InterStim Micro Post Market Clinical Follow-up Study (ELITE)
Clinical Investigational Plan Version 2.0
12-Dec-19
NCT04506866

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Evaluation of InterStim Micro System Performance and Safety (ELITE) to Confirm Long-Term Outcomes	
Clinical Investigation Plan Identifier	MDT19006 EUDAMED unique identifier will be provided under a separate cover, once available.	
Study Product Name	This Post-Market Clinical Follow-Up (PMCF) will include the following commercially approved products: ▪ InterStim Micro implantable neurostimulator ▪ InterStim SureScan MRI tined lead ▪ Patient and clinician therapy application software ▪ Wireless recharger ▪ Recharger application software ▪ Percutaneous extension (advanced therapy evaluation) ▪ Temporary lead (basic therapy evaluation) ▪ Verify external neurostimulator	
Sponsor/Local Sponsor	**United States (Sponsor):** Medtronic, Inc. 7000 Central Ave NE Minneapolis, MN 55432 USA	**Europe (Local Sponsor):** Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland **Europe (Legal Sponsor):** Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands **Canada (Local Sponsor):** Medtronic Canada ULC 99 Hereford Street Brampton, ON, L6Y 0R3 Canada 1-905-460-3800 **Australia (Local Sponsor):** Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park, NSW 2113 Australia
Document Version	2.0 12-Dec-2019	

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	A tined lead is surgically implanted and externalized via a percutaneous extension for test stimulation.
AE	Adverse Event
Basic Evaluation	A temporary test stimulation lead is surgically implanted, externalized and connected to a patient cable for test stimulation.
CCIS	Cleveland Clinic Incontinence Score
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigational Plan
CISC	Clean Intermittent Self-Catheterization
eCRF	Electronic Case Report Form
EC	Ethics Committee
EU	Europe
FI	Fecal Incontinence
[redacted]	[redacted]
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQL	Health Related Quality of Life
ICF	Informed Consent Form
OAB-q	Overactive Bladder Symptoms Quality of Life Questionnaire
IDE	Investigational Device Exemption

Term	Definition
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NOUR	Non-Obstructive Urinary Retention
OAB	Overactive Bladder
[redacted]	[redacted]
PMCF	Post-Market Clinical Follow-up
Oracle RDC	Oracle Remote Data Capture
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNM	Sacral Neuromodulation
US	United States
UF	Urgency Frequency
UI	Urinary Incontinence
UUI	Urinary Urge Incontinence

3. Synopsis

Title	Evaluation of InterStim Micro System Performance and Safety (ELITE) Post Market Clinical Follow-Up Study to Confirm Long-Term Outcomes
Clinical Study Type	Prospective, Multicenter, Global, Single-arm, Open-label, Post-market
Product Name	This post-market clinical follow-up (PMCF) will include the following commercially approved products: ▪ InterStim Micro implantable neurostimulator ▪ InterStim SureScan MRI tined lead ▪ Patient and clinician therapy application software ▪ Wireless recharger ▪ Recharger application software ▪ Percutaneous extension (advanced therapy evaluation) ▪ Temporary lead (basic therapy evaluation) ▪ Verify external neurostimulator
Sponsor	Medtronic, Inc.
Indication under investigation	The indications under investigation are overactive bladder, fecal incontinence, and non-obstructive urinary retention. Refer to geography-specific labeling for additional details on indications. There are no investigational devices used in this study, all study products will be used in accordance with the product labeling.
Investigation Purpose	Post-market clinical follow-up to confirm long-term safety and performance of the InterStim Micro System for sacral neuromodulation.
Overactive Bladder (OAB) Cohort Objectives	Primary Objective: • To demonstrate an improvement in Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) total score at 3 months post-implant compared to baseline Additional Measures: • [redacted] • [redacted] • [redacted] • [redacted]

Fecal Incontinence (FI) Cohort Objectives	Primary Objective: • To demonstrate an improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant compared to baseline Additional Measures: • [redacted]
Non-Obstructive Urinary Retention (NOUR) Cohort Objectives	Primary Objectives: • To demonstrate an improvement in number of clean intermittent self-catheterizations (CISC) per day at 3 months post-implant compared to baseline Additional Measures: • [redacted]
Safety Assessment	To characterize safety of the InterStim Micro System by summarizing the adverse device effects and serious adverse device effects during the study. Safety measures will be summarized for each cohort as well as pooled for all patients regardless of indication. Device deficiencies will also be collected and reported.

Study Design	This is a prospective, multicenter, global, single-arm, open-label, post market clinical follow-up study to characterize long-term clinical performance and safety of the InterStim Micro system. The study is intended to be conducted at approximately 40 centers in the United States (and United States Territories), Europe, Australia and Canada. Eligible subjects, who are already candidates for sacral neuromodulation, will sign a study-specific informed consent form (ICF). Each subject will only be qualified for one of the study cohorts. Subjects will complete a Baseline Visit, a Lead Placement visit, Neurostimulator Device Implant visit and Three-month, Six-month, One-year, and Two-year Follow-up Visits. All subjects who met all eligibility criteria and complete the neurostimulator implant procedure will be considered enrolled in the study.
Sample Size	Approximately 160 subjects (60 for overactive bladder cohort, 60 for fecal incontinence cohort and 40 for non-obstructive urinary retention cohort), will be enrolled in the study to achieve a minimum of 50 evaluable implanted subjects each for overactive bladder and fecal incontinence cohorts and a minimum of 30 evaluable implanted subjects for non-obstructive urinary retention cohort at 3 months post implant.

Overactive Bladder (OAB) - Cohort Eligibility Criteria	Inclusion Criteria: 1. Have a diagnosis of OAB as demonstrated on a 3-day voiding diary with greater than or equal to 8 urgency frequency episodes per day and/or by having a minimum of 3 episodes of urinary urge incontinence in 72 hours 2. Subjects 18 years of age or older 3. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling 4. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol 5. Willing and able to provide signed and dated informed consent Exclusion Criteria: 1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia) 2. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component 3. Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture) 4. Have had treatment of urinary symptoms with botulinum toxin therapy in the past 12 months 5. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy 6. Women who are pregnant or planning to become pregnant 7. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements. 8. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.* *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Contact Medtronic's study manager to determine if the subject can be enrolled in both studies.

Fecal Incontinence (FI) – Cohort Eligibility Criteria	Inclusion Criteria: 1. Have a diagnosis of fecal incontinence as demonstrated by a 7-day bowel diary as greater than or equal to 2 incontinent episodes of more than staining (i.e., either slight, moderate or severe soiling) 2. Subjects 18 years of age or older 3. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling 4. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol 5. Willing and able to provide signed and dated informed consent Exclusion Criteria: 1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia) 2. Uncorrected high grade internal rectal prolapse 3. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy 4. Women who are pregnant or planning to become pregnant 5. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements. 6. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.* *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Contact Medtronic's study manager to determine if the subject can be enrolled in both studies

Non-Obstructive Urinary Retention (NOUR) – Cohort Eligibility Criteria	Inclusion Criteria: 1. Have a diagnosis of non-obstructive urinary retention as demonstrated by a 7-day urinary voiding diary with a minimum of 5 clean intermittent self-catheterizations 2. Chronic non-obstructive urinary retention with an elevated post-void residual (PVR) that has persisted for at least six months and is documented on two or more separate occasions. 3. Subjects 18 years of age or older 4. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling 5. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol 6. Willing and able to provide signed and dated informed consent Exclusion Criteria: 1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia) 2. Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture) 3. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy . 4. Women who are pregnant or planning to become pregnant 5. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements. 6. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.* *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Contact Medtronic's study manager to determine if the subject can be enrolled in both studies.

