InterStim® BASIC Study
Clinical Investigational Plan Version 1.0
10-Jun-2019
NCT04016324

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Basic Evaluation Lead Post-Market Clinical Follow-up (BASIC) Study
Clinical Investigation Plan Identifier	MDT19002 EUDAMED unique identifier will be provided under a separate cover, once available.
Study Product Name	InterStim® Basic Evaluation lead with foramen needle and Basic Evaluation kit
Sponsor/Local Sponsor	United States (Sponsor): Medtronic Neuromodulation 7000 Central Ave NE Minneapolis, MN 55432 USA Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland Canada (Local Sponsor): Medtronic Canada ULC 99 Hereford Street Brampton, ON, L6Y 0R3 Canada 1-905-460-3800
Document Version	1.0; 10-June-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
AE	Adverse Event
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigational Plan
DD	Device Deficiency
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
OAB	Overactive Bladder
[redacted]	[redacted]
PNE	Peripheral Nerve Evaluation
[redacted]	[redacted]
Oracle RDC	Oracle Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNM	Sacral Neuromodulation
UF	Urinary Frequency
UI	Urinary Incontinence
UUI	Urinary Urge Incontinence
US	United States

3. Synopsis

Title	InterStim Basic Evaluation Lead Post Market Clinical Follow-Up (BASIC) Study
Clinical Study Type	Prospective, Multicenter, Global, Post-Market
Product Name	InterStim Basic Evaluation Lead with foramen needle and Basic Evaluation kit. There are no investigational devices used in this study, all study products will be used in accordance with the product labeling.
Sponsor	Medtronic, Inc.
Investigation Purpose	Post-market clinical follow-up for continued assessment of safety and performance of the InterStim basic evaluation lead and foramen needle(s) used during a therapy evaluation.
Intended Study Population	The study will enroll patients with overactive bladder. All subjects implanted must be candidates for sacral neuromodulation.
Primary Objective	To characterize proportion of subjects who demonstrate motor or sensory response(s) during lead placement using the InterStim Basic Evaluation Lead.
[redacted]	[redacted]
Safety Assessment	To characterize safety during the basic evaluation lead implant and therapy evaluation. Safety will be evaluated by the collection of reportable adverse events. Any adverse event meeting the definition of: serious, device related, therapy related and/or procedure related will be considered reportable for this study. Device deficiencies will be collected and reported.
Study Design	This is a prospective, multicenter, post market clinical follow-up study to characterize the clinical performance and safety of the InterStim basic evaluation lead with the commercially-approved foramen needle and basic evaluation kit. The study is intended to be conducted at approximately 30 centers in Europe, Canada, and the United States. Subjects will complete a baseline visit, basic evaluation lead placement visit, and 1-week follow-up visit. Enrollment will be

	defined as subjects who qualify for all eligibility requirements and undergo the basic evaluation lead implant procedure. The total study duration for a subject is approximately three weeks, depending on when the basic evaluation lead implant procedure is scheduled.
Sample Size	Subjects will be enrolled to obtain a sample size of approximately 100 subjects who complete a basic evaluation with motor or sensory threshold testing to confirm clinical performance. The sample size of approximately 100 subjects is driven to obtain precision of the primary endpoint. Assuming that motor or sensory response is able to be obtained in 95% of subjects during the basic evaluation lead placement, with 100 subjects, this produces a two-sided 95% Confidence Interval (CI) of 88.7-98.4% with a width equal to 9.6%. The confidence interval width will vary slightly depending on the actual proportion of subjects with motor or sensory responses.
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Subjects 18 years of age or older 2. Candidate for sacral neuromodulation in accordance with the InterStim System labeling 3. Have a diagnosis of OAB as demonstrated by either urinary urge incontinence and/or urinary frequency on a 3-day voiding diary 4. Willing and able to accurately complete study diaries, questionnaire, attend visits, and comply with the study protocol 5. Willing and able to provide signed and dated informed consent Exclusion Criteria: 1. Have neurological conditions such as multiple sclerosis, clinically significant peripheral neuropathy or spinal cord injury (e.g., paraplegia) 2. Have implantable pacemakers, or defibrillators 3. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component 4. Have knowledge of planned MRIs, diathermy, microwave exposure, high output ultrasonic exposure, or RF energy

