Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Spinal Cord Stimulation (SCS) Research Study
Clinical Investigation Plan Identifier	MDT18036 / NCT03763708
Clinical Investigation Plan Version	3.0
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Sponsor/Local Sponsor	Medtronic Restorative Therapies Group 7000 Central Ave NE Minneapolis, MN 55432 USA

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Statistics Manager
2.0	Updated with changes to CIP v2.0 • [redacted] • [redacted] • Updated Investigation Plan to be more flexible with respect to [redacted] • [redacted] • Put on 056-F285, Rev C template • [redacted]	[redacted] Principal Statistician
3.0	Updated with changes to CIP v3.0 • [redacted] • [redacted] • [redacted]	[redacted] Principal Statistician

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
AE	Adverse event
CIP	Clinical Investigation Plan
[redacted]	[redacted]onnaire
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
SAP	Statistical Analysis Plan
SCS	Spinal cord stimulation
SOC	System Organ Class
[redacted]	[redacted]

3. Introduction

Spinal cord stimulation (SCS) has been proven to be an effective therapy for pain relief. Three parameters are programmed to deliver stimulation in SCS systems: pulse width (µs), frequency (Hz), and amplitude (mA or V). Neurostimulators have the ability to stimulate in a wide range of on-label parameter settings; however, more can be understood about the effects of these parameters on patient pain relief.

This is a prospective, multi-center, post-market study to characterize the effects of stimulation parameters on pain relief [redacted].

This is an overall Statistical Analysis Plan (SAP), which provides the descriptions of the analyses and summaries that may be conducted [redacted] under the CIP, including the primary objective [redacted] as detailed in Section 4.

4. Study Objectives

4.1 Primary Objectives

To characterize the pain scores, specific to the indication associated with SCS implant, with different SCS parameters, at enrollment and during follow-up periods.

[redacted]

5. Investigation Plan

This is a prospective, multi-center, post-market study to characterize the effects of stimulation

parameters on pain relief [redacted]. It is estimated that up to 360 subjects will be enrolled [redacted] in the United States. [redacted]

The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 10 years.

Multiple on-label stimulation parameters will be studied throughout the execution of this clinical investigational plan [redacted]
A study cohort is defined as a group of subjects who share the same recommended programming parameters [redacted]
The longer enrollment period enables the research of SCS parameters over time as the science and technology in SCS develops.

[redacted]
The completion of the study is defined as the approval of the Final Clinical Study Report and closure of all sites. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6. Determination of Sample Size

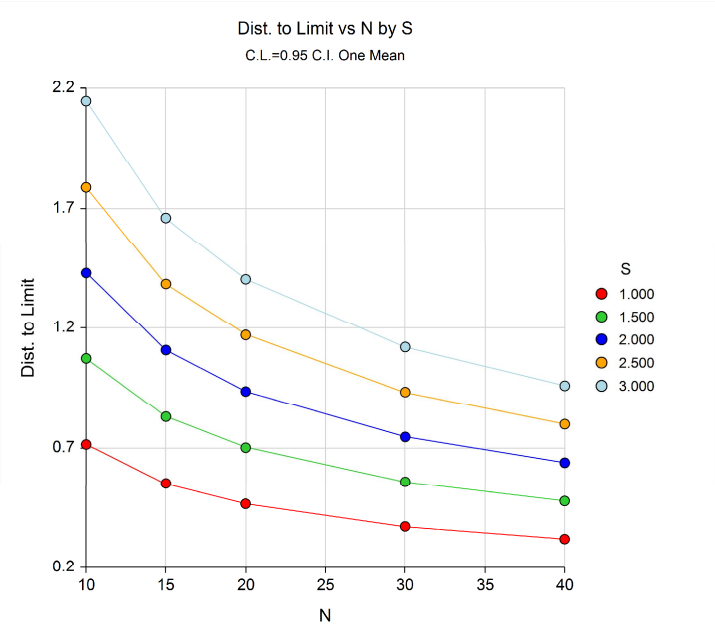
It is estimated that up to 360 subjects will be enrolled. Considering the research interests of multiple stimulation settings and longer enrollment of the study, a sample size of up to 360 subjects is deemed to be reasonable to characterize the effects of changes to stimulation settings, as well as to provide data for consideration of future studies.

