InterStim Micro Post Market Clinical Follow-up Study (ELITE)
Statistical Analysis Plan V1.0
23-Oct-2020
NCT04506866

Medtronic **Statistical Analysis Plan**		
Clinical Investigation Plan/Study Title	Evaluation of InterStim Micro System Performance and Safety (ELITE)	
Clinical Investigation Plan Identifier	MDT19006 EUDAMED unique identifier will be provided under a separate cover, once available.	
Clinical Investigation Plan Version	1.0 02-Oct-2019	
Study Product Name	This Post-Market Clinical Follow-Up (PMCF) will include the following commercially approved products: ▪ InterStim Micro implantable neurostimulator ▪ InterStim SureScan MRI tined lead ▪ Patient and clinician therapy application software ▪ Wireless recharger ▪ Recharger application software ▪ Percutaneous extension (advanced therapy evaluation) ▪ Temporary lead (basic therapy evaluation) ▪ Verify external neurostimulator	
Sponsor/Local Sponsor	**United States (Sponsor):** Medtronic, Inc. 7000 Central Ave NE Minneapolis, MvN 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 **Australia (Local Sponsor):** Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park, NSW 2113 Australia
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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

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
Basic Evaluation	A temporary test stimulation lead is surgically implanted, externalized and connected to a patient cable for test stimulation.
CCIS	Cleveland Clinic Incontinence Score
CFR	Code of Federal Regulations
CI	Confidence Interval

CIP	Clinical Investigational Plan
CISC	Clean Intermittent Self-Catheterization
DD	Device Deficiency
EU	Europe
FI	Fecal Incontinence
[redacted]	[redacted]
FAS	Full Analysis Set
HRQL	Health Related Quality of Life
OAB-q	Overactive Bladder Symptoms Quality of Life Questionnaire
MI	Multiple Imputation
NOUR	Non-Obstructive Urinary Retention
OAB	Overactive Bladder
[redacted]	[redacted]
PMCF	Post-Market Clinical Follow-up
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNM	Sacral Neuromodulation
US	United States
UF	Urinary Frequency
UI	Urinary Incontinence
UUI	Urinary Urge Incontinence

3. Introduction

This statistical analysis plan (SAP) is based on Clinical Investigational Plan Version 2.0 of the Evaluation of InterStim Micro System Performance and Safety (ELITE) Study. The SAP presents the details of the methods to be used to analyze and report the study results of the ELITE study, protocol number MDT19006.

4. Study Objectives

4.1. Overactive Bladder Cohort

4.1.1. Primary Objective

The primary objective for the overactive bladder cohort of the study is to demonstrate an improvement in Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) total score at 3 months post-implant compared to Baseline.

4.1.2. Additional Measures

- [redacted]

4.2. Fecal Incontinence Cohort

4.2.1. Primary Objective

The primary objective for the fecal incontinence cohort of the study is to demonstrate an improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant compared to Baseline.

4.2.2. Additional Measures:

- [redacted]

- [redacted]

4.3. Non-Obstructive Urinary Retention Cohort

4.3.1. Primary Objective

The primary objective for the non-obstructive urinary retention cohort of the study is to demonstrate an improvement in number of clean intermittent self-catheterizations (CISC) per day at 3 months post-implant compared to Baseline.

4.3.2. Additional Measures:

- [redacted]

4.4 Safety Assessment

To characterize safety during the study duration.

To characterize safety of the InterStim Micro System by summarizing the adverse device effects and serious adverse device effects during the study. Safety measures will be summarized for each cohort as well as pooled for all patients regardless of indication. Device deficiencies will also be collected and reported.

Summaries will be presented as number of events, number of subjects who experienced the event, and percent of subjects who experienced the event.

5. Investigation Plan

This is a single-arm, prospective, multicenter, open-label, global, post market clinical follow-up for continued assessment of safety and performance of the InterStim Micro System for sacral neuromodulation. The study is intended to be conducted at approximately 40 centers in Australia, Canada, Europe and the United States (including US territories).

Subjects will complete Baseline Visit activities after signing a study-specific informed consent form (ICF). Each subject will only be qualified for one of the study cohorts. Once it is confirmed the subject meets eligibility criteria, they will proceed first to an Evaluation Lead Implant Visit and then to a therapy evaluation.

