary Analysis Set** (PAS) will follow the intent-to-treat (ITT) principle to include randomized low-back and leg pain subjects who will be used for the primary objective, i.e., the first 28 randomized low-back and leg pain subjects.
- The **Complete Case Set** (CCS) will include all device-implanted subjects who have data available at baseline and follow-up. This set is defined for each outcome measure at each follow-up visit. [redacted]
  - [redacted]
  - [redacted]

7.2 General Methodology

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., R v4.0.0 or higher, SAS v9.4 or higher) will be used to analyze the study results.

Two formal analyses are planned for this study: one primary endpoint analysis after 28 subjects have completed the in-clinic testing and one final analysis after all subjects have completed the study. 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 mean, standard deviation, median, quartiles and range, as applicable. All confidence intervals will be presented as two-sided 95% confidence intervals, unless otherwise pre-specified.

7.3 Center Pooling

The main analyses will include data from all contributing study centers. To reduce the possibility of atypical results from a site overly influencing the study, no more than 20% of the total implanted population will be from each site unless the site gets pre-approval from Medtronic for additional enrollments.

A poolability analysis to test for difference among sites is described in the supporting analyses of the primary objective in 7.9.1.7.1. When testing for differences between sites, sites with 5 or more subjects will each be tested as separate sites. Those with less than 5 subjects will be combined into a "pooled" pseudo-site to minimize the impact of small samples on the analysis. If the pseudo-site contains more than 50% of the subjects, the sites will be combined into more than one pseudo-site. If more than one pseudo-site is needed, the sites will be randomly ordered and divided as near the midpoint as possible. If ambiguity between assigning a site to the first or second pseudo-site exits, the site will be assigned to the first pseudo-site.

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

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 as described in Section 14.9. The analysis of the primary objective will use the first 28 subjects that complete in clinic testing and provide a primary endpoint (PAS) and if, across all subjects, more than 5% (Buhi, Goodson, & Neilands, 2008) of the average intensity scores for either the open loop (OL) or closed loop (CL) period are missing Multiple Imputation (MI) methodology for missing data will be utilized.

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 methods.

The FAS will be used for the analysis of all secondary objectives and if more than 5% of subjects have missing VAS scores at baseline or the 3-month visit then MI methodology for missing data will be utilized.

[redacted]

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

[redacted]

7.5 Adjustments for Multiple Comparisons

Only one hypothesis test is planned for analysis of the primary objective, no adjustments for multiple endpoints are required.

7.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the ACS, PAS, and FAS datasets. Summaries of age at baseline, sex, race, ethnicity, primary indication, primary location of pain (low back/leg, upper limb-not neck, upper-limb neck), and medical history will be included. Additionally, we will summarize the baseline outcome measures for the ACS, PAS, and FAS datasets by primary location of pain.

7.7 Treatment Characteristics

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

7.8 Interim Analyses

No Interim analysis will be performed on the primary and secondary objectives. [redacted].

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The primary objective is to demonstrate that the proportion of low-back and leg pain subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense Off, at the randomization and in-clinic testing visit, exceeds a performance goal of 50%.
Overstimulation is defined as an uncomfortable sensation of stimulation (intense tingling, shocking, jolting) brought about by protocol-prescribed activities [redacted]. This overstimulation sensation is transient and reversed by the subject returning to a neutral position.

7.9.1.1 Hypothesis

It is hypothesized that the proportion of low-back and leg pain subjects with a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period exceeds a performance goal of 50%.

$$H_0: p \leqslant 50\%$$
$$H_A: p > 50\%$$

7.9.1.2 Endpoint definition and derivation

For every overstimulation sensation brought about by 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 intensity scores during Closed Loop and Open Loop period will be calculated for each individual subject. If the average intensity score during Closed Loop period is less than that from the Open Loop period, the subject is considered as a subject with a reduction in overstimulation sensation during Closed Loop vs Open Loop period. The proportion of subjects with a reduction in overstimulation sensation among subjects who have in clinic testing need to exceed a performance goal of 50%. 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 the OL of CL period are missing, then MI will be utilized as specified in 7.4.

7.9.1.3 Performance Requirements

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

7.9.1.4 Rationale for Performance Criteria

The Neuro Sense On setting is an additional feature to control overstimulation to be added to an existing device. It is expected that this feature will help majority of the subjects. The 50% performance goal is selected to ensure that majority of the low-back and/or leg pain subjects meet the criterion with 95% confidence.

7.9.1.5 Analysis Methods

The proportion of low-back and/or leg pain subjects with a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period will be calculated, 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 must be less than 0.025 to reject the null hypothesis.

[redacted]

7.9.1.6 Determination of Subjects/Data for Analysis

The primary analysis for the primary objective will follow the ITT principle by including the low-back and/or leg pain subjects randomized for the primary analysis (PAS). If more than 5% of the average intensity scores for either the OL or CL period are missing, then the subjects who are randomized but have missing average scoring of overstimulation sensation during Neuro Sense On and/or Neuro Sense Off period will be imputed using Multiple Imputation (MI) as described in 7.4.

