Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Spinal Cord Stimulation (SCS) Dosing Study
Clinical Investigation Plan Identifier	MDT17046
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1. Version History

Version	Summary of Changes	Author(s)/Title
[redacted]	[redacted]	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CIP	Clinical Investigational Plan
EQ-5D	European Quality of Life - 5 Dimensions
HD	High Dose
MedDRA	Medical Dictionary for Regulatory Affairs
ODI	Oswestry Disability Index
SSA	Satisfaction and Stimulation Assessment
SCS	Spinal Cord Stimulation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
VAS	Visual Analog Scale
WHO	World Health Organization

3. Introduction

This statistical analysis plan (SAP) is based on Version 1 of the SCS Dosing 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 SCS Dosing study, protocol number MDT17046.

4. Study Objectives

4.1. Primary Objective

To characterize the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction.

4.2. Secondary Objective

To characterize the minimum amplitude as a percentage of perception threshold that maintains overall pain relief.

4.3. Additional Objectives

[redacted]

4.4. Safety Objective

To characterize therapy and device related adverse events and device deficiencies.

5. Investigation Plan

5.1. Study Design

The purpose of this study is to characterize the effects of amplitude titration on subject satisfaction and pain relief with HD stimulation (90 µs and 1000 Hz) in subjects with back and leg pain being treated by SCS.

This is a prospective, multi-center, single-blind post-market feasibility study. This study will be conducted in the United States at no less than 2 sites. Approximately 60 subjects will be enrolled to get 40 subjects to proceed beyond baseline visit. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 30 subjects will be enrolled at each site. Eligible subjects will receive four different programmed amplitude settings (80%, 60%, 40%, and 20% of perception threshold), each for approximately two weeks. Subjects will be blind to the different amplitude settings and will not be informed that the amplitude is being titrated down, beginning at 80% of perception threshold.

The eligibility criteria will be assessed at both screening visit and baseline visit.

Inclusion criteria – screening visit

To be included in this study, a patient must meet the following inclusion criteria:

1. 22 years of age or older
2. Implanted with a RestoreSensor system (for back and leg pain) for at least 1 month
3. Has a program with only 1 anode and 1 cathode with 90 µs and 1000 Hz and the group that contains the program is used ≥ 50% (compared to the percent use of the other groups, if present).
4. Willing and able to provide signed and dated informed consent
5. Capable of comprehending and consenting in English
6. Capable of getting into the supine and sitting positions for perception threshold testing

7. Willing and able to comply with all study procedures and visits
8. On stable (no change in dose, route, or frequency) prescribed pain medications for at least 4 weeks before enrollment and willing to maintain dose during the study

Exclusion criteria – screening visit

To be included in this study, a patient must not meet any of the following exclusion criteria:

1. Implanted with leads for peripheral nerve stimulation or an implantable intrathecal drug delivery system
2. Had a pain-related surgery in the previous 1 month of enrollment or the intent to undergo surgery during the period of the study
3. Implanted with quadripolar lead
4. Currently enrolled or planning to enroll in a potentially confounding clinical study during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic study manager (or designee))
5. Pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study
6. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee
7. Has serious drug-related behavioral issues (e.g., alcohol dependency, substance abuse), as determined by the investigator, or designee
8. Has unresolved major issues of secondary gain (ie, secondary reason not to report improvement in health condition), as determined by the investigator, or designee

Inclusion criterion – baseline visit

To proceed on with the Baseline visit, the subject must meet the following inclusion criteria:

1. Has an average overall VAS pain score ≤ 4 based on the Baseline diary

Exclusion criteria – baseline visit

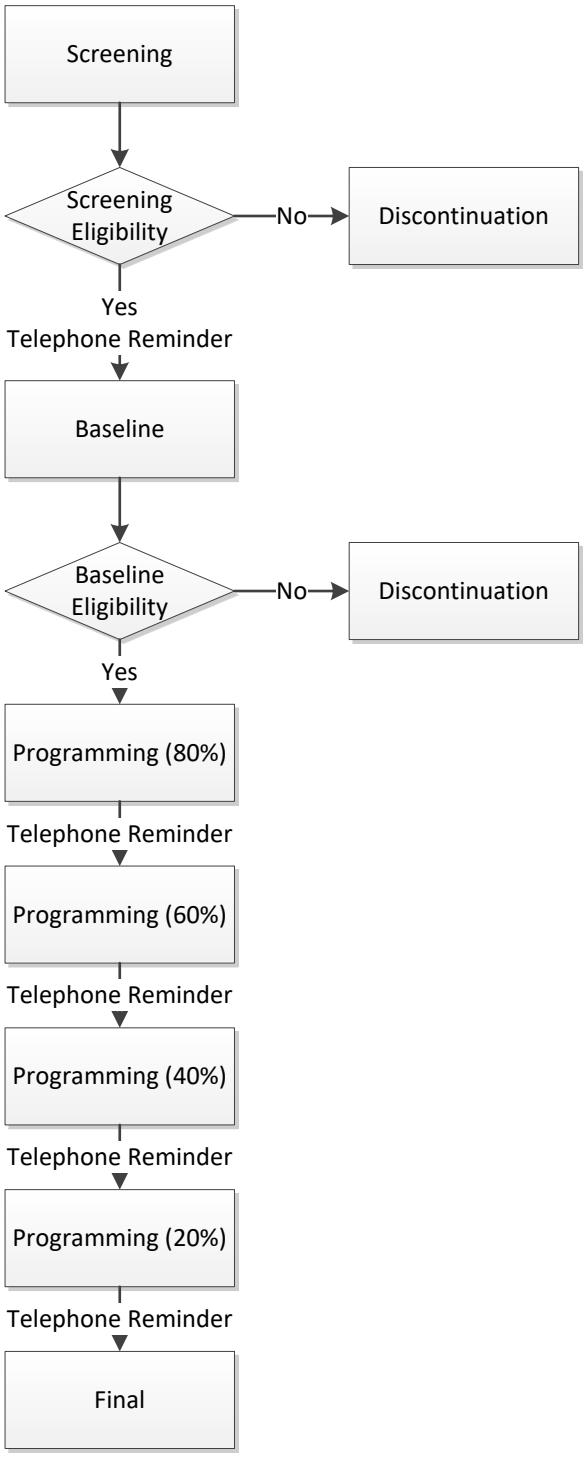
To proceed on with the Baseline visit, the subject must not meet any of the following exclusion criteria:

1. Has provided response to Baseline SSA as “Neutral”, “Somewhat unsatisfied”, or “Very unsatisfied” with the therapy
2. Completed less than 5 of the 7 days of the Baseline diary

The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 15 months. Each subject’s participation in the study is expected to last approximately 12 weeks from enrollment. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.

A summary of the study design is illustrated in Figure 1.

Figure 1: Study Visit Diagram



5.2. Study Measures

5.2.1. Efficacy Measures

5.2.1.1. Satisfaction and Stimulation Assessment (SSA)

Subjects will be asked to indicate their satisfaction with the therapy and details pertaining to any stimulation sensations. The SSA will include questions such as the following:

- Overall how satisfied or unsatisfied are you with this therapy?
  - Very satisfied
  - Somewhat satisfied
  - Neutral
  - Somewhat unsatisfied
  - Very unsatisfied
- Specify reason for this response?

- Have you felt any stimulation sensations?
  - No
  - Yes, specify the following:
    - Occasional or Continuous
    - Pleasant or Unpleasant
    - Position when felt (lying on back, lying on front, lying on right, lying on left, mobile, reclining, upright, other)

5.2.1.2. Visual Analog Scale (VAS) in Pain Diary

Pain will be assessed using the VAS in a pain diary. The VAS is a 10-cm line, with “No pain” on left and “Worst pain imaginable” on the right.

