InterStim® Amplitude Study
Statistical Analysis Plan Version 2.0
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Medtronic

Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Sr. Statistician
2.0	• No changes to document content. The document was re-approved to display RAD cover sheet with approval roles of approvers.	[redacted], Sr. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AT	As Treated
BMI	Body Mass Index
CC	Complete Case Subject Set
CIP	Clinical Investigational Plan
DD	Device Deficiency
FAS	Full Analysis Set
HRQL	Health-Related Quality of Life
ICF	Informed Consent Form
ICIQ-OABqol	International Consultation on Incontinence Modular Questionnaire - Overactive Bladder Symptoms Quality of Life Questionnaire
MedDRA	Medical Dictionary for Regulatory Affairs
OAB	Overactive Bladder
[redacted]	[redacted]
PT	Preferred Term
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNM	Sacral Neuromodulation
USADE	Unanticipated Serious Adverse Device Effect
UF	Urinary Frequency
UUI	Urge Urinary Incontinence

3. Introduction

3.1. Introduction

The InterStim Amplitude study is a prospective, multicenter, randomized, single-blind feasibility study to explore the efficacy and quality of life under 3 different amplitude settings (sub-sensory amplitudes of 50% and 80% of sensory threshold and sensory threshold). Efficacy will be characterized with change from baseline through 12 weeks in urge urinary incontinence (UUI) episodes and patient reported outcomes. Quality of life will be characterized with the International Consultation on Incontinence Modular Questionnaire - Overactive Bladder Symptoms Quality of Life Questionnaire (ICIQ-OABqol) at baseline and 12 weeks. Subject participation will last approximately 16 weeks following the enrollment visit. Subjects are exited from the study after the 12-week follow-up visit is completed.

3.2. Purpose

The purpose of this statistical analysis plan (SAP) is to document the analyses for the final study report. Revisions to the SAP may be required if the protocol changes or updates to the analysis are needed. Annual progress reports may contain a subset of the analyses described in this SAP. The study objectives are taken directly from the CIP. The SAP will further define safety and effectiveness objectives for each analysis, starting in section 7.9.

3.3. Documents used to create SAP

Documents used to create the SAP include:

- InterStim Amplitude Clinical Investigational Plan

4. Study Objectives

4.1. Primary Objective

The primary objective in the study is to explore the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold and sensory threshold) on number of UUI episodes per day.

4.2. Secondary Objective

Secondary objective of this study is quality of life (ICIQ-OABqol) for the three different amplitude settings.

4.3. Additional Measures

Additional measures include:

- Safety
- [redacted]

5. Investigation Plan

This is a prospective, multicenter, randomized, single-blind, feasibility study to explore the efficacy and quality of life of 3 different amplitude settings in subjects with UUI. Subjects will remain blinded to their assigned randomization for the duration of the study.

Eligible subjects will sign a study-specific informed consent form (ICF). Following verification of eligibility criteria, subjects will go through therapy evaluation with the InterStim II System. After qualifying for the device implant, the subject will proceed with either 1) a neurostimulator device implant (if trialed with the Tined Lead) (Figure 1) or 2) a Tined Lead implant and neurostimulator device implant (Figure 2) and randomization procedures. Subjects will be randomized to one of the three amplitude settings: 50% of sensory threshold, 80% of sensory threshold and sensory threshold. Subjects will then complete a 1-week follow-up visit, a 6-week follow-up visit and a 12-week follow-up visit (Figure 1).

The total study duration for a subject is approximately 16 weeks.

