InterStim® Amplitude Study
Clinical Investigational Plan Version 2.0
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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	InterStim® Amplitude Study
Study Product Name	InterStim II System
Sponsor/Local Sponsor	United States (Sponsor): Medtronic, Inc. 7000 Central Avenue NE Minneapolis, MN 55432 USA Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland Canada (Local Sponsor): Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada 1-905-460-3800
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Confidentiality Statement

1. Investigator Statement

Participating investigators will be provided with a separate investigator agreement to document their obligations and commitment with respect to study conduct.

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2. Glossary

TERM	DEFINITION
ADE	Adverse Device Effect
ADVANCED EVALUATION	Therapy evaluation using InterStim Tined Lead
AE	Adverse Event
AT	As Treated
AWC	Adjusted Worst Case
BASIC EVALUATION	Therapy evaluation using temporary Test Stimulation Lead
CC	Complete Case
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
NPU	Neuro Programmer Upload
OAB	Overactive Bladder
ICIQ-OABqol	International Consultation on Incontinence Modular Questionnaire - Overactive Bladder Symptoms Quality of Life Questionnaire
[redacted]	[redacted]
PNE	Peripheral Nerve Evaluation
QoL	Quality of Life
ORACLE RDC	Oracle Remote Data Capture
REPORTABLE ADVERSE EVENTS AND DEVICE DEFICIENCIES	Serious, device-related, procedure-related, therapy-related adverse events and all device deficiencies will be considered reportable for this study
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SENSORY THRESHOLD	Sensory threshold is defined as the lowest amplitude where the subject first perceives sensation of the stimulation in the perineum, perianal, vaginal, or any location deemed appropriate by the investigator while in a seated position.
SNM	Sacral Neuromodulation

TERM	DEFINITION
USADE	Unanticipated Serious Adverse Device Effect
UF	Urgency Frequency
UI	Urinary Incontinence
UUI	Urinary Urge Incontinence
US	United States
UTI	Urinary Tract Infection

3. Synopsis

Title	InterStim Amplitude Study
Clinical Study Type	Post-Market, On-Label
Product Name	InterStim II (Model 3058) and InterStim Quadripolar Lead Model 3889-XX (hereinafter referred to only as the tined lead or Model 3889) with commercially-approved accessories. Either the InterStim Tined Lead Model 3889 or the temporary Test Stimulation Lead (the lead is sold via Models 305901, 305906 or 309101, hereinafter referred to only as the Test Stimulation Lead) may be used for the therapy evaluation. In the rest of this document, "advanced evaluation" will refer to therapy evaluation using InterStim Tined Lead and "basic evaluation" will refer to therapy evaluation using temporary Test Stimulation Lead.
Sponsor	Medtronic, Inc.
Indication under investigation	The indication under investigation is overactive bladder (OAB). There are no investigational devices used in this study, all study products will be used in accordance with the product labeling.
Investigation Purpose	To assess the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold and sensory threshold) on urinary urge incontinence (UUI). Sensory threshold is defined as the amplitude where the subject first perceives the sensation of the stimulation in the perineum, perianal, vaginal, or any location deemed appropriate by the investigator while in a seated position.
Product Status	The InterStim II system is commercially approved for the treatment of patients with OAB.
Primary Objective	To explore the effect of three different amplitude settings on urinary urge incontinence (UUI).
Secondary Objective	To characterize results from the ICIQ-OABqol questionnaire for the three different amplitude settings.
Additional Measures	[redacted] to summarize safety for the three different amplitude settings.
Study Design	This is a prospective, randomized, multicenter, single-blinded study to explore the efficacy and quality of life (QoL) of 3 different amplitude settings. The study will be conducted at approximately 20 centers in the United States, Canada and Europe. Enrolled subjects who meet all eligibility criteria, have successful therapy evaluation (50% improvement in UUI or UF voiding symptoms, or return to normal voiding of < 8 voids per day for UF

	subjects) and qualify for a neurostimulator device implant in the study will be randomized to one of the 3 amplitude settings. Subjects will complete enrollment/baseline visits, lead implant, therapy evaluation, neurostimulator device implant, randomization, 1-week follow-up visit, 6-week follow-up visit and 12-week follow-up visit. The total study duration for a subject is approximately 16 weeks.
Randomization	Subjects must meet all eligibility criteria and demonstrate a successful therapy evaluation prior to being randomized to one of three therapy amplitudes: sensory threshold, 50% of sensory threshold or 80% of sensory threshold.
Sample Size	This study requires approximately 42 implanted and randomized subjects with 12-week follow-up to be analyzed for the primary objective. Approximately 60 subjects are estimated to be enrolled in the study with approximately 48 randomized; however, these numbers may vary to ensure that a minimum of 42 implanted subjects complete the study.
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Primary diagnosis of urinary urge incontinence (UUI) as demonstrated on a 3-day baseline voiding diary demonstrating at least 3 UUI episodes 2. Female subjects 18 years of age or older 3. Candidate for InterStim Lead Placement 4. Willing and able to accurately complete voiding diaries, questionnaires, attend visits, and comply with the study protocol (which includes maintenance of InterStim II programming settings over the course of the study) 5. Willing and able to provide signed and dated informed consent 6. Willing to maintain current regimen (dosage and frequency) of any overactive bladder (OAB) medication Exclusion Criteria: 1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury 2. History of diabetes unless the diabetes is well-controlled through diet and/or medications

	3. Symptomatic urinary tract infection (UTI) 4. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component 5. Treatment of urinary symptoms with botulinum toxin in the past 9 months or any plan to have botulinum toxin treatment during the study 6. Implanted with a neurostimulator, pacemaker, or defibrillator 7. 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 MRI Guidelines for InterStim Therapy 8. Women who are pregnant or planning to become pregnant 9. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements 10. Currently enrolled or planning to enroll in a potentially confounding clinical study during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic study manager (or designee)
Study Procedures and Assessments	**Study Visits:** 1. Enrollment / Baseline 2. Tined Lead or temporary Test Stimulation Lead Implant 3. Therapy Evaluation 4. Tined Lead (if applicable) / Neurostimulator Device Implant (randomization procedures) 5. One Week Follow-up Visit 6. Six Week Follow-up Visit 7. Twelve Week Follow-up Visit **Enrollment/Baseline** Subjects are considered enrolled at the time the study-specific informed consent is signed. Each subject must meet all the inclusion and no exclusion criteria to be eligible to participate in the study. At the enrollment/baseline visit, data will be gathered from subjects including relevant medical history and concomitant OAB medication. Subjects will complete the following questionnaire:

- Overactive Bladder Symptoms Quality of Life Questionnaire (ICIQ-OABqol)

The voiding diary will be explained and given to the subject to be completed for 3 consecutive days. The 3-day voiding diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant during participation in the trial, as part of the assessment for study eligibility.

Tined Lead or temporary Test Stimulation Lead Implant
If using basic evaluation, the temporary Test Stimulation Lead should be placed in accordance with the InterStim system Test Stimulation Lead Kit and Test Stimulation Lead Technical Manual.

If using advanced evaluation, the InterStim tined lead should be placed in accordance with the InterStim Therapy Model 3889 Lead Implant Manual.

For both advanced and basic evaluation, throughout the study, unilateral stimulation is required. [redacted]

[redacted]

Settings may be set per Investigator discretion during the therapy evaluation period. Any [redacted] reportable adverse events/device deficiencies will be documented and reported.

Therapy Evaluation
The therapy evaluation period should be conducted in accordance with the InterStim II System Labeling using the Verify® External Neurostimulator. The therapy evaluation period must not exceed either 14 days if using InterStim tined lead, or 7 days if using the temporary Test Stimulation Lead or the approved duration in the

	commercially available labeling in the respective country. A 3-day voiding diary will be completed towards the end of the therapy evaluation period. A minimum of a 50% improvement in voiding symptoms (either UUI or UF), or return to normal voiding of < 8 voids per day for UF subjects, is required in order to qualify for a neurostimulator implant in the study. Any [redacted] reportable adverse events/device deficiencies will be documented and reported. **Tined Lead (if applicable) / Neurostimulator Device Implant (randomization procedures)** Once the subject qualifies for the neurostimulator device implant, site personnel may proceed with the Neurostimulator Device Implant Visit and randomization procedures. If a subject does not qualify for the neurostimulator device implant, they will be exited from the study. For subjects who qualify for device implant following a successful basic evaluation, the InterStim tined lead should be placed in accordance with the InterStim Therapy Model 3889 Lead Implant Manual. [redacted] At the time of the neurostimulator device implant, site personnel will obtain a randomization assignment to randomize each subject to one of the following therapy amplitudes: sensory threshold, 50% of sensory threshold or 80% of sensory threshold. Subjects are blinded to their randomized setting. All measures should be taken to ensure that the subject does not become unblinded to their randomization throughout the study. Subjects will be implanted with the Neurostimulator in accordance with the InterStim Therapy InterStim II Model 3058 Neurostimulator Implant Manual. After the device implant is complete, it is required that subjects be programmed to 14 hertz (Hz), 210 µs pulse width (pw) and continuous stimulation for the duration of the study. During programming throughout the study, the subject's sensory threshold amplitude will be determined by following this protocol: start at 0.05 volts (V) and increase voltage in 0.05 V increments until the subject reports sensation. Prior to discharge, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. As part of the programming, impedance checks should be completed during each study visit.