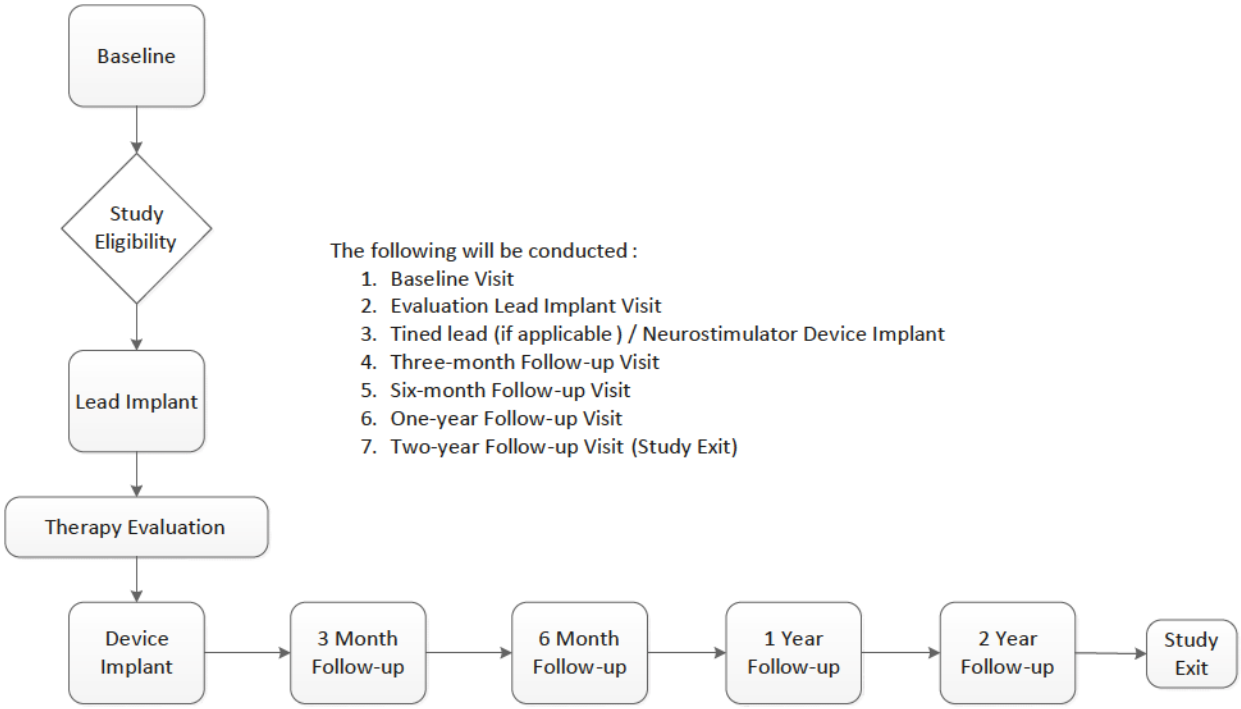
Following the therapy evaluation, once the subject qualifies for the neurostimulator device implant, site personnel may proceed with the Neurostimulator Device Implant Visit. If a subject does not qualify for the neurostimulator device implant, they will be exited from the study. All subjects who met all eligibility criteria and complete the neurostimulator implant procedure will be considered enrolled in the study.

Subjects implanted with the InterStim Micro Neurostimulator will be followed for a total of 2 years with study follow-up visits which should be scheduled within the following targeted visit windows (Table 1), when possible.

Table 1 Visit windows

(Target Visit Windows are Calculated from the Date of Neurostimulator Implant)	
Month 3 visit	13 weeks ± 7 days
Month 6 visit	26 weeks ± 14 days
Year 1 visit	52 weeks ± 28 days
Year 2 visit	104 weeks ± 28 days

Figure 1 Study visit



6. Determination of Sample Size

For the overactive bladder cohort, the primary objective is to demonstrate an improvement of Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) score at 3 months post-implant compared to Baseline.

Based on the results of HRQL in OAB-q at 3 months post-implant reported in the InSite study, a mean score change of 30 at 3 months from Baseline with the standard deviation of 27 are the assumptions used for the power calculation for this study. A sample size of 50 achieves greater than 90% power to detect a difference from Baseline of 30 points in OAB-q HRQL total score and a standard deviation of 27 with a significance level of 0.05 using a two-sided one sample t-test.

For the fecal incontinence cohort, the primary objective is to demonstrate an improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant compared to Baseline. Based on the result of meta-analysis conducted by Thin et al (2013), a mean CCIS score change of 5 at 3 months from Baseline with the standard deviation of 6.2 are the assumptions used for the power calculation for this study. A sample size of 50 achieves greater than 90% power to detect a difference from Baseline of 5 points in Cleveland Clinic Incontinence Score (CCIS) and a standard deviation of 6 with a significance level of 0.05 using a two-sided one sample t-test.