Study Procedures and Assessments	**Study Visits:** 1. Baseline Visit 2. Evaluation Lead Implant Visit 3. Tined lead (if applicable) / Neurostimulator Device Implant 4. Three-month Follow-up Visit 5. Six-month Follow-up Visit 6. One-year Follow-up Visit 7. Two-year Follow-up Visit **Baseline** Each subject must meet all the inclusion and no exclusion criteria of one of the three study cohorts to be eligible to participate in the study. At the baseline visit, data will be gathered from subjects [redacted] For subjects who qualify with the overactive bladder indication: The urinary voiding diary will be explained and given to the subject to be completed for 3 consecutive days. The diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). The Overactive Bladder Quality of Life (OAB-q) questionnaire will be collected. For subjects who qualify with the fecal incontinence indication: The bowel diary will be explained and given to the subject to be completed for 7 consecutive days. The diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). The Cleveland Clinic Incontinence Score (CCIS) [redacted] will be collected. For subjects who qualify with the non-obstructive urinary retention indication: The urinary voiding diary will be explained and given to the subject to be completed for 7 consecutive days. The diary must be completed, collection of baseline post-void residual volume and confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). [redacted]

	Evaluation Lead Implant: If using basic evaluation, the basic evaluation lead should be placed in accordance with the device implant manual. [redacted] If using advanced evaluation, the tined lead should be placed in accordance with the device implant manual. [redacted] For both advanced and basic evaluation, throughout the study, unilateral stimulation is required. Programming may be set per Investigator discretion for the duration of the study. 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 labeling using the Verify® external neurostimulator and should not exceed the therapy evaluation duration for the specific geography. A study diary will be completed towards the end of the therapy evaluation period (completed for 3 consecutive days for overactive bladder, completed for 7 consecutive days for fecal incontinence and for non-obstructive urinary retention). Therapeutic success must be achieved in order to qualify for a neurostimulator implant in the study. Any [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted] **Tined lead (if applicable) / Neurostimulator Device Implant** Once the subject qualifies for the neurostimulator device implant, site personnel may proceed with the Neurostimulator Device Implant Visit. If a subject does not qualify for the neurostimulator device implant, they will be exited from the study For subjects who qualify for neurostimulator device implant following a successful basic evaluation, the tined lead should be placed in accordance with the device implant manual. [redacted]

[redacted]. The neurostimulator should be implanted in accordance with the device's implant manual.

For subjects who qualify for neurostimulator device implant following a successful advanced evaluation, the neurostimulator should be implanted in accordance with the device's implant manual.

[redacted]

Any [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted]

[redacted]

Three-month, Six-month, One-year, and Two-year Follow-up Visits

For subjects within the overactive bladder cohort:

[redacted] The Overactive Bladder Quality of Life (OAB-q), [redacted] will be collected.

For subjects within the fecal incontinence cohort:

[redacted] The Cleveland Clinic Incontinence Score (CCIS), [redacted] will be collected.

For subjects within the non-obstructive urinary retention cohort:

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

	[redacted] For all subjects, [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted] **Unscheduled Visit** An unscheduled visit may be needed for any device-related reason. During the visit, [redacted] reportable adverse events and/or device deficiencies will be collected. [redacted] **Surgical Revision** A surgical revision may be needed for replacement, revision or explant of the tined lead, neurostimulator or both. During the visit, [redacted] reportable adverse events and/or device deficiencies will be collected. [redacted]
Statistics	For the overactive bladder cohort, the primary objective is to demonstrate an improvement of Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) score at 3 months post-implant compared to baseline. A sample size of 50 achieves greater than 90% power to detect a difference from baseline of 30 points in Overactive Bladder Quality of Life (OAB-q) Questionnaire Health Related Quality of Life (HRQL) total score and a standard deviation of 27 with a significance level of 0.05 using a two-sided one sample t-test. For the fecal incontinence cohort, the primary objective is to demonstrate an improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant compared to baseline. A sample size of 50 achieves greater than 90% power to detect a difference from baseline of 5 points in Cleveland Clinic Incontinence Score (CCIS) and a standard deviation of 6 with a significance level of 0.05 using a two-sided one sample t-test. For the non-obstructive urinary retention cohort, the primary objective is to demonstrate an improvement in number of clean intermittent self-catheterizations (CISC) per day at 3 months post-

	implant compared to baseline. A sample size of 30 achieves greater than 90% power to detect a difference from baseline of 2 clean intermittent self-catheterizations (CISC)/day and a standard deviation of 3 with a significance level of 0.05 using a two-sided one sample t-test. To accommodate attritions, approximately 160 subjects (60 for overactive bladder cohort, 60 for fecal incontinence cohort and 40 for non-obstructive urinary retention cohort), will be enrolled in the study to achieve a minimum of 50 evaluable subjects each for overactive bladder and fecal incontinence cohorts and a minimum of 30 evaluable implanted subjects for non-obstructive urinary retention cohort at 3 months post implant. For the primary objective in each cohort, the analysis on the change of primary outcome parameter at 3 months from baseline will be performed on subjects who provide complete data at baseline and 3 months. A two-sided one sample t-test, or Wilcoxon Singed Rank test will be performed to test the hypothesis depending on data normality. [redacted] Adverse events and device deficiencies of all cohorts will be summarized using summary tables displaying the frequency and percentages. Adverse events will be summarized by seriousness as well.

4. Introduction

4.1. Background

Sacral Neuromodulation (SNM) is a treatment for bladder and bowel control symptoms through the modulation of sacral nerves. SNM is delivered by sending electrical pulses to the sacral nerve to modulate the neural activity that influences the behavior of the pelvic floor, lower urinary tract, urinary and anal sphincters, and colon. SNM delivered by the Medtronic InterStim System is an advanced therapy option for the treatment of the indications specified in the clinical investigational plan.[1-4] Safety and performance have been established with long-term follow-up reported in the literature.[5-7]

This prospective clinical study will fulfill post-market clinical follow-up obligations for the InterStim Micro System and is an active mechanism to assess performance and safety in patients SNM therapy in an organized, systematic manner based on the intended use.

4.2. Purpose

The purpose of this investigation is to confirm long-term clinical performance and safety of the InterStim Micro System.

The primary objectives of the study will evaluate data at 3 months post-implant; however, subjects will be followed for 2 years for the [redacted] safety assessments.