	Following determination of sensory threshold (seated position), amplitude will be programmed based on the assigned randomization of sensory threshold, 80% of sensory threshold, or 50% of sensory threshold. Subjects will be allowed to adjust amplitude +/- 0.05 V during the study. Therapy amplitude will remain at this level (± 0.05 V) until the next follow-up visit or programming session. Any [redacted] reportable adverse events will be documented and reported. **1-Week Follow-up Visit** At the 1-week follow-up visit, any reportable adverse events, device deficiencies and [redacted] will be collected. Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. Following determination of sensory threshold, amplitude will be programmed based on the assigned randomization. Over the course of the study any changes to programmed parameters (amplitude, PW, rate or cycling) outside of the allowable settings in the study will be considered a protocol deviation; however, subjects will be encouraged to continue in the study. The voiding diary will be explained and given to the subject to be completed approximately 3 days prior to the 6-week follow-up visit. **6-Week Follow-up Visit** At the 6-week follow-up visit, the subject's voiding diary completed during the previous period will be collected. [redacted] reportable adverse events, device deficiencies and other information will be collected from the subject. [redacted] Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. Following determination of sensory threshold, amplitude will be programmed based on the assigned randomization using the sensory threshold in the seated position.

	The voiding diary will be explained and given to the subject to be completed approximately 3 days prior to the 12-week visit. **12-Week Follow-up Visit** At the 12-week follow-up visit, the subject's voiding diary completed during the previous period will be collected. [redacted] reportable adverse events, device deficiencies and other information will be collected from the subject. Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. Subjects will complete the following questionnaires: • ICIQ-OABqol [redacted] The subject is exited from the study after the 12-week follow-up visit is complete. Programming parameters after the subject has completed the study are at the Investigator's discretion. **Unscheduled Visit** If an unscheduled visit is needed for any device-related reason, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. Following determination of sensory threshold, amplitude will be programmed based on the assigned randomization using the sensory threshold in the seated position. In addition to programming activities, [redacted], reportable adverse events and device deficiencies will be collected. **Surgical Revision** If a surgical revision is required after the full system implant, the subject will be exited from the study.
Safety Assessments	Safety will be evaluated by the collection of reportable adverse events and device deficiencies.
Statistics	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 episodes per day at 12-week follow-up from baseline will be assessed under each amplitude setting.

	This study requires approximately 42 implanted and randomized subjects with 12-week follow-up to be analyzed for the primary objective. Approximately 60 subjects are estimated to be enrolled in the study with approximately 48 randomized; however, these numbers may vary to ensure that a minimum of 42 implanted subjects complete the study. Assuming a mean reduction between 1.8 to 2.3 UUI episodes per day with a standard deviation of 2.2 to 2.7 UUI episodes per day is observed, with α=0.05 two-sided and using a t-statistic to construct the confidence interval, a sample size of 14 subjects would have a precision of 1.56 UUI episodes per day for the assumption with a standard deviation of 2.7. Precision is defined as one-half of the confidence interval (also known as the distance from the confidence limits to the mean). This precision is less than our lowest assumed treatment effect (1.8 UUI), so it is expected that the lower 95% CI will be greater than 0 for all treatment arms, even in the scenario when the largest standard deviation was applied. This sample size calculation intends to be sufficient to explore the effect of each of three amplitude settings on UUI; however, the sample size is not sufficient for between group comparisons.

4. Introduction

4.1. Background

One of the most common patient complaints about sacral neuromodulation (SNM) for overactive bladder (OAB) is unwanted or uncomfortable stimulation.[1,2] It is often assumed that higher amplitude stimulation will provide better efficacy, but there is a lack of clinical evidence regarding amplitude effects of SNM for OAB. However, there is some evidence that SNM for fecal incontinence is effective at sub-sensory threshold/amplitude.[3] This study will explore whether lower amplitude stimulation can provide improved symptom control when compared to baseline. Potential effects of lower amplitude may include changes in or sustained efficacy, or reduced patient complaints due to uncomfortable stimulation. This feasibility study will provide an initial understanding of various amplitude stimulation settings and the impact on symptoms.

The effect of amplitude on SNM therapy efficacy is not well characterized clinically for either OAB[4] or fecal incontinence[5]. However, preclinical data suggest the effect of SNM is amplitude-dependent. Using the rodent model of rhythmic bladder contractions (RBC), Su et al (2012) showed that increasing amplitude of spinal nerve stimulation from motor threshold amplitude to 3x motor threshold resulted in inhibition of bladder contractions by 20 to 90%, respectively.[6] Similarly, using the RBC model in cats, Snellings and Grill (2012) showed that stimulation of the of the pudendal nerves inhibited the frequency of contractions and increased bladder capacity at 0.8, 1, and 2 times motor threshold in an intensity-dependent manner.[7] Finally, stimulation of tibial nerve and dorsal nerve of the penis produced an amplitude-dependent inhibition of bladder contractions in the rodent.[8] The sum of these studies suggest that the effect of neuromodulation on bladder function is amplitude-dependent.

Duelund-Jakobsen et al (2013) demonstrated that there was no significant difference in reduction of fecal incontinent episodes when subjects were programmed to 50%, 75%, and 100% of sensory threshold (n=19).[3] In a recent clinical study using fMRI, Gill et al demonstrated a stimulation amplitude-dependent response in brain activity in 6 patients receiving sub-sensory, sensory, and supra-sensory SNM.[6] These studies suggest SNM efficacy at sub-sensory amplitudes.

Given the preclinical data showing an amplitude-dependent effect of neuromodulation on bladder function and the clinical data demonstrating a therapeutic effect of sub-sensory amplitude, it is important to understand the efficacy of SNM at different subsensory and sensory threshold amplitudes.

4.2. Purpose

The purpose of this prospective, multicenter, randomized, single-blind feasibility study is 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 UUI episodes and patient reported outcomes. Quality of life will be characterized with the ICIQ-OABqol Questionnaire 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.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. 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

5.1.2. Secondary Objective

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

5.1.3. Additional Measures

Additional measures include:

- Safety
- [redacted]
- [redacted]

6. Study Design

This is a prospective, multicenter, randomized, single-blind, feasibility study to explore the efficacy and quality of life of 3 different amplitude settings in patients 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 a neurostimulator device implant 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.

Study requirements, including voiding diaries, quality of life questionnaires [redacted], and safety assessments will be completed as required in Figure 9-1: **Study** Visits. The study is expected to last approximately 16 weeks per subject following the enrollment visit. Subjects will be exited from the study after the 12-week follow-up visit is complete.

A minimum of forty-two implanted subjects (at least 14 subjects per arm) who have completed the 12-week follow-up visit are needed to assess the study primary objective. To account for screen failures, therapy evaluation conversion rate and loss to follow-up or missing data, it is anticipated that approximately 60 subjects will be consented and approximately 48 subjects will be implanted/randomized.

The study will be conducted at approximately 20 sites in the United States, Canada, and Europe.

This is an on-label, post-market study of an approved system. All subjects enrolled in the study will qualify under the approved indication for the InterStim II System.

6.1. Duration

Study subjects will be enrolled and will complete enrollment and baseline assessments to determine eligibility for an InterStim lead implant procedure. Subjects that do not meet eligibility criteria and/or qualify for a neurostimulator device implant will be exited from the study. All enrolled subjects that qualify for the study (meet all inclusion and no exclusion criteria) will be randomized and undergo an InterStim II device implant procedure. Post implant, subjects will be required to attend the 1-week follow-up visit (window +/- 3 days), 6-week follow-up visit (window +/- 7 days), and 12-week follow-up visit (window +/- 7 days). The visits are expected to occur over approximately 16 weeks starting at the enrollment visit.

The estimated study duration, from first subject enrollment to last subject visit, is expected to last approximately 18 months. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.

6.2. Rationale

While there is extensive literature on the safety and efficacy of SNM in patients with OAB, there is a paucity of published literature regarding amplitude programming, specifically programming to levels below sensory threshold. The purpose of this study is to explore the effect of sensory and sub-sensory stimulation using the InterStim II System. The InterStim II System is approved and will be used in accordance with commercially available product labeling for the specific geography.

7. Product Description

7.1. General

There are no investigational devices used in this study.

The study will be conducted in the US, Canada, and Europe, countries where the Neurostimulator Model 3058 (InterStim II), tined lead model 3889 and the temporary Test Stimulation Lead (sold via Models 305901, 305906 or 309101, hereinafter referred to only as the temporary Test Stimulation Lead)are commercially available as part of the InterStim system (for the treatment of OAB). The 3 amplitude settings under investigation are within the commercially-approved programming parameters. For the present study, the subject will be able to turn off the stimulator or decrease amplitude if needed for safety reasons, and to make minor increases to amplitude (if desired).