Figure 1. Study visits for Advanced Evaluation

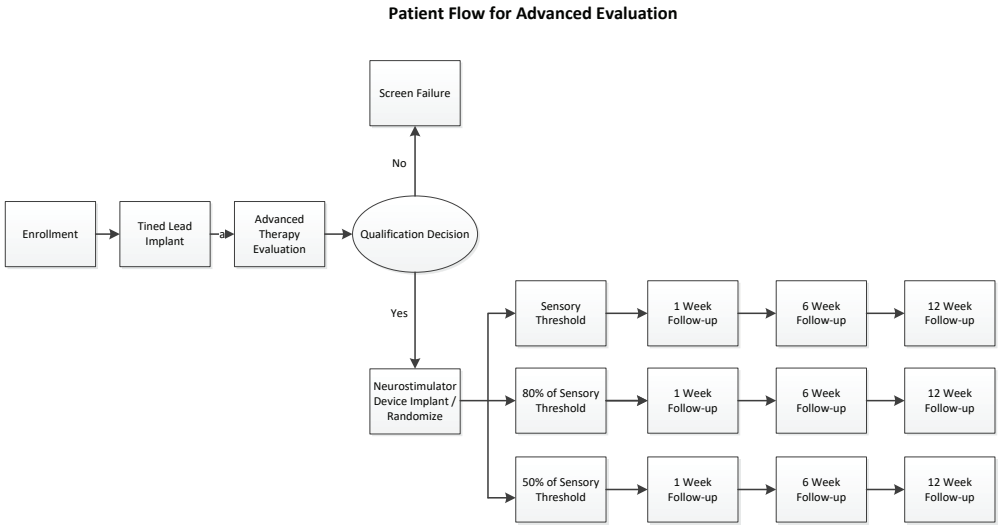
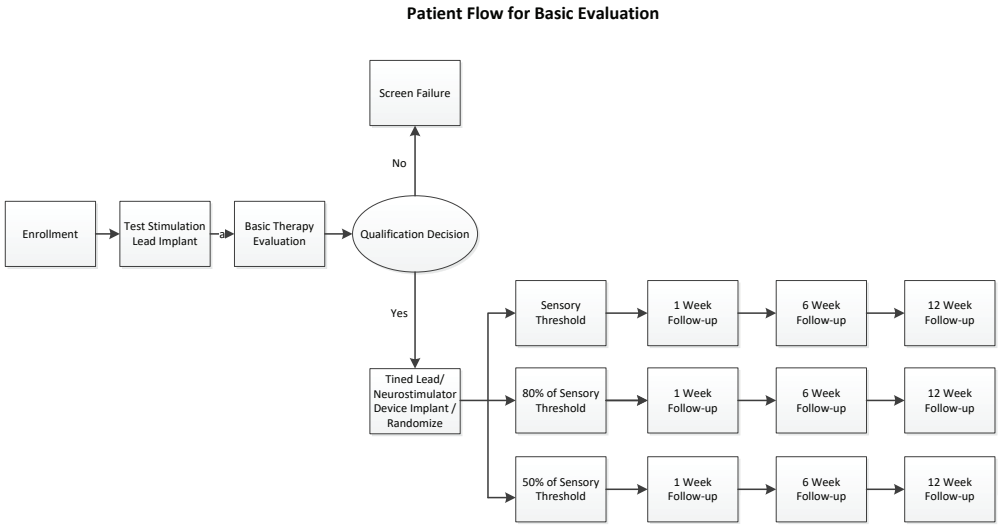


Figure 2. Study visits for Basic Evaluation



6. Determination of Sample Size

This study will explore the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold, and sensory threshold) on UUI episodes per day. Change of average UUI per day at 12-week follow-up will be assessed under each amplitude setting. This study requires approximately 42 implanted and randomized subjects with 12-week follow-up data to be analyzed for the primary objective. Assuming 10% attrition after full system implant and 80% therapy evaluation success rate, approximately 60 subjects are estimated to be enrolled in the study with approximately 48 subjects implanted and randomized in 3 arms. However, these numbers may be exceeded to ensure that a minimum of 42 subjects complete the study.

The objectives are descriptive in nature. Confidence intervals will be calculated to describe the precision of the treatment effect in each arm. Precision is defined as one-half of the confidence interval (also known as the distance from the confidence limits to the mean). Sample size calculations were completed using the PASS 11 Confidence Intervals for One Mean module.