5. Objectives

5.1. Overactive Bladder Cohort

5.1.1. Primary Objective

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

5.1.2. [redacted]

[redacted]

- [redacted]

5.2. Fecal Incontinence Cohort

5.2.1. Primary Objective

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

5.2.2. [redacted]

- [redacted]

5.3. Non-Obstructive Urinary Retention Cohort

5.3.1. Primary Objective

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

5.3.2. [redacted]

- [redacted]

6. Study Design

This is a prospective, multicenter, global, single arm, post market clinical follow-up study to confirm the clinical performance and safety of the InterStim Micro system. Commercial devices will be used within their intended use as described in each geography's approved instructions for use.

Eligible subjects, who are already candidates for sacral neuromodulation, will sign a study-specific informed consent form (ICF). All eligible subjects will complete baseline procedures, including a baseline diary [redacted] prior to the evaluation lead implant procedure. Subjects must be screened and qualify to enroll in a single cohort of the study. Following the therapy evaluation lead implant, subjects are expected to complete a study diary near the end of the therapy evaluation period. Upon completion of a successful therapy evaluation period, subjects will have a neurostimulator implant procedure. Subjects will be considered enrolled at the completion of the neurostimulator implant procedure. Study requirements, including diaries, questionnaires and safety assessments will be completed as required in section 9.1. Study follow-up is expected to last approximately 2 years following the neurostimulator implant visit. Subjects will be exited from the study after the Two-Year Follow-up Visit is completed. Any subjects that have the device permanently explanted during follow up will be exited from the study.

A minimum of 50 subjects who complete the Three-month Follow-up Visit is required for the overactive bladder and fecal incontinence cohorts. A minimum of 30 subjects who complete the Three-month Follow-up Visit is required for the non-obstructive urinary retention cohort. Each subject will only be qualified for one of the study cohorts.

The study is intended to be conducted at approximately 40 centers in Europe, Canada, Australia and the United States (and United States Territories).

This is an on-label, post-market study of an approved system. All subjects implanted in the study will qualify under the approved indications for sacral neuromodulation.

6.1. Duration

Study subjects will be consented and will complete a baseline assessment to determine eligibility for sacral neuromodulation. Subjects are considered enrolled at the time of completion of the neurostimulator implant procedure. Any subject not meeting eligibility criteria will be exited from study participation. Subjects will be required to return for follow up visits at 3 months, 6 months, 1 year and 2 years following the neurostimulator implant procedure.

The estimated study duration, from first subject enrollment to last subject visit, is expected to last approximately 3.5 years. The completion of the study is defined as approval of the Final Study Report and closure of all sites.

6.2. Rationale

This post-approval study will collect data in an organized, systematic manner based on product use to fulfill post-market clinical follow-up obligations and will confirm long-term safety and performance of the InterStim Micro System. Data related to the performance of the study device will be collected, and this may be used to support claims and intended performance of the study product. See Section 5.1 for study objectives. Evidence gathered from this study will be useful for clinicians and patients evaluating sacral neurostimulation as a potential treatment option.

7. Product Description

7.1. General

There are no investigational devices used in this study and all product will be used in accordance with the product labeling.

The Medtronic InterStim Micro System is designed to deliver therapeutic nerve stimulation through the following system components: a neurostimulator and lead with programmable electrodes. The system works by conducting electrical pulses, which are produced by the neurostimulator, through the lead system. The implantable neurostimulator is a rechargeable device and is accompanied with a wireless recharger. The implantable neurostimulator is multi-programmable and is powered by a hermetically sealed battery. A clinician programmer and patient programmer control device are used to control the parameters of stimulation produced by the implantable neurostimulator.

The estimated sample size for this study may yield approximately 160 implants with the InterStim Micro implantable neurostimulator (INS) and associated system accessory product (see table below).

Model Number	Device Description	Intended Use
97810	InterStim Micro implantable neurostimulator (INS)	The InterStim system is an implantable programmable neuromodulation system that delivers electrical stimulation to the sacral nerve.
978A1*	InterStim SureScan MRI lead	
A52200	Patient therapy application software (TAS)	
A51200	Clinician therapy application software (TAS)	
WR9220**	Wireless recharger (external ancillary device)	
A90300	Recharger application software	
3560030*	Percutaneous extension used for advanced therapy evaluation	
306001, 306006, 305901, 305906	Temporary lead for basic therapy evaluation	
3531	Verify external neurostimulator	

*Model 978B1 (lead) and model 3560022 (percutaneous extension) for InterStim II will not be used as the devices are equivalent to 978A1 (lead) and 3560030 (percutaneous extension) except for the contact spacing at the proximal end due to differences in header size between InterStim II and InterStim Micro.

**Provided in the Model RS5200 kit.

All materials and substances that may come in contact with human tissue or bodily fluids is defined in the product labeling.

The study will be conducted in the United States (and United States Territories), Canada, Australia and Europe, where the InterStim Micro System will be commercially available in the specific country prior to the start of study-specific activities.

7.2. Manufacturer

Medtronic, Inc. is the legal manufacturer of the products used in this study, identified in Section 7.1; the products will be approved for the indication in the study prior to the start of study-specific activities.

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

7.3. Intended Population

The study will enroll patients with overactive bladder, fecal incontinence and non-obstructive urinary retention. All subjects implanted must be candidates for sacral neuromodulation based on the geography-specific labeling.

7.4. Product Return

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

7.5. Product Storage & Accountability

No investigational product will be used in the study. Any requirements for commercial product storage and accountability will be outlined in the Product Accountability section of the Regulatory Binder.

8. Selection of Subjects

8.1. Study Population

The intended study population is subjects diagnosed with overactive bladder, fecal incontinence and non-obstructive urinary retention. Eligibility criteria provides use of the study device based on

adherence to the product labeling in a post-market study for subjects with the approved indications. Refer to geography-specific labeling for additional details on indications.

8.2. Subject Enrollment

Each subject must meet all the inclusion criteria and no exclusion criteria for one of the three study cohorts to be eligible to participate in the study. Each subject will only be enrolled in one study cohort.

Subjects are considered enrolled at completion of the neurostimulator implant procedure. 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. Eligibility Criteria

8.3.1. Overactive Bladder Eligibility Criteria

Overactive Bladder Inclusion Criteria

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

1. Have a diagnosis of OAB as demonstrated on a 3-day voiding diary with greater than or equal to 8 urgency frequency episodes per day and/or by having a minimum of 3 episodes of urinary urge incontinence in 72 hours
2. Subjects 18 years of age or older
3. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling
4. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol
5. Willing and able to provide signed and dated informed consent

Overactive Bladder Exclusion Criteria

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

1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia)
2. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component
3. Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)

4. Have had treatment of urinary symptoms with botulinum toxin therapy in the past 12 months
5. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy
6. Women who are pregnant or planning to become pregnant
7. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements.
8. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.*

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

8.3.2. Fecal Incontinence Eligibility Criteria

Fecal Incontinence Inclusion Criteria

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

1. Have a diagnosis of fecal incontinence as demonstrated by a 7-day bowel diary as greater than or equal to 2 incontinent episodes of more than staining (i.e., either slight, moderate or severe soiling)
2. Subjects 18 years of age or older
3. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling
4. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol
5. Willing and able to provide signed and dated informed consent