Labeling will be provided in accordance with local language and regulatory requirements.

7.2. Manufacturer

The products used in this study, identified in Section 7.1, are manufactured by Medtronic, Inc. and are approved for use in treating patients with OAB.

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA

7.3. Intended Population

The study will enroll patients with a diagnosis of OAB and associated symptoms of UUI. All subjects implanted must be candidates for InterStim Therapy.

7.4. Product Return

Since all products are commercially available, standard commercial processes should be used to return product (as applicable).

7.5. Product Accountability

All product used in the study are commercially available; therefore, no product accountability will be required for the study.

8. Selection of Subjects

8.1. Study Population

The intended study population is subjects diagnosed with OAB and associated signs and symptoms of UUI.

8.2. Subject Enrollment

Subjects are considered enrolled at the time the study-specific ICF is signed. Each subject must meet all the inclusion criteria and no exclusion criteria to be eligible to participate in this study. Any subject not meeting eligibility criteria will be excluded from study participation. Site personnel must complete logs related to recruitment and enrollment as required by the study.

8.3. Inclusion Criteria

To be eligible to participate in the study, a subject must meet all the following inclusion criteria:

1. Primary diagnosis of urinary urge incontinence (UUI) as demonstrated on a 3-day baseline voiding diary demonstrating at least 3 UUI episodes
2. Female subjects 18 years of age or older
3. Candidate for InterStim Lead Placement
4. Willing and able to accurately complete voiding diaries, questionnaires, attend visits, and comply with the study protocol (which includes maintenance of InterStim II programming settings over the course of the study)
5. Willing and able to provide signed and dated informed consent
6. Willing to maintain current regimen (dosage and frequency) of any overactive bladder (OAB) medication

8.4 Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury
2. History of diabetes unless the diabetes is well-controlled through diet and/or medications

3. Symptomatic urinary tract infection (UTI)
4. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component
5. Treatment of urinary symptoms with botulinum toxin in the past 9 months or any plan to have botulinum toxin treatment during the study
6. Implanted with a neurostimulator, pacemaker, or defibrillator
7. 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 MRI Guidelines for InterStim Therapy
8. Women who are pregnant or planning to become pregnant
9. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements
10. Currently enrolled or planning to enroll in a potentially confounding clinical study during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic Study Manager (or designee)

9. Study Procedures

The study schedule, procedures, and methods of assessment are defined in detail to enable compliance with the required activities, and to ensure that the resulting data meet the criteria for evaluability. See Figure 9-1 for Study Visit. Electronic case report forms (eCRF) will be provided for use in collecting data for all subjects; the pertinent eCRFs along with the applicable source documentation will be completed for each subject.

The following study visits will be conducted:

1. Enrollment / Baseline
2. Tined Lead or temporary Test Stimulation Lead Implant
3. Therapy Evaluation
4. Tined Lead (if applicable) / Neurostimulator Device Implant (randomization procedures)
5. One Week Follow-up Visit
6. Six Week Follow-up Visit
7. Twelve Week Follow-up Visit

9.1. Schedule of Events

Enrollment/Baseline

Subjects are considered enrolled at the time the study-specific informed consent is signed. Each subject must meet all the inclusion and no exclusion criteria to be eligible to participate in the study. At the enrollment/baseline visits, data will be gathered from subjects including relevant medical and concomitant OAB medication history. Enrollment and Baseline Visit requirements will occur at separate visits.

Subjects will complete the following questionnaire:

- Overactive Bladder Symptoms Quality of Life Questionnaire (ICIQ-OABqol)

The voiding diary will be explained and given to the subject to be completed for 3 consecutive days. The 3-day voiding diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant during participation in the trial, as part of the assessment for study eligibility.

Any reportable adverse events following informed consent will be documented and reported. Device deficiencies will be collected beginning at the time of the first exposure to the InterStim II System.

Tined Lead or temporary Test Stimulation Lead Implant

If using basic evaluation, the temporary Test Stimulation Lead should be placed in accordance with the InterStim System Test Stimulation Lead Kit and Test Stimulation Lead Technical manual.

If using advanced evaluation, the InterStim tined lead (model 3889) should be placed in accordance with the InterStim Therapy Model 3889 Lead Implant Manual.

[redacted]

[redacted]

[redacted]

Settings may be set per Investigator discretion during the therapy evaluation period and will be documented. Any [redacted] reportable adverse events/device deficiencies will be documented and reported.

Therapy Evaluation

The therapy evaluation period should be conducted in accordance with the InterStim II System Labeling. The therapy evaluation period must not exceed either 14 days if using InterStim tined lead or 7 days if using the temporary Test Stimulation Lead as defined by current labeling, or a new approved duration in an updated commercially available labeling in the respective country. A 3-day voiding diary will be completed towards the end of the therapy evaluation period**.** A minimum of a 50% improvement in UUI or UF voiding symptoms, or return to normal voiding of < 8 voids per day for UF subjects, is required in order to qualify for a neurostimulator implant in the study. Settings used during therapy evaluation will be documented during this visit. Any [redacted] reportable adverse events/device deficiencies will be documented and reported.

Tined Lead (if applicable) / Neurostimulator Device Implant (randomization procedures)

Once the subject qualifies for the neurostimulator device implant, site personnel may proceed with the neurostimulator device implant and randomization procedures. If a subject does not qualify for the neurostimulator device implant, they will be exited from the study.

For subjects who qualify for device implant following a successful basic evaluation, the InterStim tined lead should be placed in accordance with the InterStim Therapy Model 3889 Lead Implant Manual.

[redacted]

At the time of the neurostimulator device implant, site personnel will obtain a randomization assignment to randomize each subject to one of the following therapy amplitudes: sensory threshold, 50% of sensory threshold or 80% of sensory threshold. Subjects are blinded to their randomization. All measures should be taken to ensure that the subject does not become unblinded to their randomization throughout the study.

Subjects will be implanted with the Neurostimulator in accordance with the InterStim Therapy InterStim II Model 3058 Neurostimulator Implant Manual.

After the device implant is complete, it is required that subjects be programmed to 14 hertz (Hz), 210 µs pulse width (pw) and continuous stimulation for the duration of the study. During programming, the subject's sensory threshold amplitude will be determined by following this protocol: start at 0.05 volts (V) and increase voltage using fine resolution in 0.05 V increments until the subject reports sensation.

Prior to discharge, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. To determine sensory threshold, each electrode (0,1,2,3) will be programmed as the cathode (negative) in a bipolar configuration in a systematic fashion.

Following determination of sensory threshold, amplitude will be programmed based on the assigned randomization of sensory threshold, 80% of sensory threshold, or 50% of sensory threshold using the sensory threshold in a seated position. As part of the programming, impedance checks should be completed. Upon completion of programming, data will be collected via a programming printout or Neuro Programmer Upload (NPU).

Subjects will be allowed to adjust amplitude +/- 0.05 V during the study. Therapy amplitude will remain at this level (± 0.05 V) until the next follow-up visit or programming session. Any [redacted] reportable adverse events/device deficiencies will be documented and reported.

1-Week Follow-up Visit

At the 1-week follow-up visit, any reportable adverse events, device deficiencies [redacted] will be collected.

During the visit, the subject's sensory threshold amplitude will be captured by following this protocol: start at 0.05 V and increase voltage using fine resolution in 0.05 V increments until the subject reports sensation. Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. To determine sensory threshold, each electrode (0,1,2,3) will be programmed as the cathode (negative) in a bipolar configuration in a systematic fashion.

Following determination of sensory threshold amplitude, amplitude will be programmed based on the assigned randomization using sensory threshold in a seated position. Subjects will be allowed to adjust amplitude +/- 0.05 V during the study. As part of the programming, impedance checks should be completed. Upon completion of programming, data will be collected via a programming printout or NPU.

Over the course of the study any changes to programmed parameters (amplitude, PW, rate or cycling) outside of the allowable settings in the study will be considered a protocol deviation; however, subjects will be encouraged to continue in the study.

The voiding diary will be explained and given to the subject to be completed approximately 3 days prior to the 6-week follow-up visit.

6-Week Follow-up Visit

At the 6-week follow-up visit, the subject's voiding diary completed during the previous period will be collected. [redacted] reportable adverse events, device deficiencies and other information will be collected from the subject.

[redacted]

During the visit, the subject's sensory threshold amplitude will be captured by following this protocol: start at 0.05 V and increase voltage using fine resolution in 0.05 V increments until the subject reports sensation. Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. To determine sensory threshold, each electrode (0,1,2,3) will be programmed as the cathode (negative) in a bipolar configuration in a systematic fashion.