	exposure not included within the scanning conditions provided with the InterStim System labeling 5. Women who are pregnant or planning to become pregnant during participation in the study 6. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements 7. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.* *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in both studies.
Study Procedures and Assessments	**Study Visits:** 1. Baseline 2. Enrollment / Basic Evaluation Lead Implant Procedure 3. Therapy Evaluation 4. One Week Follow-up Visit (Study Exit) **Baseline** Each subject must meet all of the inclusion and no exclusion criteria to be eligible to participate in the study. At the baseline visit, data will be gathered from subjects including relevant medical history. The symptom 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 nor planning to become pregnant as part of the assessment for study eligibility. Collection of reportable adverse events and device deficiencies will begin after the informed consent form is signed. **Enrollment/Basic Evaluation Lead Implant** The basic evaluation lead(s) should be placed in accordance with the Basic Evaluation Lead Implant Manual. The therapy evaluation period using the basic evaluation lead(s) must not exceed seven days. Motor or sensory response must be tested intra-operatively during the foramen needle placement and when the basic evaluation lead(s) are placed. Prior to discharge, the sensory threshold in a seated position will be collected for all subjects. All reportable adverse events, device deficiencies and OAB medication changes will be

	collected. A daily symptom diary will be completed during the Basic Evaluation period (up to 7 days)**.** **1-Week Follow-up Visit (5-7 days post-implant)** At the 1-week follow-up visit, any reportable adverse events, changes to OAB medications and/or device deficiencies will be collected. During the visit the subject's sensory threshold amplitude will be tested. Following confirmation of sensory threshold amplitude, programming data will be collected. [redacted] The subject is exited from the study after the 1-week follow-up visit is complete. **Unscheduled Visit** If an unscheduled visit is needed for any device-related reason, any reportable adverse events and/or device deficiencies will be collected. Upon completion of any programming, programming data will be collected.
Statistics	For the primary objective, the proportion of subjects who obtain motor or sensory response and its two-sided exact binomial 95% CI will be reported. [redacted] Reportable adverse events and device deficiencies will be presented in summary tables.

4. Introduction

4.1. Background

Sacral Neuromodulation (SNM) delivered by the Medtronic InterStim System is a guideline recommended advanced therapy option for the treatment of overactive bladder.[1,2] Prior to receiving an implanted system for chronic therapy, a patient can undergo a therapy evaluation in order to assess response to the therapy. A therapy evaluation can be conducted with either a temporary trialing lead, connected to an external neurostimulator for a temporary trial (also known as the basic evaluation) or a chronic lead can be used with the same external neurostimulator for a longer duration trial, known as an advanced evaluation. Both approaches are designed to deliver stimulation to the sacral nerves in order to assess whether the patient responds to therapy, thus allowing patients the ability to "test drive" SNM prior to committing to an implanted system. This protocol uses the term basic evaluation to indicate the therapy evaluation period.

The predicate temporary trialing lead obtained CE mark in 1998, was approved by FDA in 1998 and was licensed by Health Canada in 1999. Since that time, this lead has consistently been used for Medtronic's basic evaluations as this is the only temporary trialing lead that is market released for the InterStim system. Safety and performance have been reported in the literature for many years[3-10], along with twenty years of clinical experience tracked in Medtronic's post-market surveillance reporting system.

Temporary trialing leads are intended to deliver temporary sacral neuromodulation for the duration of the therapy evaluation period. Sacral nerves are mixed nerves containing both motor and sensory fibers. In order to ensure appropriate lead placement, motor and/or sensory responses such as bellows, movement of the perineum, plantar flexion of the great toe or sensation in the rectum, scrotum or vagina[11] are assessed during the temporary trialing lead implant. The temporary trialing lead, now referred to as basic evaluation (BE) lead, foramen needles and procedure kit have been updated and the aim of this study is to evaluate the performance and safety of the recently market-released InterStim BE lead, foramen needles and BE kit (includes the updated lead and foramen needles). See Table 7-1 for product details. This prospective clinical study will fulfill post-market clinical follow-up obligations for the updated BE products and is an active mechanism to assess performance and safety in patients undergoing a basic evaluation for sacral neuromodulation in an organized, systematic manner based on their intended use.

4.2. Purpose

The purpose of this post market investigation is for continued assessment of safety and performance of the InterStim basic evaluation lead and foramen needles used during a therapy evaluation.

5. Objectives

5.1. Objectives

5.1.1. Primary Objective

To characterize the proportion of subjects who demonstrate motor or sensory response(s) during lead placement using the InterStim basic evaluation lead.

[redacted]

5.1.3. Safety Assessment

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

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

Device deficiencies will be collected and reported.

6. Study Design

This is a prospective, multicenter, global, post market clinical follow-up study to characterize the clinical performance and safety of the InterStim basic evaluation lead with the commercially-approved foramen needle and basic evaluation kit. Commercial devices will be used within their intended use as described in approved instructions for use for which approval has been obtained.

