DTM™-LE SCS Study

Statistical Analysis Plan V3.0

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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Differential-Target Multiplex Low Energy Spinal Cord Stimulation (DTM-LE SCS) Study
Clinical Investigation Plan Identifier	MDT20042
[redacted]	[redacted]
Sponsor/Local Sponsor	Medtronic, Inc. Medtronic Neuromodulation 700 Central Ave NE Minneapolis, MN, 55432 U.S.A. +1-763-514-4000

Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]
2.0	• [redacted]	[redacted]
3.0	• Corrected base program frequency range to align with CIP • Corrected reference links	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
DD	Device Deficiency
DTM	Differential-Target Multiplexed
eCRF	Electronic Case Report Form
[redacted]	[redacted]
LE	Low Energy
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NPU	Neuro Programmer Upload
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCS	Spinal Cord Stimulation
[redacted]	[redacted]
[redacted]	[redacted]
UAE	Unavoidable Adverse Event
VAS	Visual Analog Scale

3. Introduction

Spinal Cord Stimulation (SCS) uses electrical signals to modulate the nervous system, resulting in pain relief. These signals are defined by programs comprised of parameter settings for the amplitude, frequency, pulse width, active electrodes, current distribution, and therapy cycle. Non-rechargeable SCS systems have a finite energy capacity that limits the parameter settings available to meet an acceptable implant longevity. Several technologies have been developed for SCS, one of which is the Differential Target Multiplexed (DTM™) waveform. The DTM™ waveform was designed to target neural and glial cells. Preclinical research suggests the ability of DTM™ SCS to impact neural-glial cell interaction, showing statistically significant reversal of pain behaviors compared to either low or high frequency stimulation alone. In a randomized controlled trial, DTM™ SCS delivered superior back pain relief at the 3-month primary endpoint for patients with chronic back and leg pain, compared to conventional stimulation.

With the desire to provide an advanced therapy and to continue to build on the DTM™ theory, this study aims to employ a combination of energy reducing strategies (reduction in frequency, therapy cycling) to study a low energy DTM™ SCS derivative that may reduce recharge burden in RC systems and enable an acceptable device longevity in non-rechargeable systems while continuing to provide meaningful pain relief. The purpose of this study is to evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief.

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the planned analyses of the objectives listed in the study Clinical Investigation Plan (CIP). This SAP is comprehensive of the statistical methods and analyses to be included in the final study report. Unless otherwise specified, all analyses listed within this SAP will be included in the final study report.

4. Study Objectives

4.1 Primary Objective

To characterize changes in overall (back and leg) pain intensity, as measured by visual analog scale (VAS), from Baseline to 3-Month visit in subjects with devices programmed to DTM-LE SCS.

4.2 Secondary Objective

To characterize programming parameters associated with energy use from Device Trial through 12-Month visit.

[redacted]

5. Investigation Plan

This is a prospective, multi-center, open-label, post-market study to evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief. The study will be conducted in up to 15 sites in the United States.

Up to 56 subjects are expected to be enrolled in the study to allow for approximately 30 subjects to complete the 3-Month Visit. All implanted subjects with devices activated will be followed through the

12-Month/Final Study Visit. The study sample size accounts for expected attrition; therefore, subjects who discontinue prior to study completion will not be replaced.

All eligible subjects will undergo an SCS Device Trial that includes an intraoperative testing and DTM-LE programming. During the DTM-LE programming trial, DTM-LE stimulation will be programmed for pain relief and comfort. Different, simultaneously running signals within the range of FDA-approved device capabilities will be delivered at [redacted] unique locations between [redacted] T8 and [redacted] T10 vertebral levels within the following limits:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