[redacted]

7.9.2 Secondary Objectives

7.9.2.1 Secondary Objective 1: Overall Response Rates

This objective is to characterize the efficacy of spinal cord stimulation (SCS) therapy for the treatment of overall pain (for low-back and/or leg pain subjects) by evaluating the efficacy responder rate. The efficacy responder rate is defined as the percentage of implanted subjects who experience at least a 50% improvement in overall pain, as measured by the Visual Analogue Scale (VAS), from Baseline to the 3-Month Visit.

7.9.2.1.1 Hypothesis

There is no hypothesis test for this objective. The purpose is to characterize the overall efficacy responder rate at the 3-Month Visit.

7.9.2.1.2 Endpoint definition and derivation

A responder will be any low-back and/or leg pain subject who demonstrates at least a 50% improvement (percent change) in overall pain as measured by the VAS, calculated as follows:

- Absolute change (Δ) at the subject level will be calculated as:

  $$\Delta = VAS_{Follow\text{-}up} - VAS_{Base}$$

  Where VAS_{Base} and $VAS_{Follow\text{-}up}$ are the value of the overall VAS pain score at baseline and follow up, respectively. A negative value indicates an improvement (reduction) in pain.
- Percentage change at the subject level will be calculated as 100 times the absolute change divided by the baseline value.

  $$\text{Percentage change} = 100*\Delta / VAS_{Base}$$

7.9.2.1.3 Analysis Methods

A point estimate of the proportion of responders, along with a 95% confidence interval, will be presented for this objective.

7.9.2.1.4 Determination of Subjects/Data for Analysis

Information from low-back and/or leg pain subjects who provide data at baseline and the 3-Month Visit (low-back and/or leg pain subjects from the CCS) will be used for this objective.

As a sensitivity analysis, if there is greater than 5% of subjects with missing values, any subjects who were device-implanted (FAS) but are missing their VAS scores at the 3-Month Visit will be imputed using Multiple Imputation (MI). Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and transformation may be considered if they are not normally distributed. [redacted]

[redacted]

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

[redacted]

7.9.2.2 Secondary Objective 2: Pain-Specific Responder Rates

This objective is to characterize the efficacy responder rate within in each type of pain (low-back or leg) for low-back and/or leg pain subjects, as measured by the pain-specific VAS, from Baseline to the 3-Month Visit. The low-back responder rate will be characterized for subjects with baseline back VAS ≥ 60 mm, and the leg responder rate will be characterized for subjects with baseline leg VAS ≥ 60 mm.

7.9.2.2.1 Hypothesis

There is no hypothesis test for this objective. The purpose is to characterize the pain-specific efficacy responder rate at the 3-Month Visit.

7.9.2.2.2 Endpoint definition and derivation

A responder will be any low-back and/or leg pain subject who demonstrates at least a 50% improvement (percent change) in overall pain as measured by the VAS, calculated as follows:

- Absolute change (Δ) at the subject level will be calculated as:

  $$\Delta = VAS_{Follow\text{-}up} - VAS_{Base}$$

  Where VAS_{Base} and $VAS_{Follow\text{-}up}$ are the value of the VAS pain score at baseline and follow up, respectively. A negative value indicates an improvement (reduction) in pain.
- Percentage change at the subject level will be calculated as 100 times the absolute change divided by the baseline value.

  $$\text{Percentage change} = 100*\Delta / VAS_{Base}$$

7.9.2.2.3 Analysis Methods

A point estimate of the proportion of responders, along with a 95% confidence interval, will be presented for each pain category within the secondary objective. Additional results, such as the proportion of responders by pain category and site, may be provided as well.

7.9.2.2.4 Determination of Subjects/Data for Analysis

Information from subjects who provide data at baseline and the 3-Month Visit (CCS) will be used for this objective. For the analysis of back pain responder rate, the subset of CCS subjects with a baseline back VAS ≥ 60 mm will be used. For the analysis of leg pain responder rate, the subset of CCS subjects with baseline leg VAS ≥ 60 mm will be used.

As a sensitivity analysis, if there is greater than 5% of subjects with missing values, any subjects who were device-implanted (FAS) but are missing their VAS scores at the 3-Month Visit will be imputed using Multiple Imputation (MI). Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and transformation may be considered if they are not normally distributed. [redacted]

[redacted]