For the non-obstructive urinary retention cohort, the primary objective is to demonstrate an improvement in number of clean intermittent self-catheterizations (CISC) per day at 3 months post-implant compared to Baseline. Based on the literature results published in Van Kerrebroeck et al (2007), Sutherland et al (2007), Cardarelli et al (2012) and MDT-103 and SOUNDS interim reports, a mean change of 2 in the number of CISC/day between Baseline and 3 months post-implant (μ) with a standard deviation of 3 are the assumptions used for the power calculation for this study. A sample size of 30 achieves greater than 90% power to detect a difference from Baseline of 2 CISC/day and a standard deviation of 3 with a significance level of 0.05 using a two-sided one sample t-test.

The power calculations were performed using PASS 11 statistical software for all three cohorts. To accommodate attritions, approximately 160 subjects (60 for overactive bladder cohort, 60 for fecal incontinence cohort and 40 for non-obstructive urinary retention cohort), will be enrolled in the study to achieve a minimum of 50 evaluable subjects each for overactive bladder and fecal incontinence cohorts and a minimum of 30 evaluable implanted subjects for non-obstructive urinary retention cohort at 3 months post implant.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

For all the three cohorts separately, subject disposition will be summarized by study visit in a flow diagram. Discontinuation will be summarized by visit and discontinuation reasons will be provided.

7.1.2 Clinical Investigation Plan (CIP) Deviations

For all the three cohorts separately, all CIP deviations will be summarized by type of deviation. Details of CIP deviations that affect scientific integrity or patient safety may be presented.

7.1.3 Analysis Sets

- The **Consented Subject Set** includes all subjects who signed the study-specific informed consent form (ICF).
- The **Test Subject Set** includes all subjects who underwent a lead placement attempt, whether the procedure was successful or not.
- The **Full Analysis Subject Set** (FAS) includes all subjects who signed the study-specific ICF and enrolled in the study. Subjects are considered enrolled at completion of the neurostimulator implant procedure.

- The **Complete Case Subject Set** (CC) consist of the subjects implanted with the Neurostimulator Device (Enrolled) and who have data available at Baseline and at each follow up visit.

7.2 General Methodology

This is a non-randomized study to explore efficacy, safety, and quality of life (QoL) with sacral neuromodulation on three independent cohorts (OAB, FI, NOUR). The statistical analysis will be held for each cohort separately and independently, but some general methodologies will be used in all cohorts.

Continuous measures will be reported as N, means, medians, standard deviations, minimums and maximums. Categorical measures will be reported in frequency distributions. Summaries will be completed for all subjects (pooled).

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

$$\Delta = S_v - S_0$$

Percentage change will be calculated as 100 times the change divided by the Baseline score.

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

95% Confidence intervals may be also derived as follow

$$\bar{x} \pm z * \frac{\sigma}{\sqrt{n}}$$

Where $\bar{x}$ is the sample mean, z is the z-value from the standard normal distribution for the 95% confidence level, σ is the sample standard deviation and n is the sample size.

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.

7.2.1.1 Diary types

Symptom data for this study will be collected using either electronic or paper diaries.

7.2.1.1.1 Electronic Diary

Electronic diaries may be provided by the sponsor for US study centers; the electronic diary collects details associated with symptoms for each episode. The system contains reminders and allows subjects to collect real-time voiding behavior onto a secure server.

7.2.1.1.2 Paper Diary

A paper diary is also available for use in the study. If a paper diary is used, the data will be entered to the RDC database.

7.2.1.1.3 Urinary Voiding Diaries

Symptoms related to OAB and NOUR will be evaluated using either paper or electronic urinary voiding diaries. Subjects will be trained to complete the urinary voiding diaries for 3-days for OAB with diary details collected (such as time, type of episode, urgency, sleep/awake status, etc.) and for 7-days for NOUR with diary details collected (such as time, type of episode, volume, etc.) as part of the Baseline procedures. The urinary voiding diaries will be completed for 3-days for OAB and 7-days for NOUR towards the end of the therapy evaluation and prior to each subsequent follow-up visit. Every effort should be made to remind subjects of the importance of real-time diary completion.