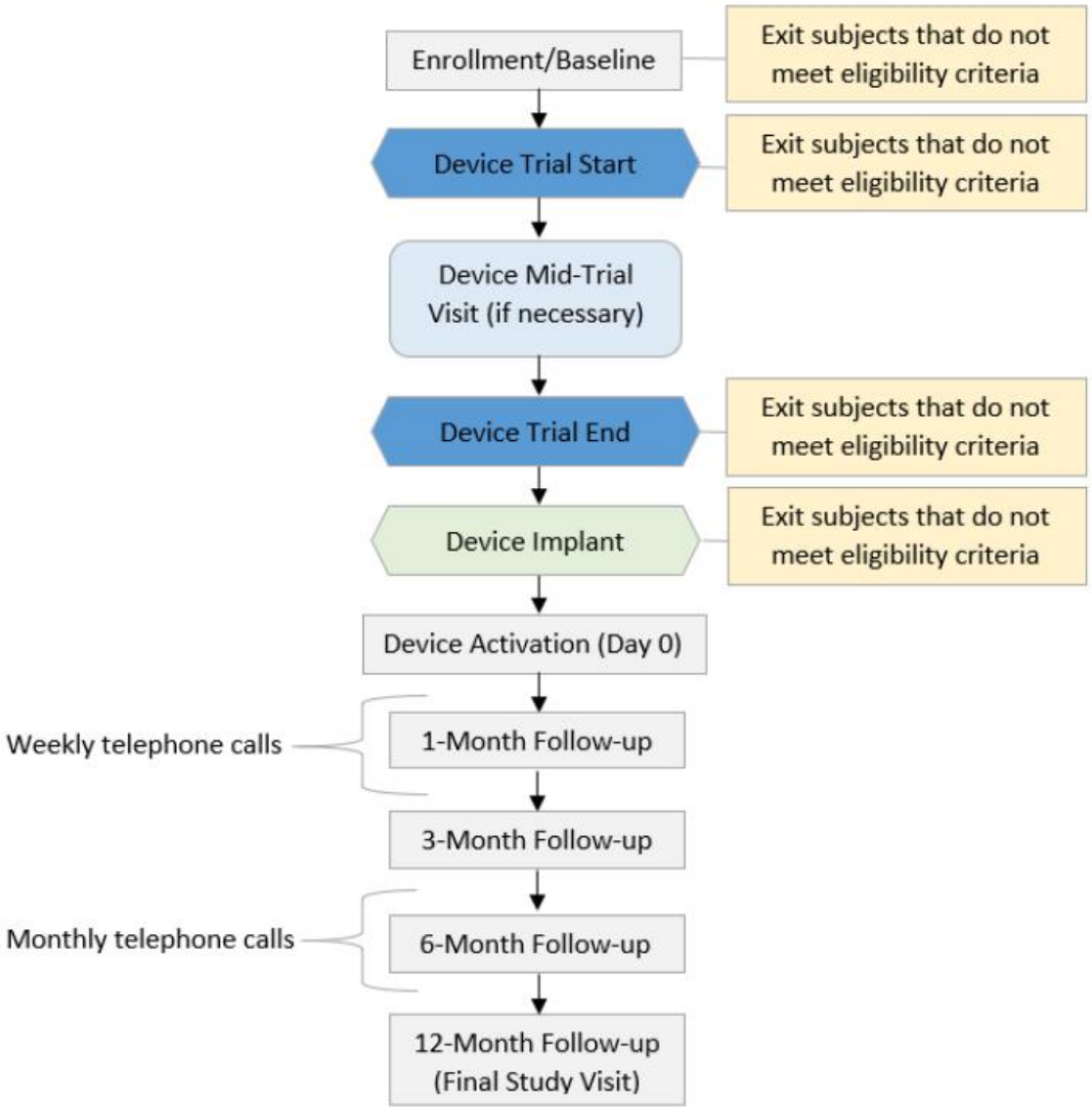
After a successful DTM-LE Device Trial, subjects will proceed with the standard of care to an implant of a Medtronic Intellis™ with AdaptiveStim™ rechargeable neurostimulator. Approximately 9-12 days post-implant, after the wound has healed, the device will be activated and programmed using DTM-LE.

Device activation will be Day 0 for the study. Subjects will complete follow-up visits at 1-, 3-, 6-, and 12-months. The primary endpoint will be evaluated at the 3-Month visit.

Subjects may be enrolled at approximately 15 study sites in the US, with no more than 10 subjects enrolled at any individual study site. Enrollment will be competitive across study sites. The per-study site enrollment cap may be increased upon Sponsor approval.

Figure 5-1 is a flow diagram of how subjects will complete the study.

Figure 5-1: Study Visit Diagram



6. Determination of Sample Size

The statistical software PASS 11 was used for sample size and precision calculation at 95% confidence level (2-sided) using the Confidence Intervals for One Mean module. The precision estimates (the distance from mean to limits) by sample size and standard deviation of VAS are provided in Table 6-1. Assuming a standard deviation of 2.6 based on internal historical studies, a sample size of 30 subjects provides an expected precision of 0.97.