Following determination of sensory threshold, amplitude will be programmed based on the assigned randomization using the sensory threshold in the seated position. Subjects will be allowed to adjust amplitude +/- 0.05 V during the study. As part of the programming, impedance checks should be completed. Upon completion of programming, data will be collected via a programming printout or NPU.

The voiding diary will be explained and given to the subject to be completed approximately 3 days prior to the 12-week visit.

12-Week Follow-up Visit

At the 12-week follow-up visit, the subject's voiding diary completed during the previous period will be collected. [redacted] reportable adverse events, device deficiencies and other information will be collected from the subject. During the visit, the subject's sensory threshold will be captured by following this protocol: start at 0.05 V and increase voltage in 0.05 V increments until the subject reports sensation. Prior to the completion of the visit, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. To determine sensory threshold, each electrode (0,1,2,3) will be programmed as the cathode (negative) in a bipolar configuration in a systematic fashion. As part of the programming, impedance checks should be completed. Upon completion of programming, data will be collected via a printout or NPU.

Subjects will complete the following questionnaires:

- ICIQ-OABqol
- [redacted]

The subject is exited from the study after the 12-week follow-up visit is complete. Programming parameters after the subject has completed the study are at the Investigator's discretion.

Unscheduled Visit

If an unscheduled visit is needed for any device-related reason, the subject's sensory threshold amplitude will be confirmed by following this protocol: start at 0.05 V and increase voltage in 0.05V increments until the subject reports sensation. Prior to the completion of the study, the amplitude at each electrode configuration that elicits a sensory response must be determined in [redacted] seated [redacted] positions. To determine sensory threshold, each electrode (0,1,2,3) will be programmed as the cathode (negative) in a bipolar configuration in a systematic fashion.

Following determination of sensory threshold amplitude, amplitude will be programmed based on the assigned randomization using the sensory threshold in a seated position. Subjects will be allowed to adjust amplitude +/- 0.05 V during the trial. As part of the programming, impedance checks should be completed. Upon completion of programming, data will be collected via a programming printout or NPU.

All efforts should be made to maintain subject in the randomized arm. If the subject must be changed from their randomized arm, subjects should be encouraged to complete a 3-day voiding diary prior to the unscheduled visit.

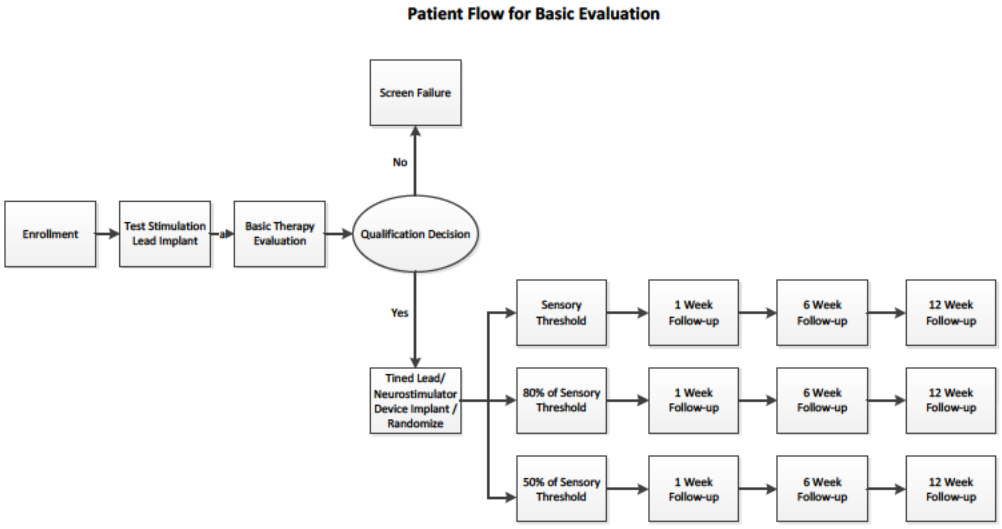
In addition to programming activities, any [redacted] reportable adverse events and device deficiencies will be collected.

Surgical Revision

If a surgical revision is required after the full system implant, the subject will be exited from the study.

Figure 9-1: **Study** Visits illustrates required study visits for basic and advanced evaluations:

Figure 9-1: Study Visits



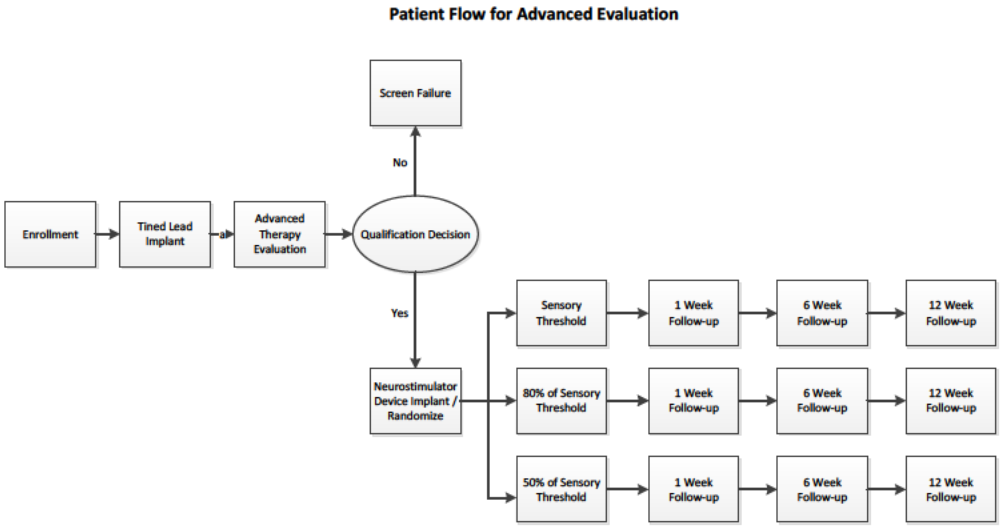


Table 9-1: Study Procedures

	Enrollment / Baseline	Tined Lead or Test Stimulation Lead Implant	Therapy Evaluation	Tined Lead (if applicable)/ Neurostimulator Device Implant	1-Week Follow-Up Visit (+/- 3 days)	6-Week Follow-Up Visit (+/- 7 days)	12-Week Follow-Up Visit (+/- 7 days)	Unscheduled Visit
Informed Consent	X*							
Randomization Procedures				X***				
Relevant Medical History	X							
ICIQ-OABqol Questionnaire	X						X	
Pregnancy Assessment	X							
[redacted]		[redacted]		[redacted]				
Assessment of Sensory Threshold		X		X	X	X	X	X
PGI-I Questionnaire						X	X	
3-Day Voiding Diary	X**		X**			X	X	X****
Device Interrogation/ Programming Data		X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assessment of Reportable Adverse Events and Device Deficiencies	X	X	X	X	X	X	X	X

* Must occur prior to any study specific activities

**50% improvement in UUI or UF voiding symptoms, or return to normal voiding of < 8 voids per day for UF subjects, required for neurostimulator implant

***Randomization must occur after study qualification; however, may be prior to or after neurostimulator device implant

****If the subject must be changed from their randomized arm, subjects should be encouraged to complete a 3-day voiding diary prior to the unscheduled visit.

[redacted]

Note: Programming settings of 14 hz, 210 pw and continuous stimulation are required following the neurostimulator device implant for the duration of the study

9.2. Subject Screening

Subjects may be recruited through the investigator's practice and referring physicians.

Potential subjects may be identified through chart reviews or as new or existing patients attend clinic visits as appropriate. If subjects are recruited from outside the investigator's practice, sites are to ensure that appropriate release for access to the subject's records (paper and/or electronic) is obtained. Any subject recruitment materials disseminated to subjects (advertisements, handouts, posters, social media) must be approved by the IRB/EC prior to use.

All subjects must be consented in accordance with the protocol prior to any study-specific procedures. Recruited subjects will be screened by the Principal Investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria.

A screening log should be completed by the site to maintain a cumulative log of all screened subjects with reason for screening failure.

The Investigator will maintain a listing of all subjects enrolled in the study.

[redacted]

9.4. Subject Consent

The informed consent process will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 21CFR§50 Protection of Human Subjects (US only), SOR/98-282 (Canada only) and in accordance with local regulatory requirements. No vulnerable patients will be allowed to be consented to participate in the study. Data will be collected and treated in accordance with applicable Data Privacy Legislation. With regard to the EU this includes Directive 95/46/EC and subsequent legislation.

Prior to entering the study, the Principal Investigator or qualified designee will explain to each subject the purpose and nature of the study, procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. The person obtaining consent will avoid any coercion or undue improper influence on, or inducement of, the subject to participate and the ICF will not waive, or appear to waive, any legal rights. Subjects will be given a copy of the IRB/EC approved ICF and will have ample time to review the document and to ask questions and will be informed of their right to withdraw from the study at any time without prejudice; ICFs will be provided in a language understandable to the subject. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and personally date the

ICF. Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent and any other written information provided to the subject.