From the randomized portion of the InSite study[2], a mean reduction of 2.1±1.8 UUI episodes per day was observed at 3 months in sacral neuromodulation (SNM) subjects; and from the all implanted cohort of InSite, a mean reduction of 2.3±2.7 UUI episodes per day was observed at 3 months in SNM subjects.

Based on this, we are assuming mean reductions between 1.8 and 2.3 will be observed in the study, along with standard deviations ranging from 2.2 to 2.7.

Based on a confidence interval constructed with a t-statistic, a two-sided type-I error rate of 0.05, and using the largest standard deviation assumed (2.7), a sample size of 14 subjects per arm will have a precision of 1.56 (Table 1). This precision is less than our lowest assumed treatment effect (1.8 UUI), so that it is expected that the lower 95% CI will be greater than 0 for all treatment arms, even in the scenario when the largest assumed standard deviation is applied.

Table 1. Standard deviation and precision

Standard deviation	Precision
2.2	1.27
2.3	1.33
2.4	1.39
2.5	1.44
2.6	1.5
2.7	1.56

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

A disposition of subjects according to their follow-up status at each visit will be provided by randomization group. Reasons for study exit will be summarized over time.

7.1.2. Clinical Investigation Plan Deviations

CIP deviations will be listed and the number of deviations will be summarized by type and overall.

7.1.3. Analysis Sets

The **full analysis subject set** (FAS) includes all subjects who signed the study-specific ICF and enrolled in the study.

The **test subject set** includes all subjects who underwent a lead placement (Tined Lead or Test Stimulation Lead) attempt, whether the procedure was successful or not.

The **randomized subject set** includes all randomized subjects.

The **complete case subject set** (CC) includes the subject set who have data available at baseline and follow-up.

Screen failures includes the subject set who enrolled in the study but did not qualify for lead implant or neurostimulator device implant/randomization.

7.2. General Methodology

7.2.1. General Statistical Considerations

Continuous measures will be reported as N, means, medians, standard deviations, minimums and maximums. All post-randomization data summaries will be provided by randomization group. Categorical measures will be reported in frequency distributions. No hypothesis testing will be performed.

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 (e.g., SAS version 9.4 or higher) will be used to analyze the study results.

7.2.2. Study Success

As the study objective is to characterize the efficacy and quality of life (QoL) of 3 different amplitude settings, there is no pass/fail criteria proposed to define study success.

7.2.3. Urinary Voiding Diary

Symptoms related to overactive bladder (OAB) will be evaluated using paper voiding diaries. Subjects will be trained to complete the urinary voiding diaries for 3 days as part of the baseline and therapy evaluation procedures. The voiding diaries will be completed at baseline, therapy evaluation and prior to the 6 and 12-week follow-up visits.

The value of the relevant data point (UUI episodes [redacted]) at each visit will be calculated as the daily average of the available diary days at that visit. Data will be included in the analyses if there is at least 1 day of diary data available at a visit.

7.3. Center Pooling

Data from all study centers will be pooled for the analysis. There are no planned statistical methods to test for treatment differences among centers.

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

Missing data imputations will not be performed.

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

Summary statistics will be provided, by randomization group, for baseline and demographic variables for subjects who are randomized, and will include:

- Age
- Sex

[redacted]

- Body Mass Index (BMI)

[redacted]

7.7. [redacted]

[redacted]

[redacted]

7.8. Interim Analyses

No formal interim analysis is planned for this study. Interim descriptive summaries may be performed; however, if provided, the study team, investigators and site personnel will be blinded to this information. No study decisions will be made from descriptive summaries; therefore, no sample size adjustment is needed.

7.9. Evaluation of Objectives

7.9.1. Primary Objective

To explore the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold, and sensory threshold) on UUI episodes per day. Descriptive statistics for change in UUI from baseline to 12 weeks will be provided in each randomized group.

Negative values for a change from baseline represent an improvement in UUI episodes and positive values represent an increase in UUI episodes.

7.9.1.1. Experimental Design

Experimental design for data collected on the urinary voiding diary is described in Section 7.2.3.