Table 6-1: Precision by Sample Size and Standard Deviation of VAS

Sample size (N)	Standard deviation (S)			
	2.4	**2.6**	2.8	3.0
26	0.97	1.05	1.13	1.21
28	0.93	1.01	1.09	1.16
30	0.90	**0.97**	1.05	1.12
32	0.89	0.94	1.01	1.08

With estimated attrition of 40% between enrollment and implant and 10% between implant and 3-Month from historical internal and external pain studies, to achieve approximately 30 subjects at 3-Month visit, up to 56 subjects may be enrolled into the study.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized by site and overall, in a table showing the number of subjects at these visits: Baseline, Device Trial Start, Implant, Device Activation (Day 0), 1-Month, 3-Month, 6-Month, and 12-Month. Additionally, the subject disposition at each visit will be depicted in a flow diagram for all enrolled subjects.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be summarized by deviation type and associated visit. A listing of protocol deviations, which will include the reason for the deviation and any other additional details about the deviation, will also be included in the final study report.

[redacted]

[redacted]

7.2 General Methodology

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.

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.

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.

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 primary analysis of the primary and secondary objectives will include subjects who follow DTM-LE programming and provide data (Per-protocol Analysis Set). Sensitivity analyses will be performed for the primary objective using Completer Analysis Set, as well as Implanted Analysis Set with the Multiple Imputation (MI) methodology for missing data.

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

Demographic and other baseline characteristics will be summarized for the Enrolled, Implanted, and/or Per-protocol Analysis Sets (section 7.1.3) as appropriate. Subjects with missing or unknown demographic data will be excluded from the relevant analysis, with a count of subjects with missing data provided. Listings of age at baseline, sex, race, and ethnicity will be included. A listing of activity goals at baseline will also be included.

7.7 Treatment Characteristics

Device exposure is summarized in section (7.10 Safety Evaluation).

The number and percent of patients who report at least a 50% improvement in pain at the Device Trial End Visit will be summarized.

Only medications used specifically for the treatment of back and/or leg pain will be collected during the study. Pain medications will be collected at baseline, and any changes to pain medications will be collected throughout the study. 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. Any changes to a subject's pain medications while they are enrolled in the study will be documented in the subject's medical records and the concomitant medications eCRF. The analysis of these concomitant medications is summarized in section 7.9.3.10.

7.8 Interim Analyses

No interim analyses are planned for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The primary objective is to characterize changes in overall (back and leg) pain intensity, as measured by visual analog scale (VAS), from Baseline to 3-Month visit in subjects with devices programmed to DTM-LE SCS.

7.9.1.1 Hypothesis

There is no hypothesis testing for the primary objective. The primary objective is to characterize the overall pain relief from baseline to 3-Month visit in subjects with DTM-LE SCS.

7.9.1.2 Endpoint definition and derivation

Pain will be assessed using a VAS (0-10 cm) with 0 cm meaning "no pain" and 10 cm meaning "worst pain imaginable". Overall pain is defined as a combination of back and leg pain, but not pain from other body parts. Subjects will be asked to report their average pain intensity (overall, back, and leg) that is related to their SCS device treatment "in the last 24 hours" by marking a line perpendicular to the VAS line at the point that represents their pain intensity. Site personnel will determine the score by measuring the distance (cm) on the 10-cm line between the left, "no pain" anchor and where the subject's mark meets the line. The total length of the line will be measured (to ensure that it is 10 cm) and the distance from the "no pain" mark to the subject's mark divided by the total distance of the line will be recorded. The scored VAS ranges from 0 – 10. The overall pain intensity as measured by VAS will be collected at both baseline and 3-Month visit. The primary endpoint of change in overall pain VAS is

calculated using VAS at the 3-Month visit minus VAS at the baseline visit. A negative change is an improvement.

7.9.1.3 Analysis Methods

The change in overall pain VAS as well as overall pain VAS at both baseline and the 3-Month visit will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.). The 95% CI of the mean change will be calculated.