The Principal Investigator or qualified (delegated) designee will document the informed consent process, including the date of consent and name of the person conducting the consent process in the subject's medical record. A copy of the signed ICF will also be placed in the subject's medical record. Throughout study participation, any significant new information will be provided to the subject as outlined in the informed consent form. As appropriate, the ICF may be revised based on new information that becomes available.

9.5. Randomization and Treatment Assignment

Once the subject meets all eligibility criteria for the study, and has a successful therapy evaluation, site personnel may proceed with the neurostimulator device implant and randomization procedures. If a subject does not meet all eligibility criteria, subjects should be exited and not proceed to the neurostimulator device implant and randomization procedures.

At the time of the device implant, site personnel will obtain randomization for one of the following therapy amplitudes: sensory threshold, 50% of sensory threshold or 80% of sensory threshold. Randomization will be assigned in a 1:1:1 ratio, and stratified by site. Site personnel will obtain the subject's randomization sequence on the Randomization eCRF which will be generated from the database.

The investigator and research staff at the study site will be instructed to keep the subject blinded to their randomization; however, subjects may or may not feel stimulation. The outcome measures in this study are based on the subject's own assessment. Therefore, keeping the subject blinded to their randomization reduces bias in the outcome measurement reporting. [redacted]

During the study, subjects will be encouraged to remain in the randomized treatment arm; however, a subject may request to be re-programmed with a different amplitude setting. If this occurs, a protocol deviation will be required and subjects should continue in the study and complete the remaining follow-up visits.

[redacted]

[redacted]

9.7. Assessment of Efficacy

Subject assessments will be performed by appropriately trained, qualified and delegated site personnel according to the usual practices of the site.

Urinary Voiding Diary

Symptoms related to 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. Every effort should be made to remind subjects of the importance of real-time diary completion.

Voiding diary data will be used to verify study inclusion criteria for UUI episodes at baseline. Diaries will also be used for comparison of efficacy from 12-week follow-up visit to baseline for the primary study endpoint of UUI [redacted]

Assessments for Quality of Life Measures

Subjects will complete the study questionnaires confidentially on paper forms without site personnel consultation and these data will be entered to OC/RDC by site personnel. Questionnaires should be completed prior to the follow-up visit when data is collected. Site personnel are encouraged to review forms for completeness.

<u>ICIQ-OABqol Questionnaire</u>

The ICIQ-OABqol is a robust, patient-completed questionnaire for evaluating quality of life (QoL) in patients with overactive bladder, for use in research and clinical practice.[9] The questionnaire used in the current study includes 26 questions which are 4-week recall for symptom assessment.

[redacted]

9.8. Assessment of Safety

9.8.1 Reportable Adverse Events and Device Deficiencies

All reportable adverse events and device deficiencies will be collected throughout the study once the informed consent form is signed.

9.9. Recording Data

This study will be conducted using a remote data capture system. The Oracle Clinical Remote Data Capture (RDC) system which allows the study centers to enter study data into the sponsor's database over a secure internet connection, will be used to capture study required Case Report Form (CRF) information. Data reported on voiding diaries and subject questionnaires will be entered to the database by site personnel. Subjects will complete the study questionnaires confidentially on paper forms without site personnel consultation and these data will be entered to OC/RDC by site personnel. Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be taken from source documents and directly entered into the study database via the CRFs by the site personnel, in accordance with applicable regulations.

Device interrogation (programming) data may be transmitted using either NPU or by manual data entry on a programming CRF.

Subject voiding diaries and questionnaires are to be completed only by the subject. Representatives from the research site may not make entries to the diaries or questionnaires except for administrative clarification on source documentation.

The Principal Investigator, Sub-Investigator, or an individual delegated by the Principal Investigator on the Delegation of Authority and Signature Form, are responsible for documenting and entering data for the study on the eCRFs. The Principal Investigator or Sub-Investigator is required to approve all data on CRFs via electronic signature.

9.10. Deviation Handling

Protocol deviations are digressions from the written protocol defined as an event where the clinical investigator or site personnel did not conduct protocol-required procedures according to the study protocol. Protocol deviations are to be preapproved by Medtronic study personnel and the IRB/EC (as required) unless the deviation is necessary to protect the health, safety, or welfare of a subject in an emergency situation. The investigator or delegated site personnel should contact the designated Medtronic study personnel to discuss the impact of the potential deviation; prior approval of deviations should be documented. Prior approval is generally not required if the deviation is due to an emergency circumstance or an unforeseen circumstance that is beyond the investigator's control; however, these deviations should be reported to Medtronic and the IRB/EC (as required) after site personnel become

aware of the deviation. Site personnel should work with subjects to ensure subject follow-up visits are scheduled within the visit window; however, any visits completed outside of the visit window will require a protocol deviation to be reported. All protocol deviations must be reported on the Protocol Deviation eCRF after the site's awareness of the deviation.

The sponsor may choose to terminate the study at a site for failure to follow the written protocol and investigator agreement. If this occurs, the Investigator, IRB/EC and governing regulatory authority (if applicable) will be notified in writing of the reasons for the termination.

9.11. Subject Withdrawal or Discontinuation

Subjects are free to voluntarily withdraw from the study at any time and for any reason. All implanted subjects will be followed until the 12-week follow-up visit, unless withdrawn from the study. Withdrawn or exited subjects will be followed under normal medical practice.

Examples of reasons for study discontinuation include, but are not limited to, those listed below:

- If the subject does not meet eligibility criteria of at least 3 UUI episodes demonstrated on a 3-day baseline urinary voiding diary
- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- Subject becomes pregnant
- Investigator terminates the subject's participation in the study due to lack of compliance, violation of/change in eligibility criteria
- Any clinical laboratory abnormality, current illness, or other medical condition or situation occurs such that continued study participation would not be in the best interest of the subject.
- Subject is not a candidate for InterStim Therapy
- Normal study completion

Prior to deeming a subject lost to follow-up, telephone calls must be documented in the subject's medical record. If a minimum of three attempts to contact the subject have failed (e.g. phone and mailed letter), and no response is received, the site should exit the subject and complete the Study Exit eCRF.

When a subject is withdrawn from the study, the Study Exit eCRF is to be completed and should include detailed notes as to why the subject was withdrawn from the study (e.g., discomfort, lack of efficacy, diary too burdensome). Withdrawn subjects will not be replaced.

Once a subject completes participation in the study, follow-up will continue in accordance with the site's standard of care. No study specific medical care will be provided for a subject after discontinuation from the study, unless outlined in the Clinical Trial Agreement and Informed Consent Form.

10. Risks and Benefits

10.1. Potential Risks

The risks outlined below are the same risks found in commercial InterStim II System use; however, based on the amplitude settings, subjects may experience less than desired improvements in OAB symptoms. No additional study specific risks are present.

10.1.1. Risks Outlined in the Instructions for Use (IFU)

Refer to the appropriate Instructions for Use (IFU) for the InterStim System components for updated list on contraindications, precautions, warnings, adverse events, directions for use and other product specific details.

In addition to the risks normally associated with surgery, implantation, or use of a neurostimulation system includes, but is not limited to, the following risks. Certain adverse events may necessitate surgical intervention.

- Adverse change in voiding function (bowel and/or bladder)
- Allergic or immune system response to the implanted materials that could result in device rejections
- Change in sensation of stimulation which has been described as uncomfortable (jolting or shocking) by some patients
- Infection
- New pain
- Pain at neurostimulator and or lead site
- Seroma, hemorrhage, hematoma
- Suspected lead or neurostimulator migration or erosion
- Suspected nerve injury
- Suspected technical device problem
- Transient electric shock

The safety of SNM has not been established for pregnant women, for an unborn fetus, or during childbirth. This precaution is provided in the InterStim Therapy commercial labeling and should be adopted in this study; thus, no one who is pregnant or planning to become pregnant will be enrolled.

If a subject learns or suspects that she is pregnant, the investigator will instruct her to turn her neurostimulator OFF and to visit the study site as soon as possible; however, this will not be considered a reportable AE.

10.2. Potential Benefits

Subjects may not receive any direct medical benefit from participation in this study but subjects will receive additional medical oversight of treatment. Participation in this study may not provide greater benefit than if the subject was receiving InterStim Therapy outside of the study, as required study programming is within approved programming specifications. Information from this study might help researchers further understand InterStim Therapy related to uncomfortable stimulation. The benefit to subjects participating in this study, and to future patients, resides in the knowledge gained from this study.

10.3. Risk-Benefit Rationale

Participation in this study will not expose the subject to greater risks than if he/she were receiving InterStim Therapy outside of the study. There might be other discomforts and risks related to InterStim Therapy and/or this study that are not foreseen at this time. In addition, based on the amplitude settings, subjects may experience less than desired improvements in OAB symptoms.