The sample size for each stimulation setting may vary based on the research interests. Table 1 shows precision estimates (the distance from mean to limits) by sample size and standard deviation of [redacted]. A sample size of 30 produces a two-sided 95% confidence interval with the precision that is equal to 0.93 when the estimated standard deviation is 2.5.

Table 1 Precision by sample size and standard deviation of [redacted]

Sample size (N)	Standard deviation (S)				
	1.0	1.5	2.0	2.5	3.0
10	0.72	1.07	1.43	1.79	2.15
15	0.55	0.83	1.11	1.38	1.66
20	0.47	0.70	0.94	1.17	1.40
30	0.37	0.56	0.75	0.93	1.12
40	0.32	0.48	0.64	0.80	0.96

Figure 3 Precision by sample size and standard deviation of [redacted]



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7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized using a flow diagram with subject disposition at study visits including number of subjects who completed visits, the number subjects with missed visits, as well as subject discontinuations.

A table will also be provided to summarize the number of subjects at scheduled visits as appropriate.

The reasons for early discontinuation will be summarized and a listing of all discontinuations will be provided.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Deviations will be summarized by type of deviation.

7.1.3 Analysis Sets

The analysis of the study objectives will use subjects who provide data.

7.2 General Methodology

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (eg, SAS version 9.4 or higher) will be used for all analyses. Summary statistics will be presented for continuous measures (N, mean, median, standard deviation, minimum and maximum) and categorical measures (N, percent, frequency distributions) with two-sided 95% confidence intervals as appropriate. Further analysis details are provided in section 7.9.

This SAP describes the statistical methods that might be used in the analyses [redacted]. These are general methodologies. [redacted]

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 sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 90 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 study objectives will use subjects who provide data. No imputation will be made.

7.5 Adjustments for Multiple Comparisons

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

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized using the method as described in Section 7.2.

7.7 Treatment Characteristics

Amount of device exposure will be summarized using descriptive statistics such as mean, standard deviation, sum, minimum, and maximum.

Programming parameters in each group will be captured in periodic progress reports to describe the treatment received.

7.8 Interim Analyses

No formal interim analysis is planned for this study. Descriptive summaries [redacted] may be captured in periodic progress reports before the entire study is complete.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

Objective

To characterize the pain scores specific to the indication associated with SCS implant with different SCS parameters at enrollment and during follow-up periods.

Hypothesis

There is no hypothesis testing for the primary objective. The purpose of the primary objective is to characterize the pain scores by different stimulation parameter groups during follow-up periods.

Experimental design

[redacted] an average overall [redacted] pain score is calculated [redacted] pain scores, [redacted]

Analysis method

The mean and standard deviation as well as median, min, max of the pain scores will be summarized at follow-up visits. Pain scores may also be summarized by different stimulation parameter groups. Subjects who provide data will be included in the analysis.

[redacted]

[redacted]

[redacted]

7.10 Safety Evaluation

Adverse Event (AE) information will be collected from the time the subject has been enrolled until they are discontinued from the study. Only those AEs which are related to the following will be collected:

- The SCS system and accessories (device-related)
- SCS therapy (therapy-related)
- SCS procedure (procedure-related)

Therapy, procedure, and device related adverse events adverse events and device deficiencies will be coded and summarized using the most recent version of Medical Dictionary for Regulatory Affairs (MedDRA). Adverse events that are classified as possible, probable, or causal are considered as related.

Adverse events will be presented in summary tables displaying the number of events, and the number and percentage of subjects with one or more events. A summary of device, therapy, and/or procedure related events by System Organ Class (SOC) and Preferred Term (PT) will also be provided. Serious AEs will be summarized in a similar manner.

Device deficiencies will be presented in summary tables displaying the number of deficiencies, and the number and percentage of subjects with device deficiencies. A summary of device deficiencies by SOC and PT will also be provided.

7.11 Health Outcomes Analyses

No health outcomes analyses are planned for this study.

7.12 Changes to Planned Analysis

There are no changes to the planned analysis in the CIP. Any deviations from this SAP will be described and justified in the 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(s) 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 shall be 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 p-value or confidence interval has been generated may need to be validated using at least Level II validation.

9. References