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

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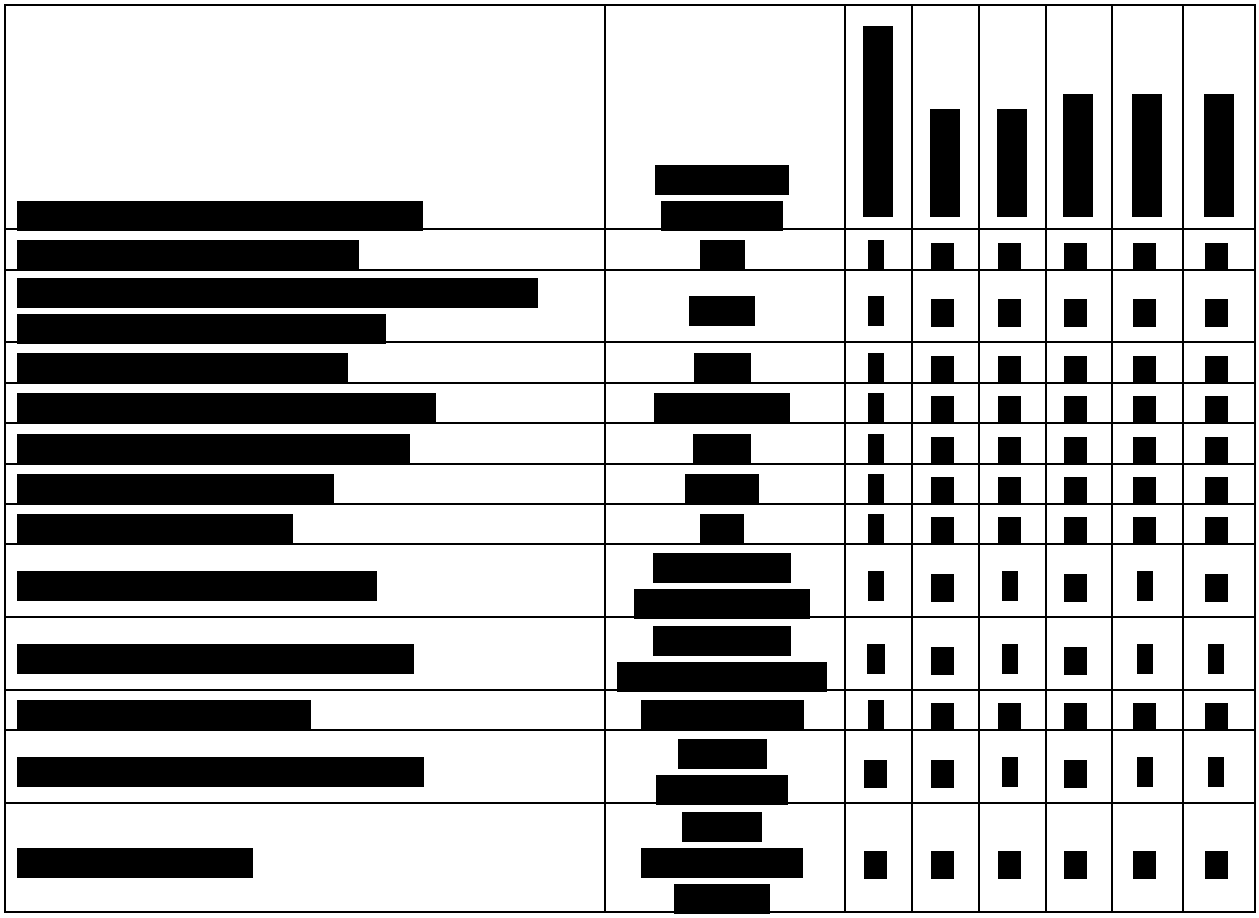

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7.10 Safety Evaluation

All device-related, therapy-related, and procedure-related adverse events (AE) and device deficiencies (DD) from the Device Trial Start Visit until study exit will be characterized in all subjects who started trialing and in all subjects who were implanted.

AEs and DDs will be coded and summarized overall and by location of pain using the most recent version of Medical Dictionary and Regulatory Affairs (MedDRA).

The AEs will also be categorized by relationship to study device and/or therapy. AEs will be presented in summary tables displaying the number of serious events, the number of events, and the number and percentage of subjects with one or more events. A summary of all device or therapy related AEs and of any deaths will also be provided. A narrative of each serious device- or therapy-related AEs will be provided.

DDs will be presented in summary tables displaying the number of deficiencies, and the number and percentage of subjects with deficiencies.

Device exposure will be summarized in those that started trialing from the ACS and the FAS and is considered from the time the subject is first exposed to the neurostimulation system (at the beginning of the device trial) until the product is explanted, or the subject discontinues from or completes the study, if later. Amount of exposure will be summarized (in months) using descriptive statistics such as mean, standard deviation, minimum, and maximum.

7.11 Health Outcomes Analyses

No Health Outcomes Analyses will be performed

7.12 Changes to Planned Analysis

Any deviations from this SAP will be described in the final study report, as appropriate.

8. Validation Requirements

Statistical programming code that affects the result of the main analysis (e.g., not including sensitivity or supporting analyses) for the primary objective shall be validated using Level I validation. Programming code that affects the result of the main analysis for the secondary objective shall be validated using at least Level II validation. In addition, those main statistical analyses that are planned for publication and have not been previously validated using 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 confidence interval has been generated may need to be validated using at least Level II validation.

9. References

Buhi, E. R., Goodson, P., & Neilands, T. (2008). Out of Sight, Not Out of Mind: Strategies for Handling Missing Data. *Am J Health Behav, 32*(1), 83-92.

Schultz, D., Webster, L., Kosek, P., Dar, U., Tan, Y., & Sun, M. (2012). Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician, 15*(1), 1-12. Retrieved from https://pubmed.ncbi.nlm.nih.gov/22270733

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