The risks associated with InterStim II System are minimized in this study by selecting only qualified Investigators experienced in InterStim Therapy, selecting an appropriate patient population via inclusion/exclusion screening, and monitoring subject progress and events reported for this study. The review and minimization of the potential risks to the patient and the potential benefits to the patient support the conduct of this study.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Any adverse event meeting the definition of: serious, device related, therapy related and/or procedure related as well as all device deficiencies will be considered reportable for this study. The term “investigational device” is part of ISO14155 definitions. The term “investigational device” refers to any device used in the study including market released devices. Adverse events and device deficiencies are defined as follows:

- Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the InterStim II System
- Procedure Related: An adverse event that occurs due to any procedure related to the implantation or surgical modification of the InterStim II System. The procedure is defined as the lead placement or implant procedure.
- Therapy Related: An adverse event related to therapy delivery by device e.g. device stimulation issue (normally therapy-related events resolve when the device is turned off or reprogrammed).

Table 11-1: Adverse Event & Device Deficiency Definitions

Term	General
Adverse Event (AE) (ISO 14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)* (ISO 14155:2011 3.1)	Adverse event related to the use of an investigational medical device. NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD)* (ISO 14155:2011 3.15) (ISO 14155:2011 3.27)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE 1 Device deficiencies include malfunctions, use errors, and inadequate labeling. ▪ Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

(ISO 14155:2011 3.43)	▪ Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user NOTE 2 Use error includes slips, lapses, mistakes. NOTE 3 An unexpected physiological response of the subject does not in itself constitute a use error.
SERIOUSNESS	
Serious Adverse Event (SAE)* (ISO 14155:2011 3.37)	Adverse event that a) led to a death, b) led to a serious deterioration in the health of the subject, that either resulted in: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. c) led to foetal distress, foetal death or a congenital abnormality or birth defect. NOTE Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)* (ISO 14155:2011 3.36)	Adverse device effect that resulted in any of the consequences characteristic of a serious adverse event
Unexpected Serious Adverse Device Effect (USADE)*	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

(ISO 14155:2011 3.42)	NOTE Anticipated serious adverse device effect (ASADE) is an effect by which its nature, incidence, severity or outcome has been identified in the risk analysis report.
RELATEDNESS	
Relationship of Adverse Events	The relationship of the adverse event to the study treatment (device, therapy, procedure) will be described using the following terms: • Not related • Unlikely • Possible • Probable • Causal relationship

*Reportable event categories that will be collected during this study

11.2. Report of Adverse Events

Any adverse event meeting the definition of serious, device-related, procedure-related and/or therapy-related as well as all device deficiencies as defined above will be considered reportable for this study.

The following are not adverse events:

- Transient effects that occur during the implant procedure or programming and resolve without reprogramming.
- Any normal expected postoperative complaints or symptoms unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. Expected postoperative outcomes include headache, incisional pain, nausea, vomiting, low grade fever, oozing at dressing, dizziness, irritability, sleepiness, nervousness, insomnia, constipation, urinary retention, confusion and similar events.
- Worsening of OAB symptoms will be collected as part of the efficacy measures and are not considered a reportable adverse event.

For reporting of all serious adverse events and/or serious adverse device effects, the following emergency Sponsor contact may be used:

Phone: 1+763.526.8102
Email: rs.pelvichealthresearchnetwork@medtronic.com
Address: 7000 Central Avenue NE, RCE 375 | Minneapolis, MN, 55432 | USA

All reportable adverse events will be classified using the following responsibility matrix:

Table 11-2 Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Relatedness	Investigator	Procedure related Device related Therapy related
USADE potential	Medtronic	USADE
Seriousness	Investigator	SAE/SADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Medtronic	MedDRA term assigned based on the data provided by investigator

All reportable adverse events must be recorded in the subject's medical record and on an Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic based on Table 11-2. IRB/EC reporting must be completed in accordance with the policies of the governing IRB/EC. Governing regulatory authority reporting should be completed in accordance with applicable local regulations.

Reports of adverse events and device deficiencies will include the following information, at a minimum:

- Date of event
- Diagnosis or description of the event
- Assessment of the seriousness and relationship to the product(s) under study
- Treatment
- Outcome and date of resolution

It is the responsibility of the Investigator to identify the occurrence of reportable adverse events and device deficiencies and to ensure the required information is accurately documented on the eCRF.

The clinical course of each adverse event must be followed until resolution or subject discontinuation from the study, whichever comes first. "Ongoing" adverse events and device deficiencies must be assessed at each protocol required visit, and new or updated information must be documented on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic and if applicable to the IRB/EC. Commercial medical device reporting processes will be followed for complaint handling.

If necessary, the Investigator may report to the sponsor initially by telephone or email and follow-up with completed eCRFs and, if possible, copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

Medtronic study personnel will promptly review all reported adverse events and device deficiencies and

if necessary request clarification and/or additional information from the Investigator. If Medtronic disagrees with the Investigator's assessment of the adverse event relationship to device, therapy and/or procedure, Medtronic study personnel will document the disagreement and report or ensure reporting of both opinions to IRB/EC as necessary. All reported adverse events and device deficiencies will be reviewed by a Medtronic Medical Advisor to ensure consistent reporting

11.2.1. Device Deficiencies

A device deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling. All device deficiencies must be documented and submitted to Medtronic on the Device Deficiency eCRF. In addition, the Investigator must also determine and document on the eCRF device deficiencies that did not lead to adverse event but could have led to a serious adverse device effect:

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate

11.2.2. Deaths

All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but no more than 5 working days after learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. If limited information is known, the Adverse Event eCRF must be completed with available information as soon as possible. As information becomes available, the eCRF will be updated. If the death occurs at a location remote from the study site, it is the study site's responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's death summary of the known events surrounding the death to Medtronic or its designee. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system, therapy, and/or procedure. If the death is evaluated as device, therapy and/or procedure related and unanticipated, the event will be reported as a USADE by Medtronic or its designee to the appropriate regulatory agencies. In addition, the principal investigator should follow commercial medical device reporting requirements. The principal investigator should provide as much of the following supporting documentation as possible for deaths:

- Death certificate
- Death summary/hospital records, if allowed by state/local law
- Autopsy report, if allowed by state/local law

All device system components that were being used at the time of the death should be returned to Medtronic for analysis, if applicable. Any subject death will be reported on the Adverse Event and Study Exit CRFs.

12. Data Review Committees

This study will not use a Clinical Events Committee or Data Monitoring Committee. Instead, all reported adverse events and device deficiencies will be reviewed by a Medtronic Medical Advisor to ensure consistent reporting as defined in Section 11.2.

13. Statistical Design and Methods

13.1 General Statistical Considerations

This study is a three-arm parallel design to explore effectiveness, and quality of life under three amplitude settings. For the primary objective, the primary analysis will be performed in the complete case (CC) population, or the population of subjects who have data available at baseline and follow-up based on their randomization. [redacted] Details of the primary and supporting analyses are outlined in the sections below.

Continuous measures will be reported as N, means, medians, standard deviations, minimums and maximums. All summaries will be provided by group. Categorical measures will be reported in frequency distributions.

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.2 or higher) will be used to analyze the study results.

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

13.1.1 Study Sample Size Justification

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 48 subjects will be 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[13], a mean reduction of 2.1±1.8 UUI episodes per day was observed at 3 months in 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 13-1). 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 13-1. Standard deviations 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

13.1.2 Description of demographic and baseline variables

Summary statistics will be provided, by group, for baseline and demographic variables for subjects who are enrolled and randomized.

13.1.3 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. The study will be conducted at approximately 20 centers in the United States, Canada and Europe.

13.1.4 Missing Data

Missing data imputations will not be performed.

13.1.5 Interim Analysis

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.

13.1.6 Reports

A final report will be generated for this study. Periodic progress reports may also be generated for the study.

13.1.7 Study Success

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

13.1.8 Subgroup Analyses

Subgroup analyses will be detailed in the SAP, if any will be conducted.

13.1.9 Patient Populations

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

The complete case (CC) patient set will consist of the subject set who have data available at baseline and follow-up.

13.2 Primary Objective

13.2.1 Primary objective

To explore the effect of three different amplitude settings (50% of sensory threshold, 80% of sensory threshold, and sensory threshold) on urinary urge incontinence (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.

13.2.2 Experimental design

Subjects' number of UUI episodes will be reported in the voiding diary. Data will be collected daily in the 3 days prior to each visit for all subjects and the value reported at each visit will be calculated as the daily average of the available diary days at that visit. All available data will be used for analysis, regardless of whether 1 day is available or 3 days are available. The change in scores from Baseline to 12 weeks will be calculated for each subject and the average change across all subjects in each group will be reported.

13.2.3 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.

13.2.4 Analysis methods

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

13.2.5 Analysis populations and sensitivity analyses

The analysis population for this objective will be on the CC population, as described in Section 13.1.9.

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 include the population of subjects who have data available at baseline and 12 weeks, but will analyze subjects according to the treatment they receive.