Subjects will record their overall, back, and leg pain using a paper pain diary once a day for a 7-day period prior to the scheduled study visits. For the initial baseline pain diary, completed prior to the baseline visit, subjects are required to complete at least 5 of the 7 days to ensure diary compliance during the study.

For the scheduled follow-up visits, the subject will be reminded to complete the diary for a 7-day period prior to the scheduled follow-up visit and the last 3 days of the diary will be used for the assessment.

The pain diary questionnaire will consist of questions such as the following:

- Please rate your pain by making a vertical slash mark through the line that best describes your average overall pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)
- Please rate your pain by making a vertical slash mark through the line that best describes your average back pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)

- Please rate your pain by making a vertical slash mark through the line that best describes your average leg pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)

[redacted]

[redacted]

[redacted]

5.2.2. Safety measures

Safety will be evaluated by the collection of device deficiencies and adverse events related to the following:

- The implanted SCS system and accessories
- Spinal cord stimulation therapy

6. Determination of Sample Size

An estimated 60 subjects will be enrolled in order for at least 40 subjects to proceed beyond the Baseline visit. A sample size of 40 subjects is reasonable to characterize the distribution of the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction, as well as to provide data for consideration of future studies.

[redacted]

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition will be summarized using a flow diagram. Reasons for subject discontinuations will be summarized.

7.1.2. Clinical Investigation Plan (CIP) Deviations

All CIP deviations will be summarized by type of deviations. Details of CIP deviations that affect scientific integrity or patient safety may be presented.

7.1.3. Analysis Sets

Treated Analysis Set

Treated analysis set will include subjects who proceed beyond the baseline visit and receive at least one programmed amplitude setting.

Baseline Analysis set

Baseline analysis set will include subjects who met inclusion and exclusion criteria at both screening and baseline visits. These are the subjects who responded to HD stimulation, which is defined as having an average overall pain VAS ≤ 4 at baseline. The baseline characteristics will be summarized for one of the additional objectives.

Safety Analysis set

All subjects will be included in the safety analysis set.

7.2. General Methodology

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used for the analyses of the study results (e.g., SAS).

This SAP is developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

7.3. Center Pooling

The investigators of this study will conduct the study according to a common protocol and use the same CRFs to collect study data. The site study personnel will be trained prior to the study initiation at each site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements.

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 30 subjects will be enrolled at each 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.

The analysis of the primary and secondary objectives will use subjects who provide data. The purpose of the study is to characterize the minimum amplitude that maintains SCS therapy satisfaction and overall pain relief; in case subjects drop out during follow-up, the percentage of amplitude prior to dropout will be used to summarize the minimum amplitude.

7.5. Adjustments for Multiple Comparisons

As there is no hypothesis testing, adjustment for multiple endpoints is not required.

7.6. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized in the report for all subjects who complete the Baseline visit and meet the Baseline eligibility requirements.

7.7. Treatment Characteristics

Subjects are implanted before enrolling into the study, so the surgical procedures are not described in the study. The neurostimulator and lead(s) model will be summarized. Subjects proceed beyond baseline visit will receive 4 different programmed amplitude setting in the following order: 80%, 60%, 40%, and 20% of perception threshold amplitude, each for approximately two weeks. Subject assessments are collected at each following up visit.

Subjects' pain medications will be collected. All pain medications will be coded using the appropriate version of the World Health Organization (WHO) Drug Dictionary at the appropriate Anatomical Therapeutic Chemical (ATC) level.

7.8. Interim Analyses

There is no planned interim analysis for the primary and secondary objectives in this study.

7.9. Evaluation of Objectives

7.9.1. Primary Objective

To characterize the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction.

7.9.1.1. Hypothesis

There is no hypothesis testing for the primary objective. The purpose of the primary objective is to characterize the minimum amplitude that maintains SCS therapy satisfaction.