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 urinary voiding diary and assessment of medical history, prior to the BE lead implant procedure. Subjects will be considered enrolled at the time of the BE lead procedure. During the BE lead implant procedure, an assessment of motor or sensory response will be completed. Subjects will be discharged for the therapy evaluation and instructed to start completing a daily urinary voiding diary. Subjects will return for a 1-

week follow-up visit. The urinary voiding diary will be collected. Study requirements, including [redacted] sensory threshold testing and safety assessments will be completed as required in section 9.1. Study follow-up is expected to last up to 7 days following the BE lead implant visit. Subjects will be exited from the study after the 1-week follow-up visit is completed.

A minimum of 100 subjects who complete the BE lead implant procedure with motor or sensory threshold testing is required to confirm clinical performance.

The study is intended to be conducted at approximately 30 centers in Europe, Canada, and the United States.

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

6.1. Duration

Study subjects will be consented and will complete baseline assessment to determine eligibility for an InterStim therapy evaluation. Subjects are considered enrolled at the time of the BE lead implant procedure. Any subject not meeting eligibility criteria will be excluded from study participation. Following the BE lead implant, subjects will be required to return for the 1-week follow-up visit (no later than 7 days following the lead implant procedure).

The estimated study duration, from first subject enrollment to last subject visit, is expected to last approximately 12 months. 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. 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.

7. Product Description

7.1. General

There are no investigational devices used in this study.

The designs of the BE lead, updated foramen needles and the BE kit reflect incremental changes and technological advancements from the market-released leads, needles and procedure kit. A description

of the updated BE lead, foramen needles and BE kit are described below. The estimated sample size for this study may yield approximately 100 BE kits (Model 309201); however, individual or multipack of leads (Model 306001, 306006) and foramen needles (Model 041838, 041839) may also be used in place of the kit. Up to two leads may be placed during one implant procedure.

Table 7-1 Study Product

Model	Description of the Device	Intended Use
306001	A packaging configuration that includes one updated lead	The lead consists of a coiled, insulated, multi-stranded wire with a stainless-steel connector pin on the proximal end and a single electrode on the distal end. The lead is pre-loaded with a stylet that is removed after lead placement. The basic evaluation kit is a procedural kit intended for the basic evaluation of Sacral Neuromodulation Therapy (SNM), also referred to as "test stimulation" or "therapy evaluation". The kit contains the basic evaluation lead, also referred to as “test stimulation lead”, foramen needles and accessories for the lead implant procedure.
306006	A package of six updated leads	
041838	Foramen needle package (six 8.8 cm needles)	
041839	Foramen needle package (two 12.6 cm needles)	
309201	Basic evaluation kit components: **Sterile components in kit:** • One basic evaluation lead • One test stimulation cable (also referred to as “test stimulation cable mini-hook”) • Two foramen needles (8.8 cm) • One foramen needle (12.6 cm) • Surgical drape • Applicator - sponge tip • Surgical marker • Ruler • Anesthetic needle • Syringe • Gauze pads • Transparent medical dressing **Non-sterile components in kit:** • One ground pad package (containing two ground pads) • One Model 3676 Patient cable (with ground pad connection) • One Model 3579 Patient cable (without ground pad connection) • Product literature	

The BE lead and foramen needle will come into contact with the subject's tissue during the therapy evaluation. [redacted]

Study devices will be connected to the approved Verify external neurostimulator and operated by each regions' patient and/or clinician programmer.

The study will be conducted in the United States, Canada and Europe, where the InterStim basic evaluation Lead, foramen needle and basic evaluation kit 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 Study Population

The study will enroll patients with overactive bladder. All subjects implanted must be candidates for sacral neuromodulation.

7.4. Product Return

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

7.5. Product Accountability

All product used in the study are commercially available; therefore, no product accountability is required based on the applicable regulations.

8. Selection of Subjects

8.1. Study Population

This study has been designed to collect data in a setting that represents real world use, for the expected lifetime of these devices. The BASIC study will enroll patients with symptoms of OAB at a broad set of enrolling centers in various geographies. [redacted]

In summary, the BASIC study will provide pertinent real-world evidence to the overall body of evidence of InterStim therapy.