In addition to the summaries described above, responder rate analyses will be conducted to further describe the treatment effect of each randomization group. Responder rates will be described as the percent of patients who achieve therapeutic success, defined as $\geqslant$ 50% reduction in average UUI episodes/day from baseline to 12 weeks, divided by the number of subjects included in the analysis.

Responder rate analyses will be completed based on the CC and AT analyses described above.

13.3 Secondary Objective

13.3.1 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.

13.3.2 Experimental design

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 group will be reported.

13.3.3 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.

13.3.4 Analysis methods

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

13.3.5 Analysis populations and sensitivity analyses

The analysis population for this objective will be on the CC population, as described in Section 13.1.9.

In addition to the primary analysis of the secondary objective, an as-treated (AT) sensitivity analysis will be completed to assess the robustness of results. The AT analysis will include the population of subjects who have data available at baseline and 12 weeks, but will analyze subjects according to the treatment they receive.

13.4 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.

Additional measures to summarize are:

- Incidence of device-related, procedure-related and/or therapy-related adverse events

[redacted]

[redacted]

Reportable device-related, procedure-related and/or therapy-related adverse events will be summarized for subjects who are implanted and randomized under each amplitude setting. Device-deficiencies will be summarized in the similar fashion. In addition, serious adverse events will be summarized.

[redacted]

[redacted]

[redacted]

14. Ethics

14.1. Statement(s) of Compliance

The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC/IRB approval, study training, and risk benefit assessment. In addition, all applicable laws and regulatory requirements of the country/ies in which the study is conducted will be followed and in accordance with GCP.

- In the US, the study will be conducted in accordance with 21 CFR§11 Electronic Records, Electronic Signatures, 21CFR§50 Protection of Human Subjects, 21CFR§56 IRB, and 21CFR§803 Medical Device Reporting. Financial disclosures will be collected; however, this study is not considered a "covered study" under 21 CFR§54 Financial Disclosure by Clinical Investigators.

- In Europe, the study will be conducted in accordance with regional or national regulations, as appropriate.

- In Canada, the study will be conducted in accordance with Canada Medical Devices Regulations, 1998 (SOR/98-282), and the Guidance document for Mandatory Problem Reporting.

Any additional requirements imposed by the IRB/EC or governing regulatory authority shall be followed, if appropriate.

Medtronic will distribute the approved version of the CIP and all other materials required to conduct the study. Prior to site activation, Medtronic will provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities. Medtronic will not activate any site until the required approval/favorable opinion from the Institutional Review Board (IRB)/Ethics Committee (EC) or notification/approval from a regulatory authority have been obtained, if appropriate.

Site personnel must inform Medtronic of any change in status of the IRB/EC approval once the site has started enrollment.

14.2. Principal Investigator Oversight

The Principal Investigator will provide adequate oversight to ensure the study is conducted in accordance with all protocol requirements, all applicable regulatory requirements and any applicable institutional requirements related to the conduct of clinical research. The Principal Investigator will ensure no study-related activities occur prior to regulatory and IRB/EC approval. Any actions taken by the IRB/EC with respect to the investigation will be forwarded to Medtronic as soon as possible. The Principal Investigator is responsible for submitting all required reports to the sponsor and/or IRB/EC. Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. It is the responsibility of the Investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB/EC responsible for oversight of the study. Investigators should report serious adverse events, device-, procedure- and therapy-related adverse events and device deficiencies to Medtronic after the Investigator learns of the event in accordance with Table 14-1.

In addition, Principal Investigator, or designated personnel will provide Medtronic with the following minimum information related to serious adverse events, device-, procedure- and/or therapy-related adverse events and device deficiencies:

- Date of adverse event or device deficiency
- Treatment provided
- Resolution date
- Assessment of seriousness
- Relationship to the device, therapy and/or procedure

Failure to perform the investigator obligations or to complete corrective and preventive actions identified during monitoring or auditing activities may result in Principal Investigator or site personnel disqualification, and/or lead to suspension or termination of the study at the site.

Table 14-1 includes minimum reporting requirements for investigators participating in studies in Europe, the US and Canada. Medtronic study personnel will immediately report Adverse Events and Device Deficiencies, related to a CE marked or FDA approved device used during the study, to Medtronic's Compliant Handling Unit who will ensure prompt review and appropriate reporting. The Therapeutic Products Directorate is a division of Heath Canada, and is responsible for regulating therapeutic products including Food, Drugs, Medical Devices, Natural Health Products, Cells, Tissues and Organs and Cosmetics. Table 14-1 includes minimum reporting requirements in Canada.

Table 14-1 Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event **All other geographies:** Report to the sponsor, without unjustified delay, all serious adverse events
IRB/EC	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Regulatory Authorities	**All geographies:** Reporting timeframe as per local requirement
Serious Adverse Device Effects (SADEs), Unanticipated Serious Device Effects (USADEs) and Unanticipated Adverse Device Effects (UADEs)	

Investigator submit to:	
Medtronic	**US:** As **soon** as possible to meet regulatory reporting requirements, but no later than 10 days after the date you become aware **Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event **All other geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements
IRB/EC	Reporting timeframe as per local EC/IRB requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) to submit to Health Canada:** As **soon** as possible to meet regulatory reporting requirements within **10 days** after the date Medtronic becomes aware **All other geographies:** Reporting timeframe as per local requirement
All Other Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event
IRB/EC	**All geographies:** Reporting timeframe as per local EC/IRB requirement
Deaths	
Investigator submit to:	
Medtronic	**All geographies:** All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but no more than 5 working days of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy
IRB/EC	**All geographies:** All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but no more than 5 working days of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy
USADE, SADE, DD (Canada only) (referred to here as "incidents") occurring outside Canada requiring corrective action or imposed by local regulatory authorities	
Sponsor submit to:	
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) to submit report to Health Canada:** When Medtronic has indicated to a regulatory authority of the country in which the incident occurred, intention to take corrective action, or if the regulatory authority has required Medtronic to take corrective action. In this case, the incident must be reported to the Health Canada as soon as possible after either Medtronic has reported to the local regulatory authority or a corrective action has been imposed by the local regulatory

	authority.
Device Deficiencies that has resulted in an SAE (Canada only)	
Sponsor submit to:	
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) to submit report to Health Canada:** As soon as possible to meet regulatory reporting requirements within **10 days** after the date Medtronic becomes aware
Device Deficiencies (DD) with SADE potentials	
Investigator submit to:	
Medtronic	**US & Europe:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency **All geographies:** Report to the sponsor, without unjustified delay, all device deficiencies that could have led to a serious adverse device effect
IRB/EC	**All geographies:** Reporting timeframe as per local EC requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB requirement
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) submits to Health Canada:** As soon as possible to meet regulatory reporting requirements within **30 days** after the date Medtronic becomes aware **All other geographies:** Reporting timeframe as per local requirement
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency
IRB/EC	**All geographies:** Reporting timeframe as per local EC requirement
Withdrawal of IRB Approval	
Investigator submit to:	
Medtronic	**All geographies:** Report a withdrawal of the reviewing EC/IRB approval within **5 days** of investigator notification
Protocol Deviations for Emergency Reasons	
Investigator submit to:	
Medtronic	**US:** Submit to Medtronic and IRB within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject) **Canada:** Per institutional guidelines, report protocol deviations to Medtronic
EC/IRB	**US:** Submit to Medtronic and IRB **within 5 working** days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject) **Canada:** Per institutional guidelines, report protocol deviations to the

	reviewing IRB
Prior Notification of Protocol Deviations	
Medtronic	**All geographies:** Except in the occurrence of an emergency deviation, the Investigator must obtain prior approval from Medtronic of protocol deviations. Prior approval from the IRB may also be required according to local requirements.
EC/IRB	**All geographies:** Except in the occurrence of an emergency deviation, the Investigator must obtain prior approval from Medtronic of protocol deviations. Prior approval from the IRB may also be required according to local requirements.
Failure to Obtain Informed Consent	
Investigator submit to:	
Medtronic	**US and Europe:** The Investigator must notify Medtronic within **5 working days** upon awareness **Canada:** The Investigator must notify Medtronic within **5 working** days after procedure
EC/IRB	**US and Europe:** The Investigator must notify the EC/IRB within **5 working days** after upon awareness **Canada:** The Investigator must notify the EC/IRB within **5 working** days after procedure
Final Report	
Medtronic	**US and Europe:** Study reports must be submitted within **6 months** after termination or completion of the investigation or as required by applicable regulation **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation
EC/IRB	**US and Europe:** Study reports must be submitted within **6 months** after termination or completion of the investigation or as required by applicable regulation **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation

15. Study Administration

15.1. Sponsor

This study is sponsored by:

Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432
USA

A list of sponsor's study staff will be provided as a separate document to site personnel. Sponsor will maintain an updated list of contact information.

15.2. Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the study as well as ensure data integrity and the rights, safety and well-being of the patients involved in the study. Site selection criteria will be documented and utilized to ensure adequate site selection.