7.2.1.1.4 Bowel Diaries

Symptoms related to FI will be evaluated using either paper or electronic voiding diaries. Subjects will be trained to complete the bowel voiding diary for 7-days as part of the Baseline procedures with diary details collected (such as time, type of episode, urgency, sleep/awake status, etc.). The bowel diaries will be completed for 7-days towards the end of the therapy evaluation [redacted] Every effort should be made to remind subjects of the importance of real-time diary completion.

7.2.1.2 Diary Collection Timepoints

7.2.1.2.1 Baseline Diary

For subjects who qualify with the overactive bladder indication: The urinary voiding diary will be explained and given to the subject to be completed for 3 consecutive days.

For subjects who qualify with the fecal incontinence indication: The bowel diary will be explained and given to the subject to be completed for 7 consecutive days.

For subjects who qualify with the non-obstructive urinary retention indication: The urinary voiding diary will be explained and given to the subject to be completed for 7 consecutive days.

7.2.1.2.2 Therapy Evaluation Period Diary

The applicable diary for the study cohort diary will be completed towards the end of the therapy evaluation period (completed for 3 consecutive days for OAB, completed for 7 consecutive days for FI and completed for 7 consecutive days for NOUR).

7.2.1.2.3 Follow-up visits Diary

Diaries will be collected for each cohort at each follow-up visits (Three-month, Six-month, One-year, and Two-year Follow-up Visits) and possible unscheduled visit as follow:

- [redacted]
- For subjects within the NOUR cohort: The voiding diary will be given to the subject to be completed for 7 days approximately 1 week prior to each follow-up visit.

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, i.e., 12 subjects for OAB cohort, 12 subjects for FI cohort, and 8 subjects for NOUR cohort, will be enrolled at each site unless the site gets pre-approval from the 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. The potential bias due to missing data depends on the mechanism causing the data to be missing, and the analytical methods applied to amend the missingness.

Subjects who will not pass screening tests will not be used in the analysis as they will not be implanted. After implant, subjects who will be lost to follow-up or will withdraw or discontinued from the clinical investigation without providing data at three-months analysis will be considered missing.

For the primary objective of each cohort, data summaries will be based on those subjects with complete data (CC set), with complete defined as having data at the visit(s) used in analysis (Baseline and 3 months follow up).

All attempts will be made to minimize missing data for primary objective. If 5% of the data or fewer are missing for the analysis, no imputation will be used and the data will be analyzed as specified in the previous section. Otherwise, a sensitivity analysis with multiple imputation will be used for the analysis of the key primary objective.

Prior to the MI, the distribution of the continuous variables will be assessed for normality (using the Shapiro-Wilk test) to determine whether regression ($P \geqslant 0.05$) or predictive mean matching ($P<0.05$) multiple imputation will be used for each variable.

- If normality assumption is met, the missing data will be imputed using the fully conditional specification (FCS) method (also known as imputation by chained equations/ICE or sequential generalized regression) in SAS (version 9.4 or higher) with SEED=13951639 and number of imputations=30. After MI procedure, m (m=30) imputed data are obtained. Following imputation of the missing data, change in OAB-q HRQL (OAB cohort) OR CCIS (FI cohort) OR number of CISC (NOUR cohort) will be calculated for each subject within each imputed dataset. The mean and standard error of the change in in OAB-q HRQL (OAB cohort) OR CCIS (FI cohort) OR number of CISC (NOUR cohort) will be calculated within each imputed dataset and they will be analyzed using MI analysis methods, with the following specifications:
    - Adjusted degrees of freedom (EDF) = Treated Analysis Set sample size – 1
    - Theta0 = 0
    - Alpha = 0.05
    - ModelEffects = mean change in OAB-q HRQL (OAB cohort) OR CCIS (FI cohort) OR number of CISC (NOUR cohort)
    - StdErr = standard error of change in OAB-q HRQL (OAB cohort) OR CCIS (FI cohort) OR number of CISC (NOUR cohort)

  The output ParameterEstimates dataset from the MI analysis will contain the adjusted estimate of the mean and standard error of change in OAB-q HRQL (OAB cohort) OR CCIS (FI cohort) OR number of CISC (NOUR cohort), the 95% confidence interval for the mean change, and the associated t-statistic and p-value from the test of the null hypothesis.