Fecal Incontinence Exclusion Criteria

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

1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia)
2. Uncorrected high grade internal rectal prolapse
3. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy
4. Women who are pregnant or planning to become pregnant
5. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements.
6. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.*

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Contact Medtronic's study manager to determine if the subject can be enrolled in both studies

8.3.3. Non-Obstructive Urinary Retention Eligibility Criteria

Non-Obstructive Urinary Retention Inclusion Criteria

To be eligible to participate in the non-obstructive urinary retention cohort of the study, a subject must meet all the following inclusion criteria:

1. Have a diagnosis of non-obstructive urinary retention as demonstrated by a 7-day urinary voiding diary with a minimum of 5 clean intermittent self-catheterizations
2. Chronic non-obstructive urinary retention with an elevated post-void residual (PVR) that has persisted for at least six months and is documented on two or more separate occasions.
3. Subjects 18 years of age or older
4. Candidate for sacral neuromodulation therapy in accordance with the InterStim Micro System labeling
5. Willing and able to accurately complete study diaries, questionnaires, attend visits, device recharging and comply with the study protocol
6. Willing and able to provide signed and dated informed consent

Non-Obstructive Urinary Retention Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in the non-obstructive urinary retention cohort of the study:

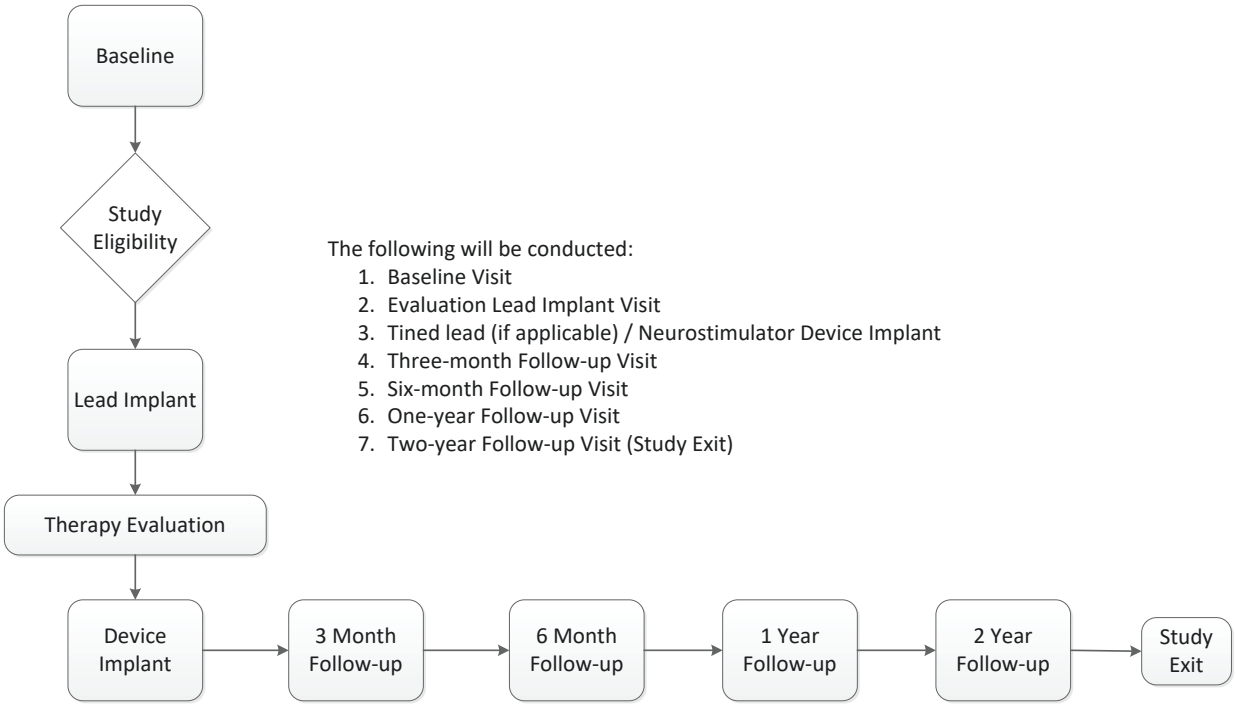
1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia)
2. Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)
3. Have knowledge of planned shortwave diathermy, microwave diathermy, or therapeutic diathermy .
4. Women who are pregnant or planning to become pregnant
5. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements.
6. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.*

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

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 meets the criteria for evaluability. See Section 9.1. 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.

Figure 9-1: Study Procedures



9.1. Schedule of Events

Baseline

Each subject must meet all the inclusion and no exclusion criteria to be eligible to participate in the study. At the baseline visit, data will be gathered from subjects [redacted]

For subjects who qualify with the overactive bladder indication:

The urinary voiding diary will be explained and given to the subject to be completed for 3 consecutive days. The diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). The OAB-q questionnaire will be collected.

For subjects who qualify with the fecal incontinence indication:

The bowel diary will be explained and given to the subject to be completed for 7 consecutive days. The diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). The CCIS [redacted] Questionnaire will be collected.

For subjects who qualify with the non-obstructive urinary retention indication:

The urinary voiding diary will be explained and given to the subject to be completed for 7 consecutive days. The diary must be completed along with confirmation that the subject is not pregnant or planning to become pregnant as part of the assessment for study eligibility (female subjects of child bearing potential only). [redacted]

Evaluation Lead Implant:

If using basic evaluation, the basic evaluation lead should be used in accordance with the device implant manual. If using advanced evaluation, the tined lead should be placed in accordance with the device implant manual with a motor response confirmed based on the recommendations below.

Amplitude	Lead placement recommendation
Less than 1 milliamp	If strong motor responses are observed, the proximity of the lead to the intended sacral nerve may require programming adjustments to allow for patient comfort.
1 to 2 milliamps	Desired range
2 to 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.
Greater than 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.

[redacted]

For both advanced and basic evaluation, throughout the study, unilateral stimulation is required. Programming may be set per Investigator discretion for the duration of the therapy evaluation. 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 labeling using the Verify external neurostimulator and should not exceed the therapy evaluation duration for the specific geography.

The applicable diary for the study cohort diary will be completed towards the end of the therapy evaluation period (completed for 3 consecutive days for OAB, completed for 7 consecutive days for FI and completed for 7 consecutive days for NOUR). Therapeutic success must be achieved in order to qualify for a neurostimulator implant in the study. A successful therapy evaluation is recommended as:

- 50% or greater improvement from baseline in average voids/day or a return to normal voiding (less than 8 voids/day) for subjects with urgency frequency at baseline*
- 50% improvement from baseline in average leaks/day for subjects with urinary incontinence at baseline*
- 50% improvement from baseline in average fecal incontinence episodes/week for subjects with fecal incontinence at baseline
- 50% reduction from baseline in average number of CISC/day for subjects with non-obstructive urinary retention at baseline

*Subjects with both urgency frequency and urinary urge incontinence at baseline must meet at least one of the above criteria to be considered a success.

Any [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted]

Tined lead (if applicable) / Neurostimulator Device Implant

Once the subject qualifies for the neurostimulator device implant, site personnel may proceed with the Neurostimulator Device Implant Visit. If a subject does not qualify for the neurostimulator device implant, they will be exited from the study.