15.3. Clinical Trial Agreement

A Clinical Trial Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement.

15.4. Curriculum Vitae

A curriculum vitae from each Investigator participating in the study shall be obtained.

15.5. Monitoring

Medtronic is responsible for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on CRFs. The Principal Investigator, his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data or certified copies (e.g., paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the CRFs as well as other documentation supporting the conduct of the study. The monitor

will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed. The monitoring plan contains the strategy for frequency of monitoring visits and source data verification to be performed for this study.

15.6. Medtronic Representative Role

Medtronic representatives may participate in the conduct of the study to the extent listed below.

Medtronic representatives can provide technical support to the investigator and other health care personnel as needed during study visits. This support may include the training of site personnel on use of the Medtronic equipment or the protocol-related procedures and forms.

In addition, Medtronic personnel can perform certain activities to ensure study quality. These activities may include:

- Observing testing or medical procedures to provide information relevant to protocol completion
- Reviewing collected data and study documentation for completeness and accuracy
- Perform device programming or device interrogation under the direction of the investigator(s)

Medtronic personnel will not:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the health care provider.
- Complete CRFs or make entries in the subject's medical record

15.7. Data Management

Medtronic personnel will perform routine edit and consistency checks for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data discrepancies; investigators and site personnel will review data discrepancies and respond to the discrepancies in a timely manner. The resolved discrepancy will become a part of the eCRF record for the subject.

The Oracle Clinical Remote Data Capture (RDC) system which is 21CFR§11 Part E compliant controls user access, and ensures data integrity. This system is a fully validated system. The RDC system maintains an audit trail of entries, changes or corrections in eCRFs. User access will be granted to each individual based on his or her delegation of authority and completion of required training. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the Principal Investigator, or authorized delegate, to re-sign the eCRF.

The Principal Investigator, or designated representative, is responsible for the data submitted and must review all data for accuracy and provide his/her approval of the eCRF and sign each form with an electronic signature.

15.8. Direct Access to Source Data/Documents

Source data is all information, original records (or certified copies) of clinical findings, observations or other activities in a study necessary for the reconstruction and evaluation of the study. Examples of these originaldocuments and records include, but are not limited to: hospital/clinic records, phone records, laboratory reports, etc. Site personnel should clearly indicate the subjects' participate in the study within the medical records.

Principal Investigator and Institution must permit study-related monitoring, audits, IRB/EC review and regulatory inspections(s) by providing direct access to source data/documents. Medtronic or third-party auditors representing Medtronic may perform clinical site audits to verify the performance of the monitoring process and study conduct, and to ensure compliance with applicable regulations. Representatives for regulatory bodies such as the FDA may also perform site inspections related to this clinical study. The Principal Investigator, site personnel, and institution will provide auditors with direct access to primary source data and all study-related documentation.

In accordance with GCP and regulatory requirements, Medtronic will investigate suspected cases of fraud.

15.9. Confidentiality

Subject confidentiality is assured through the use of subject identification numbers, and the de-identifying of photocopied or records obtained by the Sponsor. In addition to the review of records on site, release of de-identified records to Medtronic may be necessary, such as in the evaluation of adverse events.

For purposes of monitoring this study, access to clinic and hospital records must be available to Medtronic, agents of Medtronic (e.g. CRO), the FDA, and other regulatory agencies.

Health Insurance Portability and Accountability Act (HIPAA) language will be required to be included at every site in the US. HIPAA language may be included within the US ICF template.

15.10. Liability

15.10.1. Study Funding

The costs associated with study conduct will be documented in separate Clinical Trial Agreements that will be signed by Medtronic, the Principal Investigator, and/or the management of the institution.

Subject compensation (if applicable) is detailed in the Patient Informed Consent Form.

15.10.2. Insurance

Medtronic of Canada, Ltd., Medtronic International Trading SARL, and Medtronic Logistics LLC are wholly owned subsidiaries of Medtronic, which as the parent company of such entities maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC, governing regulatory authority (if applicable) and/or the IRB.

15.10.3. Warranty

Warranty information is provided in the product packaging for commercially available products.

15.10.4. Indemnification

Indemnification language will be contained in the Clinical Trial Agreements.

15.11. CIP Amendments

Protocol amendments may be initiated by Medtronic to address changes to the conduct of the study. Protocol amendments must be approved by Medtronic and submitted to the IRB/EC and governing regulatory authority (if applicable); protocol amendment approval and approval of any associated changes to the informed consent document must be obtained prior to implementation of the amendment except:

- When necessary to eliminate an immediate/or apparent immediate hazard to participating subjects
- When the change involves purely administrative or logistical aspects of the study

15.12. Record Retention

At a minimum, the investigator is responsible for the preparation, review, and retention of the records listed below:

- Essential correspondence that pertains to the investigation

- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation), such as:
    - Signed and dated ICFs
    - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses notes
    - All reportable adverse event information
    - Data related to the SNM therapy session
- Documentation of any deviation to the protocol, including the date and the rationale for such deviation
- Signed Investigator Agreement and curriculum vitae for all Investigators
- The protocol and any amendments

The Principal Investigator is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years following completion of the study or longer if required per local regulations. Medtronic will be notified in writing of any transfer of study documentation.

15.13. Publication and Use of Information

This feasibility study will provide an initial understanding of various amplitude stimulation settings and impact on symptoms. The study will be registered on clinicaltrials.gov and the results of the study may be published.

15.14. Suspension or Early Termination

Medtronic reserves the right to suspend or terminate the study at any time. Reasons may include, but are not limited to, the following:

- Insufficient enrollment to complete the study within the expected timeframe
- Identification of unacceptable safety profile; suspicion of an unacceptable risk will result in a suspension, confirmation of an unacceptable risk will result in termination
- Product performance/product supply issues

Medtronic reserves the right to suspend or terminate the study at an individual site. Reasons may include, but are not limited to, the following:

- Noncompliance with the protocol
- Serious or repeated deviations at the site
- Failure to implement required corrective and preventive actions
- Insufficient enrollment to complete the study within the expected timeframe
- Loss of appropriately trained site personnel

Investigators are required to notify the IRB/EC and governing regulatory authority (if applicable) of study suspension/termination. Subjects will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

16. References

1. Siegel SW, Catanzaro F, Dijkema HE, Elhilali MM, Fowler CJ, Gajewski JB, Hassouna MM, Jonas U, van Kerrebroeck PE, Lycklama a Nijeholt AA, Oleson KA, Schmidt RA. Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. Urology 56: 87-91. 2000.

2. Noblett K, Benson K, and Kreder K. Detailed analysis of adverse events and surgical Interventions in a large prospective trial of sacral neuromodulation therapy for Overactive bladder patients. Neurourology Urodynamics 36:1136-1139. 2017.

3. Duelund-Jakobsen J, Buntzen S, Lundby, Laurberg S. Sacral nerve stimulation at subsensory threshold does not compromise treatment efficacy: results from a randomized, blinded crossover study. Ann Surg 257: 219-223. 2013.

4. Gleason JL, Kenton K, Greer WJ, Ramm O, Szychowski JM, Wilson T, Richter HE. Sacral neuromodulation effects on periurethral sensation and urethral sphincter activity. Neurourology Urodynamics. 32(5):476-9. 2013.

5. Uludağ O, Koch SM, Vliegen RF, Dejong CH, van Gemert WG, Baeten CG. Sacral neuromodulation: does it affect the rectoanal angle in patients with fecal incontinence? World J Surg. 34(5):1109-14. 2010.

6. Su X, Nickles A, Nelson DE. Optimization of Neuromodulation for Bladder Control in a Rat Cystitis Model. Am J Physiol Renal Physiol 302: F477-486. 2012a.

7. Snellings AE and Grill WM. Effects of stimulation site and stimulation parameters on bladder inhibition by electrical nerve stimulation. BJU Int 110: 136-143. 2012.

8. Gill B, Pizarro-Berdichevsky J, Bhattacharyya P, Brink TS, Marks B, Quirouet A, Vasavada, S, Jones SE and Goldman HB. Real-time changes in brain activity during sacral neuromodulation for overactive bladder. J Urol, In Review. 2017.

9. 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.

10. Vecchioli-Scaldazza C, Morosetti C, Berouz A, Giannubilo W, Ferrara V. Solifenacin succinate versus percutaneous tibial nerve stimulation in women with overactive bladder syndrome: Results of a randomized controlled crossover study. Gynecologic and Obstetric Investigation 2013; 75(4):230-234.

11. Yalcin I, Bump R. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol. 2003;189(1):98-101.

12. Tincello D, Owen R, Slack M, Abrams K. Validation of the Patient Global Impression scales for use in detrusor overactivity: secondary analysis of the RELAX study. BJOG 2013; 120: 212–216.

13. 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 Therapy at 6-Months in Subjects with Mild Symptoms of Overactive Bladder. Neurourology and Urodynamics 2015 Mar; 34(3): 224-30.

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