8.2. Subject Enrollment

Each subject must meet all the inclusion criteria and no exclusion criteria to be eligible to participate in the study. Subjects are considered enrolled at the time of the BE lead 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. Inclusion Criteria

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

1. Subjects 18 years of age or older
2. Candidate for InterStim sacral neuromodulation in accordance with the InterStim System labeling
3. Have a diagnosis of OAB as demonstrated by either urinary urge incontinence and/or urinary frequency (see Section 9.1 for definition) on a 3-day voiding diary
4. Willing and able to accurately complete study diaries, questionnaire, attend visits, and comply with the study protocol
5. Willing and able to provide signed and dated informed consent

8.4. Exclusion Criteria

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

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

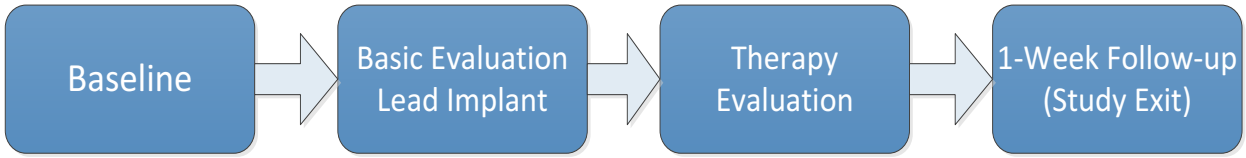
*Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in both studies.

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.

The following will be conducted:

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



9.1. Schedule of Events

Baseline

The study-specific informed consent form must be signed prior to any study-specific procedures. Each subject must meet all inclusion and no exclusion criteria to be eligible to participate in the study. At the baseline visit, data will be gathered from subjects including relevant medical history.

The urinary voiding diary will be explained and given to the subject to be completed for a minimum of 3 consecutive days for verification of OAB (either UUI or UF). Urinary urge incontinence is defined involuntary loss of urine associated with urgency[12] and urinary frequency is defined as $\geq$ 8 voiding episodes per day.[13] 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.

Collection of reportable adverse events and device deficiencies will begin after the informed consent form is signed.

Basic Evaluation Lead Implant Procedure

The BE lead(s) should be placed in accordance with the Basic Evaluation Lead Implant Manual. A subject is considered enrolled after all eligibility criteria is met but prior to the BE lead implant procedure. Motor or sensory response must be tested intra-operatively during foramen needle placement and confirmed when the BE lead(s) are placed. The motor or sensory response will be confirmed for each lead placed. Sensory threshold is defined as the lowest amplitude where the subject first perceives sensation of the stimulation. Motor threshold is defined as the lowest amplitude of electrical stimulation where a motor response (e.g. bellows response, anal wink and/or plantar flexion of the big toe) is observed. [redacted]

[redacted]. Prior to discharge, the sensory threshold in a seated position will be collected for all subjects. Programming parameters for the therapy evaluation will be at the institution's discretion. Programming data will be collected via a programming printout or Medtronic's programming upload system.

Therapy Evaluation

The subject will then be discharged to start the therapy evaluation. A daily urinary voiding diary will be completed for the entire therapy evaluation period (a minimum of 3 days)**.** The therapy evaluation must not exceed seven days. Any device-related visit that occurs prior to the one-week follow-up visit will be captured as an unscheduled visit.

Surgical Modifications

If a surgical modification (replacement) of the BE lead is required, each procedure will require the associated lead implant CRF and one-week follow-up CRF completed.

1 Week Follow-up Visit (Study Exit)

At the 1-week follow-up visit, any changes to OAB medications, reportable adverse events and/or device deficiencies will be collected. During the visit the subject's amplitude level for their sensory threshold will be re-assessed while in the seated position. [redacted]. Programming data will be collected via a programming printout or Medtronic's Programming Upload System.

[redacted]

The subject is exited from the study after the 1-week follow-up visit is complete.

<u>Unscheduled Visit</u>

If an unscheduled visit is needed for any device-related reason, any reportable adverse events and/or device deficiencies will be collected. Upon completion of any programming, data will be collected via a programming printout or Medtronic's programming upload system.

Table 9-1: Study Procedures

	Baseline	BE Lead Implant (Visit #1)	Therapy Evaluation***	One Week Follow-up Visit (5-7 days) (Visit #2)	Unscheduled Visit (Visit #3)
Informed Consent	X*				
Relevant Medical History	X				
Pregnancy Assessment	X				
Assessment of Sensory Threshold		X**		X	
Assessment of Motor Threshold		X**			
Urinary Voiding Diary	X		X		
Device Interrogation/ Programming Data		X		X	X
[redacted]				[redacted]	
Concomitant OAB Medications	X	X	X	X	X
Assessment of Reportable Adverse Events and Device Deficiencies	X	X	X	X	X
*Must occur prior to any study-specific activities **Sensory response, motor response or both may be collected during the lead implant procedure *** Therapy evaluation must not exceed 7 days from the time of BE lead implant					

9.2. Subject Screening

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

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

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

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

9.3. Concomitant Medications

OAB medication use will not be restricted during the trial; however, all OAB medication will be collected on a study-specific medication log.