For subjects who qualify for neurostimulator device implant following a successful basic evaluation, the tined lead should be placed in accordance with the device implant manual. Motor response(s) must be confirmed [redacted] during the lead implant procedure based on the recommendations below.

Amplitude	Lead placement recommendation
Less than 1 milliamp	If strong motor responses are observed, the proximity of the lead to the intended sacral nerve may require programming adjustments to allow for patient comfort.
1 to 2 milliamps	Desired range
2 to 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.
Greater than 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.

Following placement of the lead, the neurostimulator should be implanted in accordance with the device's implant manual. [redacted]

For subjects who qualify for neurostimulator device implant following a successful advanced evaluation, the neurostimulator should be implanted in accordance with the device's implant manual.

Any [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted]

Three-month, Six-month, One-year, and Two-year Follow-up Visits

Follow-up visits should be scheduled within the following targeted visit windows, when possible:

(Target Visit Windows are Calculated from the Date of Neurostimulator Implant)	
Three-month visit	13 weeks ± 7 days
Six-month visit	26 weeks ± 14 days
One-year visit	52 weeks ± 28 days
Two-year visit	104 weeks ± 28 days

For subjects within the OAB cohort:

[redacted] The OAB-q, [redacted] will be collected.

For subjects within the FI cohort:

[redacted] The CCIS, [redacted] will be collected.

For subjects within the NOUR cohort:

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

For all subjects, any [redacted] reportable adverse events/device deficiencies will be documented and reported. [redacted]

Unscheduled Visit

An unscheduled visit may be needed for any device-related reason. During the visit, any [redacted] reportable adverse events and/or device deficiencies will be collected. [redacted]

Surgical Revision

A surgical revision may be needed for replacement or explant of the tined lead or neurostimulator. [redacted] Intra-procedural motor response will be collected in procedures with a new tined lead implant, based on the recommendations below.

Amplitude	Lead placement recommendation
Less than 1 milliamp	If strong motor responses are observed, the proximity of the lead to the intended sacral nerve may require programming adjustments to allow for patient comfort.
1 to 2 milliamps	Desired range
2 to 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.
Greater than 3 milliamps	Consider repositioning the lead to achieve the desired range of 1 to 2 milliamps.

[redacted]

Any [redacted] reportable adverse events/device deficiencies will be documented and reported.

Table 9-1: Study Procedures

	Baseline	Evaluation Lead Implant	Tined Lead Implant** / Neurostimulator Implant	Follow-up Visits	Unscheduled Visit	Surgical Revision
All Cohorts						
Informed Consent*	X					
[redacted]						
Pregnancy Assessment	X					
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
Assessment of Reportable Adverse Events and Device Deficiencies	X	X	X	X	X	X
Overactive Bladder						
OAB-q Questionnaire	X			X		
Completed 3-day Urinary Voiding Diary	X					
Fecal Incontinence						
CCIS Questionnaire	X			X		
Completed 7-day Bowel Diary	X					
[redacted]						
Non-Obstructive Urinary Retention						
Completed 7-day Urinary Voiding Diary	X		X	X	X***	
[redacted]						
[redacted]						

*Must be completed prior to any study-specific procedures

[redacted]

***If applicable

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 referred 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 pre-screen (recruitment) log will be completed for all subjects screened but not consented for the study. No subject-specific information will be collected on this log, only the date of review and the reason for the screen failure.

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

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

9.3. Subject Consent

Informed consent should be obtained in written format and using a form approved by the local IRB/EC, if applicable. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. 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.

[redacted]

9.5. Assessment of Efficacy

Subject assessments will be administered by appropriately trained, qualified and delegated site personnel according to the usual practices of the site. Subjects will complete the study questionnaires confidentially on paper forms without site personnel consultation during the visit and these data will be entered to OC/RDC by site personnel. Bowel and Voiding Diaries should be completed prior to or directly after the follow-up visit when data are collected. Site personnel should review forms for completeness.

Overactive Bladder Quality of Life Questionnaire (OAB-q)

The Overactive Bladder Quality of Life Questionnaire (OAB-q) is a 33-item validated questionnaire that was developed to assess symptom bother and the impact of overactive bladder (OAB) on health-related quality of life (HRQL).[9] The questionnaire used in the current study includes a 4-week recall for symptom assessment. The questionnaire may also be used to drive health state utilities.

This questionnaire will be completed by the subject at Baseline, Three-month, Six-month, One-year, and Two-year Follow-up Visits.

Cleveland Clinic Incontinence Score

The Cleveland Clinic Incontinence Score (Wexner Score) is an established 5-item questionnaire that was developed to assess the frequency and severity of fecal incontinence.[10]

This questionnaire will be completed by the subject at Baseline, Three-month, Six-month, One-year, and Two-year Follow-up Visits.

Urinary Voiding Diary

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

Bowel Diary

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

[redacted]

[redacted]

9.6. Assessment of Safety

All reportable adverse events (see Section 11.1) and device deficiencies will be collected throughout the study once the informed consent form is signed until the subject is exited from the study.

9.7. Recording Data

Oracle Clinical Remote Data Capture (RDC)

This study will be conducted using a remote data capture system. The Oracle Clinical (OC) 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 urinary voiding diaries and subject questionnaires will be entered into 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 eCRFs by the site personnel, in accordance with applicable regulations.

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 eCRFs via electronic signature.

[redacted]

Urinary Voiding Diaries & Bowel Diaries

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

Electronic Diary

Electronic diaries may be provided by the sponsor for US study centers; the electronic diary collects details associated with symptoms for each episode. The system contains reminders and allows subjects to collect real-time voiding behavior onto a secure server. The system controls user access and maintains an audit trail. The information in the diary is de-identified and the data transmission contains two points of encryption. The de-identified data export files will be filed in the subject's medical record.

Paper Diary

A paper diary is also available for use in the study. If a paper diary is used, the data will be entered to the RDC database by center personnel. Center personnel may not complete the diary for subjects except for data fields confirmed by the subject as documented within source documentation.

Diaries are to be completed only by the subject. Representatives from the research site may not make entries to the diaries or questionnaires except for data fields confirmed by the subject as documented within source documentation.

9.8. 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. The investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects. The investigator or delegated site personnel should contact the designated Medtronic study personnel to discuss the impact of the potential deviation. Site personnel should work with subjects to ensure subject follow-up visits are scheduled within the visit window. All protocol deviations must be reported on the Protocol Deviation eCRF promptly after the site's awareness of the deviation and submitted to the IRB/EC and CA(as required). Any deviations resulting in signification updates to the clinical investigational plan will require CA notification and/or approval, where required.

Deviations will be reviewed by Medtronic on an ongoing basis. 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 competent authority (if applicable) will be notified in writing of the reasons for the termination.

9.9. 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 Two-year 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:

- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- 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.
- 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 use of InterStim Micro System. No study specific risks are present. The clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the clinical investigation plan and constantly monitored.