In addition, percentage of change in overall pain VAS will be calculated for each patient using change in overall pain VAS divided by overall pain VAS at baseline. A negative percentage of change in VAS is a percentage of reduction in VAS, thus an improvement. The percentage of change in overall pain VAS will be summarized using descriptive statistics, (e.g., median and inter-quartile range, etc.)

7.9.1.4 Determination of Subjects/Data for Analysis, Sensitivity Analysis

The primary analysis will use subjects who are implanted with Intellis neurostimulator, follow DTM-LE programming, and provide outcome measures at both baseline and 3-Month visit (Per-protocol Analysis Set).

Two sensitivity analyses will be performed. The first uses the Completers Analysis Set (7.1.3) who have outcome measures at both baseline and 3-Month visit and will be performed in the same way as the primary analysis method above. The other sensitivity analysis uses the Implanted Analysis Set (7.1.3) and will be performed using Multiple Imputation (MI) method for missing data at the 3-Month Visit. For scheduled 3-Month visit, if an Unscheduled Visit occurred within the 3-Month visit window, and the VAS is collected at the Unscheduled Visit, the VAS from the Unscheduled Visit will be used in the analysis of the 3-Month visit. Otherwise, the missing VAS will be imputed using 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. The model variables in MI may include, but are not limited to study site, subject age, gender, primary diagnosis, VAS at baseline, 1-Month visit. The fully conditional specification method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed VAS are restricted to values ranging from 0-10. Following imputation, the objective will be evaluated using MI analysis method.

7.9.2 Secondary Objective

To characterize programming parameters associated with energy use from Device Trial through 12-Month visit.

7.9.2.1 Hypothesis

There is no hypothesis testing for the secondary objective. The secondary objective is to characterize programming parameters associated with energy use.

7.9.2.2 Endpoint Definition and derivation

Subject's programmed settings (frequency, pulse width, and amplitude) together with the impedance range measurements and cycling ON-OFF time will be summarized.

7.9.2.3 Analysis Methods

The programming parameters associated with energy use will be summarized using descriptive statistics, (e.g., mean, standard deviation, etc.) from Device Trial through 12-Month visit. Where possible, the energy use may be summarized by average recharge interval.

7.9.2.4 Determination of Subjects/Data for Analysis

The analysis will use subjects who are implanted with the Intellis neurostimulator, follow DTM-LE programming, and have available data at Device Trial, 1-Month, 3-Month, 6-Month, or 12-Month visits (Per-protocol Analysis Set). One sensitivity analysis will be performed using the Completers Analysis Set, which will use subjects with available data at baseline and follow up visits of Device Trial, 1-Month, 3-Month, 6-Month, and 12-Month visits, respectively.

An overview of the additional objectives is given in Table 7-1Table 7-1.

Table 7-1: Overview of Additional Objectives

End Point of Additional Objective	Scale/Data Collection	Baseline	1-Month	3-Month	6-Month	12-Month
1. Change from baseline in overall pain intensity [A]	VAS	X	✓	A	✓	✓
[redacted]						

A. Primary Objective is to characterize change from baseline to 3-months.

7.9.3.1 Change in overall pain (VAS)

Changes in overall pain intensity, as measured by VAS, from Baseline to 1-, 6-, and 12-Month visit will be analyzed for both the Per-protocol Analysis Set and the Completers Analysis Set. Change in overall pain intensity will be calculated using VAS at the 1-, 6-, and 12-Month visit minus VAS at the baseline visit. A negative change is an improvement. The 95% CI of the mean change will be calculated. Scores at all visits will be summarized.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.10 Safety Evaluation

All device-related, therapy-related, and procedure-related adverse events and device deficiencies from the Device Trial Start Visit until study exit will be characterized.

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 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.

Device exposure will be summarized by analysis set 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.

Data from the Scheduled Follow Up CRF will be evaluated for subjects in the Completer Analysis Set to determine whether subjects were programmed within DTM-LE limits during the study. For subjects who

were programmed within DTM-LE limits, the months of DTM-LE exposure will be computed in the same way as above, with the Cut-off Date for DTM-LE extending until the date at which it was reprogrammed out of DTM-LE limits.

7.11 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 should 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 confidence interval has been generated may need to be validated using at least Level II validation.

9. References

[redacted]

7. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther*. 2004;27(1):26-35. doi:10.1016/j.jmpt.2003.11.003

10. Appendices