7.9.1.2. Endpoint Success Definition

This objective is to explore and characterize the reduction in number of UUI episodes under each amplitude setting from baseline. There are no pass/fail criteria proposed to define this endpoint success.

7.9.1.3. Analysis Methods

Descriptive statistics including mean, standard deviation, 95% confidence intervals, median, minimum and maximum will be provided by randomization group.

Change will be calculated as the difference between average of daily UUI episodes from follow-up to baseline. This will be calculated for each subject and the average change will be reported with descriptive statistics. UUI episodes will be included in the calculation irrespective of urgency status.

7.9.1.4. Analysis Populations and Sensitivity Analyses

The analysis population for this objective will be on the CC population, and subjects will be analyzed according to their randomization assignment for the primary analysis. In addition to the primary analysis, an as-treated (AT) sensitivity analysis will be completed to assess the robustness of results. The AT analysis will be completed on the CC population but will analyze subjects according to the treatment they receive. Subjects must have received a given treatment for > 50% of their time in the study to be analyzed in that treatment group. Groups for the AT analysis will include 50% sensory threshold, 80% of sensory threshold, sensory threshold, and OFF/other treatment.

[redacted]

Additionally, reduction in number of UUI episodes per day [redacted] will be assessed at 6 weeks on the CC population, according to their randomization assignment, to assess the effect of different amplitude settings over time.

7.9.2. Secondary Objective

To explore the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold, and sensory threshold) on quality of life with the ICIQ-OABqol Questionnaire.

Descriptive statistics for the change in all domains of this questionnaire from baseline to 12 weeks will be provided in each randomized group.

7.9.2.1. Experimental Design

The ICIQ-OABqol is a robust, patient-completed questionnaire for evaluating QoL in patients with overactive bladder, for use in research and clinical practice.[1]

The subject-completed questionnaire consists of 4 subscales and a single item on urinary symptom interference. The four subscales of Concern (7 items), Coping (8 items), Sleep (5 items), and Social (5 items) are measured on a scale from 0-100 using a range percentile transformation on the summed value from individual listed items. The Health-Related Quality of Life (HRQL) score is a calculated score with a range from 0 to 100 using a range percentile transformation on the summed value from the subscales. A higher score indicates better quality of life for the HRQL and its subscales; a lower score indicates better quality of life for urinary symptom interference.

7.9.2.2. Endpoint Success Definition

This objective is to explore and characterize the QoL under each amplitude setting from baseline to 12 weeks. There are no pass/fail criteria proposed to define this endpoint success.

7.9.2.3. Analysis Methods

Descriptive statistics including mean, standard deviation, 95% confidence intervals, median, minimum and maximum will be provided by randomization group. The change in each subscale score from Baseline to 12 weeks will be calculated for each subject and the average change across all subjects in each randomization group will be reported.

7.9.2.4. Analysis Populations [redacted]

The analysis population for this objective will be on the CC subject set, and subjects will be analyzed according to their randomization assignment for the primary analysis.

[redacted]

7.9.3. Additional Measures

Additional measures have been added to provide relevant information on parameters of interest in SNM therapy under different amplitude settings and to provide additional information.

7.9.3.1. Incidence of Device Related, Therapy Related and/or Procedure Related Adverse Events

The objective of this measure is to summarize device related, therapy related and/or procedure adverse events (AEs). This objective summarizes device related, therapy related and/or procedure related adverse events, by randomization group, in the post-neurostimulator device implant period. Further analysis of AEs and other safety measures is described in Section 7.10.

Experimental Design

AEs will be considered as device, therapy, or procedure related if they are classified as possibly, probably, or causally related to the device (lead, neurostimulator, or external study device), study procedure, or therapy delivery by the device (e.g. device stimulation).

Endpoint Success

This objective is to summarize device related, therapy related and/or procedure adverse events under each amplitude setting throughout the study. There are no pass/fail criteria proposed to define this endpoint success.

Analysis Methods

Events will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Summaries will be presented as the number of events, the number of subjects who experienced the event, and the percent of subjects who experienced the event. Events will be summarized in the post-neurostimulator device implant period, and subjects will be analyzed by randomization group.