- If normality assumption is not met, the fully conditional method (FCS) with Predictive mean matching (PMM) is chosen to perform multiple imputation for continuous variables (primary objective effectiveness). The Predictive mean matching (PMM) model is implicit (Little and Rubin 2002), which means that there is no need to define an explicit model for the distribution of the missing values. Because of this, predictive mean matching is less vulnerable to model misspecification than the regression methods. The fully conditional method (FCS) does not assuming a joint distribution but instead uses a separate conditional distribution for each imputed variable, and FCS method does not require a monotone missing data pattern. The combination of FCS with PMM method is selected due to these reasons. SAS MI procedure will be used with SEED=13951639 and number of imputations=30. After MI procedure, m (m=30) imputed data are obtained. The resulting distribution is likely to be skewed, therefore median will be used to summarize the m imputed datasets instead of mean. The standard error of median calculated from each imputed dataset will be estimated through bootstrap method. Then MIANALYZE procedure is used to combine the results.

The model variables in the MI analysis in both cases (normality and non normality) may include:

- For OAB cohort:
    - Age

- Gender
- Baseline OABq HRQL
- Baseline UUI episodes
- Baseline voids
- Secondary OAB diagnosis: Stress incontinence, Urinary frequency, retention, pelvic pain, interstitial cystitis, or none
- Medical history
- The number of ongoing OAB medications used at baseline
- Motor response at tined lead implant

- For FI cohort:
  - Age
  - Gender
  - Baseline CCIS
  - Baseline movements
  - Baseline accidents
  - Medical history
  - Motor response at tined lead implant
  -
- For NOUR cohort:
  - Age
  - Gender
  - Baseline number of catheterizations
  - Baseline voids
  - Medical history
  - Motor response at tined lead implant

For diary data analyses, although subjects are required to record at least 3 full days (OAB) and at least 7 full days (NOUR/FI) of dairy data, missing data imputations will not be performed and all subjects who have at least one full 24-hour period in a visit will be included in analysis for that visit.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons because the three cohorts are enrolled and analyzed completely independently from each other. No results or conclusions will be derived from the three cohorts together.

7.6 Demographic and Other Baseline Characteristics

Demographics and Baseline characteristics will be summarized for each cohort separately for all enrolled subjects using the FAS.

Demographics and other Baseline characteristics summarized will include:

- Age, sex, and race
- [redacted]

For NOUR cohort only:

- Baseline self-catherization per day
- [redacted]

7.7 Treatment Characteristics

[redacted]

7.8 Interim Analyses

There is no planned interim analysis for this study.

7.9 Evaluation of Objectives

7.9.1 Overactive Bladder Cohort

7.9.1.1 Primary objective

The primary objective for overactive bladder cohort of the study is to demonstrate there is an improvement in Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) total score at 3 months post-implant compared to Baseline.

Change on OAB-q HRQL at 3 months post-implant compared to Baseline will be calculated as the difference between average of total score at 3 months post-implant visit and at Baseline. This will be calculated for each subject and the average change will be reported with descriptive statistics.

Positive values represent an improvement in OAB-q HRQL total score.

7.9.1.2 Hypothesis

The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in OAB-q HRQL total score from Baseline to 3 months post-implant. P-value will be evaluated at alpha level of 0.05.

7.9.1.3 Experimental Design

Subjects will complete the Overactive Bladder Quality of Life Questionnaire (OAB-q) at Baseline, Three-month, [redacted] The Overactive Bladder Quality of Life Questionnaire (OAB-q) is a 33-item validated questionnaire that was developed to assess symptom bother and the impact of overactive bladder (OAB) on health-related quality of life (HRQL). The questionnaire used in the current study includes a 4-week recall for symptom assessment.

7.9.1.4 Analysis Methods and Presentation Format

In case the normality assumption of data will hold (Shapiro Will test), a two-sided one sample t-test will be performed to test the hypothesis described in section 7.9.1.2.

In case the normality assumption of data will not hold (Shapiro Will test), a Wilcoxon Singed Rank test will be performed to test the hypothesis described in section 7.9.1.2.

In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in HRQL total score will be calculated and reported.

In cases where subject's OAB-q HRQL total score is missing at Baseline and/or at 3 months post-implant for any reasons, the percentage of missing data will be summarized and a sensitivity analysis using multiple imputation will be performed as described in section 7.4.

7.9.1.5 Determination of Subject for Analysis

The primary analysis will include all complete case subjects (CC) who have data available at Baseline and Three-months follow up visit. Sensitivity analysis will include all implanted subjects (FAS) by imputing missing data as described in section 7.4.

7.9.1.6 Additional Measure

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.9.2 Fecal Incontinence Cohort

7.9.2.1 Primary objective

The primary objective for fecal incontinence cohort of the study is to demonstrate there is an improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant compared to Baseline. Change on CCIS at 3 months post-implant compared to Baseline will be calculated as the difference between average of total score at 3 months post-implant visit and at Baseline. This will be calculated for each subject and the average change will be reported with descriptive statistics.