10.1.1. Risks Outlined in the Instructions for Prescribers (IFP)

Refer to the appropriate Information for Prescribers (IFP) manual for the InterStim Micro System components for an updated list on contraindications, precautions, warnings, adverse events, directions for use and other product specific details on the InterStim Micro System.

The risk level for the devices and implant procedure is the same if the subject is in this clinical trial or not. Certain adverse events may necessitate surgical intervention. For a comprehensive summary of adverse events, refer to the Information for Prescribers manual.

There might be other discomforts and risks related to an InterStim Micro System implant, sacral neuromodulation therapy with the InterStim Micro System and/or this study that are not foreseen at this time.

The following inconveniences may occur due to participation in the study:

- The time needed to complete your study diary may be an inconvenience
- You may find some of the questions or completing the study diary embarrassing

10.2. Potential Benefits

Subjects will not receive any direct medical benefit from participation in this study. Participation in this study will not provide greater benefit than if the subject was receiving an InterStim Micro System implant and sacral neuromodulation therapy with the InterStim Micro System outside of the study. Information from this study might help researchers further understand the InterStim Micro System. 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 an InterStim Micro System implant and sacral neuromodulation therapy with the InterStim Micro System outside of the study.

The risks associated with an InterStim Micro System implant and sacral neuromodulation therapy with the InterStim Micro System are minimized in this study by selecting only qualified Investigators experienced in sacral neuromodulation, 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 adverse events and/or adverse device effects as well as all device deficiencies will be considered reportable for this study and will be collected after the subject is consented to participate in the study through study exit. The term “investigational device” is part of ISO 14155:2011 definitions. The term “investigational device” refers to any device used in the study including market released devices.

Reportable adverse event terms are defined as follows:

- Device Related: An adverse event that results from the presence or performance (intended or otherwise) of any component of the InterStim Micro System
- Procedure Related: An adverse event that occurs due to any procedure related to the implantation or surgical revision of the InterStim Micro System. The procedure is defined as the lead placement, neurostimulator implant procedure and surgical revision (including explant 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).

Adverse events that are classified as possible, probable or causal are considered to be related for analysis purposes.

The following are not adverse events:

- Any normal expected postoperative (implant or revision) 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.
- Any non-clinically significant, transient (lasting for only a short time) stimulation-related effects that occur during the implant/revision procedure, programming and follow-up period.
- Worsening of OAB, FI and/or NOUR symptoms will be collected as part of the study objectives and/or additional measures and are not considered a reportable adverse event.

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. STUDY SPECIFIC NOTE: These are considered the device related, therapy related and/or procedure related.
Device Deficiency (DD)* (ISO 14155:2011 3.15) (ISO 14155:2011 3.27) (ISO 14155:2011 3.43)	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 ▪ 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 Event (SAE)* (MPSV § 2 Definitions Abs 5)	A serious adverse event is an event that occurs in a clinical investigation subject to approval or occurring in a performance evaluation which led, might have led or could lead directly or indirectly to death or serious deterioration of health of the subject, the user or a third party, without consideration if the event has been caused by the medical device itself; this applies accordingly to serious adverse events occurring in a clinical investigation or performance evaluation for which an exemption of the approval authorization as per MPG § 20 paragraph 1 sentence 2 has been granted.
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 STUDY SPECIFIC NOTE: For this study, all reportable adverse events will be collected however adverse events for system revisions (e.g. explants, revisions or replacements) will be considered non-serious unless the subject has clinical sequela which meets the seriousness definition outlined in the CIP.

	Any extended hospitalizations for implants and surgical revisions due to non-medical reasons will not be considered a reportable serious adverse event.
RELATEDNESS	
Term	**Definition**
Not related	Relationship to the device or procedures can be excluded when: - the event is not a known[1] side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis[2], when applicable; - harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. [1]When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered “not related”. Yet, the unexpected effect shall not be excluded from evaluation and reporting. [2]If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition.

Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis[1], when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. [1] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

*Reportable event categories that will be collected during this study

11.2. Reporting of Adverse Events

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

Phone: 1+763.514.4000
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, Medtronic	Procedure related Device related Therapy related
Seriousness	Investigator, Medtronic	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 eCRF and promptly reported to Medtronic based on Table 15-1. IRB/EC reporting must be completed in accordance with the policies of the governing IRB/EC. Governing competent authority reporting along with safety and vigilance reporting will be completed in accordance with applicable local regulations.

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

- Model and identifier (serial, lot number) for the involved device (if applicable)
- 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 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 must be assessed at each protocol required visit, and new or updated information must be documented on the Adverse Event eCRF and promptly reported to Medtronic and if applicable to the CA or IRB/EC (by the institution or by Medtronic, as necessary). 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 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 CA, IRB/EC as necessary. All reported adverse events 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. Death

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. 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

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used for the analyses of the study results (e.g. SAS version 9.4 or higher).

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods 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. Sample Size Justification

OAB Cohort

For OAB cohort to demonstrate a statistically significant improvement of OAB-q HRQL score at 3 months post-implant from baseline, a two-sided one sample t-test, assuming normal distribution, was built as follows:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in OAB-q HRQL total score from baseline to 3 months post-implant.

The power calculations were performed using PASS 11 statistical software. Based on the results of HRQL in OAB-q at 3 months post-implant reported in the InSite study, a mean score change of 30 at 3 months from baseline with the standard deviation of 27 are the assumptions used for the power calculation for this study. At an alpha level of 0.05, a sample size of 50 evaluable subjects results a power greater than 90% for this cohort.

The HRQL module and its subscales for International Consultation on Incontinence Questionnaire (ICIQ)-OABqol and OAB-q questionnaires are the same measures.[9,19]

The attrition between implant and the primary endpoint at the 3-month Follow-up Visit is expected to be less than 10%. To accommodate attritions between implant and 3-month Follow-up Visit as well as during long-term follow-up, approximately 60 subjects will be implanted for this cohort. Based on historical Medtronic sponsored SNM studies (InSite study and SNS bowel), attrition at 2 year long-term follow-up visits is typically around 20%. Therefore, we expect attrition in this post-market study to be similar. In all cases of missing data, the reason will be collected and sensitivity analyses will be performed to evaluate the impact of missing data on primary objective.

FI Cohort

For FI cohort, to demonstrate a statistically significant improvement in Cleveland Clinic Incontinence Score (CCIS) at 3 months post-implant from baseline, a two-sided one sample t-test, assuming normal distribution, was built as follows:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in CCIS total score from baseline to 3 months post implant.

The power calculations were performed using PASS 11 statistical software. Based on the result of meta-analysis conducted by Thin et al (2013), a mean CCIS score (μ) change of 5 at 3 months from baseline with the standard deviation of 6.2 are the assumptions used for the power calculation for this study. At an alpha level of 0.05, a sample size of 50 evaluable subjects results in a power greater than 90% for this cohort.

The attrition between implant and the primary endpoint at the 3-month Follow-up Visit is expected to be less than 10%. To accommodate attritions between implant and 3-month Follow-up Visit as well as during long-term follow-up, approximately 60 subjects will be implanted for this cohort. Based on

historical Medtronic sponsored SNM studies (InSite study and SNS bowel), attrition at 2 year long-term follow-up visits is typically around 20%. Therefore, we expect attrition in this post-market study to be similar. In all cases of missing data, the reason will be collected and sensitivity analyses will be performed to evaluate the impact of missing data on primary objective.