Analysis Populations

The analysis population for this objective will be on the randomized subject set, and subjects will be analyzed according to their randomization assignment.

7.9.3.2.

[redacted]

[redacted]

7.9.3.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.10. Safety Evaluation

In the study, all serious, device related, therapy related, and/or procedure related AEs, and all device deficiencies (DDs) are considered as reportable for this study. All reportable AEs and DDs will be summarized. AEs will be considered device, therapy, or procedure related if they are classified as possibly, probably, or causally related to the lead, neurostimulator, external study device, study procedure, or therapy delivery by the device (e.g. device stimulation).

AEs and DDs, referred to as "events" within this section, will be summarized separately. Events will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Summaries will be presented as the number of events, the number of subjects who experienced the event, and the percent of subjects who experienced the event. For AEs, these summaries will be reported for serious adverse events (SAE) as well.

AEs and DDs will be summarized by study phase ([redacted] Post-Neurostimulator Device Implant) with the denominator corresponding to the number of subjects in each phase, as described in Section 7.10.7. Events that occur post-neurostimulator device implant will be summarized by randomization group, and overall.

7.10.1. [redacted]

[redacted]

[redacted]

7.10.2. Device Related, Therapy Related and/or Procedure Related Adverse Events

Adverse events will be summarized separately by device related, therapy related and/or procedure related events, and overall. Summaries are also provided by MedDRA System Organ Class (SOC) and Preferred Term (PT). [redacted] For adverse events in Post-Neurostimulator Device Implant Period, the adverse events will be summarized as described in Section 7.10.6.3. In addition to the analyses by time period, an overall summary will be provided.

7.10.3. Serious Adverse Events

SAEs will be summarized by time period ([redacted] Post-Neurostimulator Device Implant, as described in Section 7.10.6), and overall.

7.10.4. [redacted]

[redacted]

7.10.5. SADEs and USADEs

Narratives of SADEs (Serious Adverse Device Effects) and Unanticipated Serious Adverse Device Effects (USADEs) will be provided. USADEs are considered a subset of SADEs.

7.10.6. [redacted]

[redacted]

7.10.7. Time Periods

7.10.7.1. [redacted]

[redacted]

7.10.7.2. [redacted]

[redacted]

7.10.7.3. Post-Neurostimulator Device Implant

Events that have an onset date on or after the day of the neurostimulator implant procedure will be summarized as Post-Neurostimulator Device Implant Events. Events that occur post-neurostimulator device implant will be summarized by randomization group [redacted] The [redacted] denominator for the summary by randomization group will be the randomized subject set.

7.11. Changes to Planned Analysis

Any change 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 for programming code that affects the result of the main analysis for the objective as specified in Section 7.9.1 will be validated using Level I validation (peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer). Programming code that affects the results of the objectives as specified in Section 7.9.2 will be validated using Level II validation (peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output). In addition, those main statistical analyses that are planned for publication and have not been previously validated should be validated with at least Level II validation. Level III validation (original Statistical Programmer performs a visual inspection of the code and output to confirm functionality) may be used for any previously validated program where only minor/administrative changes were made (e.g., change the location of the data directory). Additional measures may need to be validated as determined by statistical management.

9. References

1. Coyne, K., Revicki, D., Hunt, T., Corey, R., Stewart, W., Bentkover, J., Kurth, H., Abrams, P. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual.Life.Res.* 2002; 11(6); 563-574.
2. Siegel S, Noblett K, Mangel J, Griebling T, Sutherland S, Bird E, Comiter C, Culkin D, Bennett J, Zylstra S, Berg K, Kan F, Irwin C. Results of a Prospective, Randomized, Multicenter Study Evaluating Sacral Neuromodulation with InterStim Therapy Compared to Standard Medical
3. Therapy at 6-Months in Subjects with Mild Symptoms of Overactive Bladder. Neurology and Urodynamics 2015 Mar; 34(3): 224 - 30.