Negative values for a change from Baseline represent a decrease in CCIS and positive values represent an increase in CCIS.

7.9.2.2 Hypothesis

The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in CCIS from Baseline to 3 months post-implant. P-value will be evaluated at alpha level of 0.05.

7.9.2.3 Experimental Design

Subjects will complete the Cleveland Clinic Incontinence Score (CCIS) at Baseline, Three-month, [redacted] The Cleveland Clinic Incontinence Score (Wexner Score) is an established 5-item questionnaire that was developed to assess the frequency and severity of fecal incontinence.

This questionnaire will be completed by the subject at Baseline, Three-month, [redacted]

7.9.2.4 Analysis Methods and Presentation Format

In case the normality assumption of data will hold (Shapiro Will test), a two-sided one sample t-test will be performed to test the hypothesis described in section 7.9.1.2.

In case the normality assumption of data will not hold (Shapiro Will test), a Wilcoxon Singed Rank test will be performed to test the hypothesis described in section 7.9.1.2.

In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in CCIS will be calculated and reported.

In cases where subject's CCIS is missing at Baseline and/or at 3 months post-implant for any reasons, the percentage of missing data will be summarized and a sensitivity analysis using multiple imputation will be performed as described in section 7.4.

7.9.2.5 Determination of Subject for Analysis

The primary analysis will include all complete case subjects (CC) who have data available at Baseline and Three-months follow up visit. Sensitivity analysis will include all implanted subjects (FAS) by imputing missing data as described in section 8.4.

7.9.2.6 Additional Measure

[redacted]

[redacted]

7.9.3 Non-Obstructive Urinary Retention Cohort

7.9.3.1 Primary objective

The primary objective for the non-obstructive urinary retention cohort of the study is to demonstrate an improvement in number of clean intermittent self-catheterizations (CISC) per day at 3 months post-implant compared to Baseline.

Change on the number of CISC per day at 3 months post-implant compared to Baseline will be calculated as the difference between average number of CISC per day at 3 months post-implant visit and at Baseline. This will be calculated for each subject and the average change will be reported with descriptive statistics.

Negative values for a change from Baseline represent a decrease in the number of CISC per day and positive values represent an increase in the number of CISC per day.

7.9.3.2 Hypothesis

The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in the number of CISC per day from Baseline to 3 months post-implant. P-value will be evaluated at alpha level of 0.05.

7.9.3.3 Experimental Design

Subjects will be trained to complete the urinary voiding diaries for 7-days for NOUR with diary details collected (such as time, type of episode, volume, etc.) as part of the Baseline procedures. The urinary voiding diaries will be completed for 7-days for NOUR towards the end of the therapy evaluation and prior to each subsequent follow-up visit. Every effort should be made to remind subjects of the importance of real-time diary completion.

7.9.3.4 Analysis Methods and Presentation Format

In case the normality assumption of data will hold (Shapiro Will test), a two-sided one sample t-test will be performed to test the hypothesis described in section 7.9.3.2.

In case the normality assumption of data will not hold (Shapiro Will test), a Wilcoxon Singed Rank test will be performed to test the hypothesis described in section 7.9.3.2.

In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in number of CISCwill be calculated and reported.

In cases where subject's number of CISC per day is missing at Baseline and/or at 3 months post-implant for any reasons, the percentage of missing data will be summarized and a sensitivity analysis using multiple imputation will be performed as described in section 7.4.

7.9.3.5 Determination of Subject for Analysis

The primary analysis will include all complete case subjects (CC) who have data available at Baseline and Three-months follow up visit. Sensitivity analysis will include all implanted subjects (FAS) by imputing missing data as described in section 7.4.

7.9.3.6 Additional Measure

[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 all consented subjects (Consent Subject Set), all subjects who go through lead placement procedure, as well as separately prior to INS implant (Test Subject Set) and after INS implant (Full 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, as well as separately prior to INS implant (Test Subject Set) and after INS implant (Full Analysis Set). For safety evaluation after INS implants, it will be summarized for subjects with INS implant only. The severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the devices or procedure or therapy will be provided as listing. The number of events, the number of subjects who experience an event, and the percentage of subjects who experienced one or more events will be summarized for each cohort as well as well as pooled for the three cohorts together. A listing of deaths and reasons for deaths will be provided for each cohort as well as pooled for the three cohorts together, if any death occur in the study.

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 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 additional measures 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. 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

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