NOUR Cohort

For NOUR cohort, to demonstrate a statistically significant improvement in the number of CISC at 3 months post-implant from baseline, a two-sided one sample t-test, assuming normal distribution, was built as follows:

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in the number of CISC/day from baseline to 3 months post implant.

The power calculations were performed using PASS 11 statistical software.

Based on the literature results published in Van Kerrebroeck et al (2007), Sutherland et al (2007), Cardarelli et al (2012) and MDT-103 and SOUNDS interim reports, a mean change of 2 in the number of CISC/day (μ) between baseline and 3 months post-implant (μ) with a standard deviation of 3 are the assumptions used for the power calculation for this study.

At an alpha level of 0.05, a sample size of 30 evaluable subjects results in a greater than 90% for this cohort.

The attrition between implant and the primary endpoint at the 3-month Follow-up Visit is expected to be less than 10%. To accommodate the attritions between implant and 3-month Follow-up Visit as well as during long-term follow-up, approximately 40 subjects will be implanted for this cohort. Based on historical Medtronic sponsored SNM studies (InSite study and SNS bowel), attrition at 2 year long-term follow-up visits is typically around 20%. Therefore, we expect attrition in this post-market study to be similar. In all cases of missing data, the reason will be collected and sensitivity analyses will be performed to evaluate the impact of missing data on primary objective.

13.1.2. Investigation Site Pooling

The investigators of this study will conduct the study according to this protocol and use the same CRFs to collect study data. The site study personnel will be trained prior to the study initiation at each site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements.
There is no a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined

results, no more than 20% subjects, i.e., 12 subjects for OAB cohort, 12 subjects for FI cohort, and 8 subjects for NOUR cohort, will be enrolled at each site unless the site gets pre-approval from the Medtronic for additional enrollments.

13.1.3. Other Specific Considerations

Adjustment for Baseline Covariates

There is no plan to make adjustment of baseline covariates for the primary objective.

Handling Missing Data

Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring. All efforts will be made to ensure patient follow-ups are completed with limited attrition to ensure interpretability of study results.

For the primary objectives, in case subject's Baseline Visit and/or Three-month Follow-up Visit data are missing, a sensitivity analysis will be performed by imputing missing data using multiple imputation method.

Adjustment for Multiple Endpoints

Adjustment for multiple endpoints is not required as the study focuses on three independent and different cohorts with independent endpoints and cutoff times. There is only one primary objective within each cohort.

Interim Analysis

There is no planned interim analysis for the primary objective in this study.

Analysis Population

The analysis on the primary outcome parameter and for the additional measures will be performed on subjects who provide complete data at baseline and 3 months (complete cases). For all primary objectives, a sensitivity analysis will be performed on imputed data using Multiple Imputation (MI) techniques. The details of MI will be described in the study SAP.

13.1.4. Reports

A final clinical study report will be generated for this study. Annual progress reports will also be generated for the study. A Cohort specific report may be generated if subjects from one cohort complete study follow-up. Reports may be submitted to the regulatory authorities, as required based on applicable local regulations.

13.2. Demographics

Demographics and baseline characteristics will be described and summarized in the report either by means and standard deviations for continuous data, or by number and percentages for categorical data.

13.3. Treatment Characteristics

Treatment characteristics using InterStim Micro System will be described and summarized in the report either by means and standard deviations as appropriate for continuous data, or by number and percentages for categorical data.

13.4. Overactive Bladder Cohort

13.4.1. Primary Objective

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

Hypothesis

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

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in OAB-q HRQL total score from baseline to 3 months post-implant.

Analysis Methods

A two-sided one sample t-test or Wilcoxon Singed Rank test will be performed to test the hypothesis depending on data normality. In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in HRQL total score will be calculated and reported.

In cases where subject's OAB-q HRQL total score is missing at baseline and/or at 3 months post-implant for any reasons, a sensitivity analysis using multiple imputation will be performed.

In addition, the OAB-q HRQL total score at baseline and 3 months post-implant will be summarized.

13.4.2. [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

13.5. Fecal Incontinence Cohort

13.5.1. Primary Objective

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

Hypothesis

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

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in CCIS from baseline to 3 months post-implant.

Analysis Methods

A two-sided one sample t-test or Wilcoxon Singed Rank test will be performed to test the hypothesis depending on data normality. In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in CCIS total score will be calculated and reported.

In cases where subject's CCIS is missing at baseline and/or at 3 months post-implant for any reasons, a sensitivity analysis using multiple imputation will be performed.

In addition, the CCIS at baseline and 3 months post-implant will be summarized.

13.5.2. [redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

13.6. Non-Obstructive Urinary Retention Cohort

13.6.1. Primary Objective

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

Hypothesis

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

H_0: $\mu = 0$

H_a: $\mu \neq 0$

Where μ indicates the mean change in number of CISC per day from baseline to 3 months post-implant.

Analysis Methods

A two-sided one sample t-test or Wilcoxon Singed Rank test will be performed to test the hypothesis depending on data normality. In addition to the hypothesis testing, the two-sided 95% confidence interval for the mean change in number of CISC/day will be calculated and reported. In cases where subject's number of CISC per day is missing at baseline and/or at 3 months post implant for any reasons where missing data occur, a sensitivity analysis using multiple imputation will be performed.

In addition, the number of CISC/day at baseline and 3 months post-implant will be summarized.

13.6.2. [redacted]

- [redacted]

[redacted]

[redacted]

13.7. Safety Assessment

To characterize safety during the study duration.

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

Summaries will be presented as number of serious events, number of events, number of subjects who experienced the event, and percent of subjects who experienced the event. All adverse events and device deficiencies will be reported for each cohort as well as pooled for the three cohorts together.

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, competent authority approval (if applicable), study training, and risk benefit assessment. In addition, all applicable laws and regulatory requirements of the country/(s) 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, 21 CFR§54 Financial Disclosure by Clinical Investigators and 21CFR§803 Medical Device Reporting.

- In Europe, the study will be conducted in accordance with European Union Medical Device Regulation in addition to 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 (H164-145/2011E).
- In Australia, all applicable local laws and regulations will be followed.

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

Medtronic will report all reportable AEs and device deficiencies according to post-market vigilance and safety reporting requirements, 21 CFR 803 and to meet local, regional and geographical regulatory requirements. This study will be posted on ClinicalTrials.gov and EUDAMED once available, as part of Medtronic's commitment to full disclosure for ongoing studies that meet the requirements for public posting.

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. All subject reimbursement (if provided) and insurance (if required) will be disclosed to the IRB/EC. 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 governing competent 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.

15. Study Administration

15.1. 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 shall not begin at any site until the required approval/favorable opinion from the Ethics Committee (EC)/Institutional Review Board (IRB) or notification/approval from a regulatory authority have been obtained, if appropriate. 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 Authorities (if applicable).

