InterStim® BASIC Study
Statistical Analysis Plan Version 1.0
14-Sep-2020
NCT04016324

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Basic Evaluation Lead Post-Market Clinical Follow-up (BASIC) Study
Clinical Investigation Plan Identifier	MDT19002
Clinical Investigation Plan Version	1.0
Sponsor/Local Sponsor	United States (Sponsor): Medtronic Neuromodulation 7000 Central Ave NE Minneapolis, MN 55432 USA Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland Canada (Local Sponsor): Medtronic Canada ULC 99 Hereford Street Brampton, ON, L6Y 0R3 Canada 1-905-460-3800
Document Version	1.0

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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
BASIC	Basic Evaluation Lead Post-Market Clinical Follow-up
BE	Basic Evaluation
BMI	Body Mass Index
CI	Confidence Interval
CIP	Clinical Investigational Plan
DD	Device Deficiency
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
SAP	Statistical Analysis Plan

3. Introduction

This statistical analysis plan (SAP) is based on Version 1.0 of the Basic Evaluation Lead Post-Market Clinical Follow-up (BASIC) Study. The SAP presents the details of the methods to be used to analyze and report the study results of the BASIC study, protocol number MDT19002.

4. Study Objectives

4.1 Primary Objective

To characterize the proportion of subjects who demonstrate motor or sensory response(s) during lead placement using the InterStim Basic Evaluation (BE) Lead.

[redacted]

4.3 Safety Assessment

To characterize safety during the BE lead implant and therapy evaluation.

Safety will be evaluated by the collection of reportable adverse events (AEs). Any AE meeting the definition of: serious, device related, therapy related and/or procedure related will be considered reportable for this study.

Device deficiencies (DDs) will be collected and reported.

5. Investigation Plan

This is a single-arm, prospective, multicenter, post market clinical follow-up study to characterize the clinical performance and safety of the InterStim BE lead with the commercially-approved foramen needle and BE kit. The study is intended to be conducted at approximately 30 centers in Europe, Canada, and the United States.

Subjects will complete a baseline visit, BE lead placement visit, and 1-week follow-up visit. Enrollment will be defined as subjects who qualify for all eligibility requirements and undergo the BE lead implant procedure.

The total study duration for a subject is approximately three weeks, depending on when the BE lead implant procedure is scheduled. If a CIP amendment impacts the integrity of a study, the data collected before and after the amendment will be analyzed statistically to assess the effect of the amendment on performance, effective or safety analysis. This analysis will be included in the clinical investigation report.

Inclusion Criteria:

1. Subjects 18 years of age or older
2. Candidate for sacral neuromodulation in accordance with the InterStim System labeling
3. Have a diagnosis of OAB as demonstrated by either urinary urge incontinence and/or urinary frequency on a 3-day voiding diary
4. Willing and able to accurately complete study diaries, questionnaire, attend visits, and comply with the study protocol
5. Willing and able to provide signed and dated informed consent

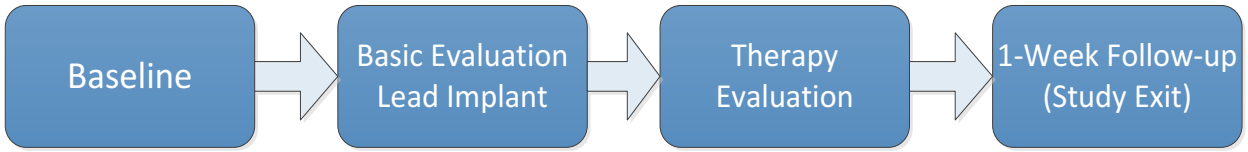
Exclusion Criteria:

1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia)
2. Have implantable pacemakers, or defibrillators
3. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component
4. Have knowledge of planned MRIs, diathermy, microwave exposure, high output ultrasonic exposure, or RF energy exposure not included within the scanning conditions provided with the InterStim System labeling
5. Women who are pregnant or planning to become pregnant during participation in the study
6. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements
7. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.*

*Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in both studies.

The following will be conducted:

1. Baseline
2. Enrollment / Basic Evaluation Lead Implant Procedure
3. Therapy Evaluation
4. One Week Follow-up Visit (Study Exit)



6. Determination of Sample Size

Subjects will be enrolled to obtain a sample size of approximately 100 subjects who complete a BE lead placement with motor or sensory threshold testing to confirm clinical performance. The sample size of approximately 100 subjects is driven to obtain precision of the primary endpoint. Assuming that motor or sensory response is able to be obtained in 95% of subjects who qualify for a BE lead placement, with 100 subjects, this produces a two-sided 95% Confidence Interval (CI) of 88.7-98.4% with a width equal to 9.6%. The CI width will vary slightly depending on the actual proportion of subjects with motor or sensory responses.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition according to their follow-up status will be summarized. Reasons for subject discontinuations will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All CIP deviations will be summarized by type of deviation. Details of CIP deviations that affect scientific integrity or patient safety may be presented. The protocol pre-specifies a visit window of 5-7 days for the 1-week follow-up visit. The minimum required therapy evaluation period is 3 days, so the subjects could have follow-up visit starting 4-days post implant procedure. Therefore, a visit at 4-days will be allowed without requiring a deviation and data will be reported.

7.1.3 Analysis Sets

Safety Analysis set

The safety analysis set will include all subjects who meet eligibility criteria and signed the informed consent. The safety analysis set will be used for the reporting of serious AEs.