7.9.1.2. Experimental Design

The measurement of SSA is described in Section 5.2.1.1. Subject dissatisfaction with the therapy is defined as subjects choosing either 'somewhat unsatisfied' or 'very unsatisfied'. The SSA is collected at baseline and scheduled follow-up visits.

7.9.1.3. Analysis Methods and Presentation Format

The frequency and percentage of subjects satisfied with the therapy will be summarized at baseline and scheduled follow-up visits. In case subjects drop out during follow-up, a category of missing data will be included in the summary so that the percentage is not inflated because of missing data. As an additional analysis, if a subject drops out of the study due to dissatisfaction with the therapy, the subject will be treated as dissatisfied (same level at dropout) at the subsequent lower percentages of amplitude where data was not collected

The percentage of amplitude from perception threshold for maintaining subjects' satisfaction with the therapy will be summarized too. In case subjects drop out during follow-up, the percentage of amplitude prior to subject dropout will be used as the minimum amplitude in the summary.

7.9.1.4. Determination of Subject for Analysis

Subjects who proceed beyond the baseline visit and receive at least one programmed amplitude setting (treated analysis set).

7.9.2. Secondary Objective

To characterize the minimum amplitude as a percentage from perception threshold that maintains overall pain relief. Maintaining overall pain relief is defined as having $\leqslant$ 2 points increase in average overall pain VAS during study follow-up.

7.9.2.1. Hypothesis

There is no hypothesis testing for the secondary objective. The purpose of the secondary objective is to characterize the minimum amplitude that maintains overall pain relief of equal or less than 2 points increase in average overall VAS pain scores.

7.9.2.2. Experimental Design

The measurement of pain score is described in Section 5.2.1.2. For baseline, an average overall VAS pain score is calculated using all 7 days of the diary. For scheduled follow-up visits, an average overall VAS pain score is calculated using the last 3 days of the diary prior to the scheduled visit, to ensure that there is no residual treatment effect from the previous period. The pain scores are collected at baseline and scheduled follow-up visits.

7.9.2.3. Analysis Methods and Presentation Format

The mean and standard deviation of the pain scores (including overall, back, and leg pain) will be summarized at each follow-up visit. The change in pain scores will be summarized too. As an additional analysis, if a subject drops out of the study due to dissatisfaction with the therapy, the subject's pain scores at dropout will be used at the subsequent lower percentages of amplitude where data was not collected

The percentage of amplitude from perception threshold for maintaining overall pain relief will be summarized. In case subjects drop out during follow-up, the percentage of amplitude prior to subject dropout will be used as the minimum amplitude in the summary.

In addition, a repeated measure analysis may be applied to examine the relationship between the change in pain score and percent amplitude. The dependent variable will be the change in pain score,

the independent variables will be percent amplitude and visit as fixed effects, and subject as the random effect. The interaction term of percent amplitude by visit will be tested and kept out of the model if it is not significant.

7.9.2.4. Determination of Subject for Analysis

Subjects who proceed beyond the baseline visit and receive at least one programmed amplitude setting (treated analysis set).

7.9.3. Additional Objectives

[redacted]

[redacted]

7.10.Safety Evaluation

The safety objective is to characterize therapy and device related adverse events and device deficiencies.

Adverse events and device deficiencies will be coded and summarized using the most recent version of Medical Dictionary for Regulatory Affairs (MedDRA).

The adverse events will also be categorized by relationship to study device and/or therapy. Adverse events 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 adverse events and of any deaths will also be provided. A detailed narrative of each serious device or therapy related adverse event will be provided.

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

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 secondary object 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.

9. References

i. Hakkinen A, Kautiainen H, Jarvenpaa S, Arkela-Kautiainen M, Ylinen J. Changes in the total Oswestry Index and its ten items in females and males pre- and post-surgery for lumbar disc herniation: a 1-year follow-up. *Eur Spine J.* Mar 2007;16(3):347-352.

[ii]. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976).* Nov 15 2000; 25(22):2940-2952; discussion 2952.

[iii]. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.