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 15-1. It is the responsibility of the investigator and Medtronic personnel to report all product complaint(s) associated with a medical device related to intended use, misuse or abuse. All regional reporting requirements shall be followed.

In addition, Principal Investigator, or designated personnel will provide Medtronic with requested information related to serious adverse events, device-, procedure- and/or therapy-related adverse events.

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 15-1 includes minimum reporting requirements for investigators participating in studies in Europe, the US (including US territories), Australia and Canada. Medtronic study personnel will immediately report Adverse Events and Device Deficiencies, related to a CE marked, Canadian licensed or FDA approved device used during the study, to Medtronic's Complaint 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 15-1 includes minimum reporting requirements. The Sponsor will complete reporting activities in accordance with timeframe as per local requirement.

Table 15-1 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
EC/IRB	**All other geographies:** Reporting timeframe as per local EC/IRB per local Requirement. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.
Serious Adverse Device Effects (SADEs)	

Investigator submit to:	
Medtronic	**US:** As **soon** as possible to meet regulatory reporting requirements, but no later than 10 working 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:** Reporting timeframe as per local requirement
EC/IRB	Reporting timeframe as per local EC/IRB requirement. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.
All Other Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB requirement. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.

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 10 working days of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy.
EC/IRB	**Canada:** All subject deaths must be reported the EC as soon as possible, but no more than 72 hours of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. **All geographies:** All subject deaths must be reported 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. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.
Device Deficiencies (DD) with SADE potentials	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency **All other geographies:** Reporting timeframe as per local requirement
EC/IRB	**All other geographies:** Reporting timeframe as per local EC requirement. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency
EC/IRB	**All geographies:** Reporting timeframe as per local EC requirement. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations.
Withdrawal of IRB Approval	
Investigator submit to:	
Medtronic	**All geographies:** Report a withdrawal of the reviewing EC/IRB approval within **5 working 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 **All other geographies:** Reporting timeframe as per local EC/institutional requirements
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 **All other geographies:** Reporting timeframe as per local EC/institutional 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 **All other geographies:** Promptly notify Medtronic upon awareness
EC/IRB	**US and Europe:** The Investigator must notify the EC/IRB within **5 working days** after upon awareness. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations. **Canada:** The Investigator must notify the EC/IRB within **5 working** days after procedure **All other geographies:** Reporting timeframe as per local EC/institutional requirements

Final Report	
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. For institutions in Europe, reporting will be completed by Medtronic directly to EC and competent authorities, based on local regulations. **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation **All other geographies:** Study reports must be submitted per EC requirements

15.2. 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.

15.3. 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.

15.4. Clinical Trial Agreement

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement.

15.5. Curriculum Vitae

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

15.6. 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. Monitoring and monitoring oversight will be provided by representatives of Medtronic who will support the investigation including center qualification, initiation, on-site monitoring, and study closure.

[redacted]

15.7. 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

15.8. 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.

15.9. Direct Access to Source Data/Documents

The Principal Investigator and center personnel will provide the Medtronic monitor(s) with complete access to primary source data (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.

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 original documents 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. Principal Investigator should be available to support study activities, such as study-related monitoring, audits, IRB/EC review and regulatory inspection(s). 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 or Health Canada 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.

15.10. 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, Health Canada 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.

15.11. Liability

15.11.1. 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.

15.11.2. Insurance

Medtronic Canada ULC., Medtronic International Trading SARL, Medtronic Australasia Pty Ltd and Medtronic Logistics LLC are indirectly owned subsidiaries of Medtronic, Inc. which 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 competent authority (if applicable) and/or the IRB.

15.11.3. Warranty

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

15.11.4. Indemnification

Indemnification language will be contained in the Clinical Trial Agreements.

15.12. 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 competent 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

15.13. 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 InterStim Micro System and InterStim Therapy.
- 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 according to local regulatory requirements, whichever is greater. The retention period may be longer If required by Medtronic or local or global regulatory requirements; Medtronic will be responsible for notifying sites of extensions to the 2-year minimum record retention requirements. The Principal Investigator will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic. Medtronic will be notified in writing of any transfer of study documentation. Medtronic will retain the study records according to Medtronic policy.

15.14. Publication and Use of Information

Medtronic intends to publish the results from the study in a timely manner upon study completion. These publication activities may include abstracts, presentations/posters to scientific meetings, and manuscripts.

Investigators who gathered data for this study (i.e., enrolled subjects, contributed quality data and complied with the protocol) and are interested in publishing may have the opportunity to write or contribute to the writing of abstracts and manuscripts based on the results of this study. Principal investigators who meet the study-specific criteria above will be considered for abstract/manuscript authorship if they meet the International Committee of Medical Journal Editors, Ethical Considerations in the Conduct and Reporting of Research criteria available via the following link: http://www.icmje.org. Specifically, authorship credit should be based on the following and should meet all criteria listed below:

- Substantial contributions to conception or design; or the acquisition, analysis and interpretation of data for the work;
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Medtronic employees who meet the International Committee of Medical Journal Editors criteria for authorship will have the right to authorship.

All contributors who do not meet the criteria for authorship are to be listed in an acknowledgment section according to the guidelines of the applicable scientific journal. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

15.15. 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
- Inadequate subject adherence to follow-up requirements
- 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, including Inadequate subject adherence to follow-up requirements
- 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 competent authority (if applicable) of study suspension/termination. In addition, Investigators should assess whether or not to continue the study based on reasons above. Subjects will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

16. References

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17. Appendices

17.1 Additional Information for Sites

Detailed sponsor contact information, including the contact information for the local sponsor/legal representative in Europe, Medical Advisor, not outlined in the Clinical Investigational Plan will be provided under a separate cover.

17.2 Institutional Review Boards/Ethics Committees

At the time of the completion of the Clinical Investigation Plan, site selection is not yet complete. Therefore, a complete list of participating IRB/EC names, locations, and the Chairperson(s) will be distributed under a separate cover when available.

17.3 Participating Investigators and Institutions

At the time of completion of the Clinical Investigation Plan, site selection is not yet complete. Therefore, a complete list of names, addresses, contact details and professional positions of the clinical investigators and institutions will be distributed under a separate cover when available. No coordinating principal investigator will be assigned for the global portion of the study.

17.4 Informed Consent Materials

Copies of all informed consent materials will be provided to the site under a separate cover, based on regional requirements.

17.5 Labeling

Copies of the InterStim System Information for Prescribers will be provided to the site under a separate cover, based on regional and local language requirements. All other labeling for commercial products used in the study will be provided through commercial channels.

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• 'Not Applicable, New Document'	[redacted]
2.0	• European Legal Sponsor was added to title page • Study title and purpose was updated to include confirmation of long-term outcomes. Updates based on this change were made throughout the document where applicable. • Table 11-1: added MPSV (German Safety Plan for Medical Devices) SAE definition • Section 13.1.1: sample size justification was elaborated to include expected attrition rates and to provide historical rationale for the estimate. • Section 13.1.3: "All efforts will be made to ensure patient follow-ups are completed with limited	[redacted]

	attrition to ensure interpretability of study results" was added to the Handling Missing Data paragraph. • Minor grammatical updates throughout	