Full Analysis Set (FAS):

The FAS will include all subjects who meet eligibility criteria, signed the informed consent, and undergo the BE lead implant procedure. Subjects will be considered enrolled at the time of the BE lead procedure. The FAS will be used for reporting of the primary endpoint [redacted]

Additionally, it will be used for the analysis on the device, therapy, and/or procedure related AEs and DDs.

7.2 General Methodology

There is no hypothesis testing in this study.

Continuous measures will be reported as N, means, medians, standard deviations, minimums and maximums. Categorical measures will be reported in frequency distributions including counts and percentages.

For outcomes examining change from baseline, change (Δ) will be calculated as follow-up scores (S_v) minus baseline scores (S_0).

$$\Delta = S_v - S_0$$

Percent change will be calculated as 100 times the change divided by the baseline score.

$$\text{Percent change} = 100*\Delta/S_0$$

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 version 9.4 or higher).

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 20 subjects will be implanted at each site unless the site gets pre-approval from Medtronic for additional enrollments.

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.

For the primary objective of motor or sensory response, in case subject's motor or sensory response is not tested or response data are lost during lead placement, a sensitivity analysis will be performed by displaying the full range of proportions on the potential impact of missing data by running an analysis assuming all missing values as not obtaining motor or sensory response (worst case) to all missing values as obtaining motor or sensory response (best case).

7.5 Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons because no hypothesis testing will be conducted.

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized in the report for all enrolled subjects using the FAS.

Demographics and other baseline characteristics summarized will include:

- Age, sex, race, and ethnicity
- [redacted]
- [redacted]
- Body Mass Index (BMI) [kg/m2] = $\frac{\text{weight [kg]}}{\text{height [m]}^2}$
- [redacted]
- [redacted]
- Primary diagnosis per baseline diary (UIU, UF, both)
- Baseline leaks per day for UUI subjects (UUI subjects are defined as patients who have recorded at least one leak with urgency in their baseline diary), baseline voids per day for UF subjects (UF subjects are defined as patients who have recorded 8 or more voids per day in their baseline diary), and average degree of urgency
    - Average degree of urgency per day will be calculated based on the urgency rating where None=0, Mild=1, Moderate=2, Severe=3, and Very Severe=4 across all episodes reported per day. This will be performed separately for leaks and voids.

7.7 Treatment Characteristics

Lead implant data including motor and sensory thresholds, sensory assessment, discharge test stimulator settings, and number of leads placed (unilateral vs. bilateral) will be summarized. Motor and sensory response of the needle will also be summarized.

7.8 Interim Analyses

There is no planned interim analysis for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Objective - Motor or Sensory Response

To characterize the proportion of subjects who demonstrate motor or sensory response(s) during lead placement using the InterStim BE Lead. This will be done separately for leads and the needles used to place the leads.

7.9.1.1 Hypothesis

There is no formal hypothesis.

7.9.1.2 Experimental Design

During the lead placement procedure using the InterStim BE lead, subject's motor and/or sensory response will be collected. Subjects may be implanted with more than one BE lead. In this case, the subject's motor and/or sensory response from all implanted BE leads will be recorded, and the subject will be considered as demonstrating a response if motor or sensory response is obtained from at least one BE lead.

More than one needle may be used to place the lead. In this case the subject's motor and/or sensory response from the needle used to determine final lead placement will be used. In cases where subjects have more than one lead placed, thresholds from the needles used to place each lead will be used, and the subject will be considered as demonstrating a response if motor or sensory response is obtained from at least one needle.

7.9.1.3 Analysis Methods and Presentation Format

Subjects who had the BE lead placement and provide data will be included in the primary analysis. The primary analysis will report the proportion of subjects who obtain motor or sensory response and its two-sided exact binomial 95% CI among those who had lead placement. This will be done separately for leads and the needles used to place the leads.

In cases where surgical modifications for BE leads are needed, motor or sensory response from the initial lead placement will be used for the primary analysis.

In cases where subject's motor or sensory response is not tested, or response data are lost during lead placement, or other reasons where missing data occur, a sensitivity analysis will be performed by displaying the full range of proportions on the potential impact of missing data by running an analysis assuming all missing values as not obtaining a response (worst case) to all missing values as obtaining motor or sensory response (best case).

In addition to the subject level analysis described above, a lead and needle level supporting analysis will be performed by estimating the proportion of BE Leads and needles that had motor or sensory response(s) during initial lead placement. The leads and needles that had motor or sensory responses during replacement BE lead implant will be summarized separately.

7.9.1.4 Determination of Subject for Analysis

The analysis will include all FAS subjects who provide data.

[redacted]

[redacted]

7.10 Safety Evaluation

All serious, device-related, procedure-related and/or therapy-related AEs and all DDs will be considered reportable for this study. All reportable AEs and DDs will be collected throughout the study once the informed consent form is signed. AEs and DDs will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Serious AEs will be summarized for the safety analysis set; device-related, procedure-related and/or therapy-related AEs and DDs will be summarized for all subjects who go through lead placement procedure. Summaries include the number of events, the number of subjects who experience an event, and the percentage of subjects who experienced one or more events.

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 (e.g., not including sensitivity or supporting analyses) 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.

Programming code for randomization and 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 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 p-value or confidence interval has been generated (eg, Motor or Sensory Response of the Needles) shall be validated using at least Level II validation.