9.4. Subject Consent

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

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

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

9.5. Assessment of Efficacy

Motor and sensory response

A motor or sensory response will be determined at the time of lead placement with the foramen needle and confirmed with the BE lead. Amplitude will be titrated up from 0 until a response is reported and/or observed. A sensory response is defined as the lowest amplitude where the subject first perceives sensation of the stimulation. A motor response is defined as the lowest amplitude of electrical stimulation where a motor response (e.g. bellows response, anal wink and/or plantar flexion of the big toe) is observed.

Urinary Voiding Diary
Symptoms related to OAB will be evaluated using paper voiding diaries. Subjects will be trained to complete the urinary voiding diaries for 3-days as part of the baseline procedures. The urinary voiding diaries will be completed daily following the BE lead implant until the 1-week follow-up visit. Every effort should be made to remind subjects of the importance of real-time diary completion.

Diaries will be used for comparison from the 1-week follow-up visit to baseline for the additional study measure of characterizing changes in bladder symptoms.

[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.

9.7. Recording Data

This study will be conducted using a remote data capture system. The Oracle Clinical Remote Data Capture (RDC) system which allows the study centers to enter study data into the sponsor's database over a secure internet connection, will be used to capture study required Case Report Form (CRF) information. Data reported on urinary voiding diaries and subject questionnaire will be entered to the database by site personnel. Subjects will complete the study questionnaire confidentially on paper forms without site personnel consultation and these data will be entered to OC/RDC by site personnel.

Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be taken from source documents and directly entered into the study database via the CRFs by the site personnel, in accordance with applicable regulations.

Device interrogation (programming) data may be transmitted using either Medtronic's programming upload system or by manual data entry on a programming CRF.

Urinary voiding diaries [redacted] are to be completed only by the subject. Representatives from the research site may not make entries to the diaries [redacted] except for data fields confirmed by the subject on source documentation.

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

9.8. 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 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; however, any visits completed outside of the visit window will require a protocol deviation to be reported. All protocol deviations must be reported on the Protocol Deviation eCRF promptly after the site's awareness of the deviation and submitted to the IRB/EC (as 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 regulatory 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 1-week follow-up visit, unless withdrawn from the study. Withdrawn or exited subjects will be followed under normal medical practice.

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

- 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 the BE lead and foramen needle. 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) / Instructions for Use (IFU)

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

Patients should be appropriate candidates for therapy evaluation and for potential surgical implant of a SNM system. Patients are contraindicated for therapy evaluation if they are unable to properly operate the handset, external neurostimulator (ENS), and accessories.

In addition to the risks normally associated with surgery, the following adverse events may occur with use of the BE lead and accessories.

- Tissue damage
- Infection
- Technical device problems

The following adverse events may occur with implantation or use of a neuromodulation system for sacral neuromodulation.

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

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.

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 a therapy evaluation with the BE lead, foramen needles or procedure kit outside of the study. Information from this study might help researchers further understand the BE lead implant procedure and therapy evaluation. 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 a BE lead implant procedure and therapy evaluation outside of the study. There might be other discomforts and risks related to a BE lead implant and therapy evaluation and/or this study that are not foreseen at this time.

The risks associated with a BE lead implant and therapy evaluation 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, device related, therapy related and/or procedure related as well as all device deficiencies will be considered reportable for this study. The term "investigational device" is part of ISO 14155 definitions. The term "investigational device" refers to any device used in the study including market released devices. Adverse events and device deficiencies are defined as follows:

- Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the BE lead, foramen needle or BE kit
- Procedure Related: An adverse event that occurs due to any procedure related to the implantation or surgical modification of the BE lead. The procedure is defined as the lead placement / implant procedure and surgical modification (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.

Table 11-1: Adverse Event & Device Deficiency Definitions

Term	General
Adverse Event (AE) (ISO 14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved.

	NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)* (ISO 14155:2011 3.1)	Adverse event related to the use of an investigational medical device. NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD)* (ISO 14155:2011 3.15) (ISO 14155:2011 3.27) (ISO 14155:2011 3.43)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE 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 1 Use error includes slips, lapses, mistakes. NOTE 2 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. STUDY SPECIFIC NOTE For this study, all adverse events will be collected however adverse events for system modifications (e.g. lead explants, revisions or replacements) will be considered non-serious unless the subject has clinical sequala which meets the seriousness definition outlined in the CIP.
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
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

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

The following are not adverse events:

- Any normal expected postoperative complaints or symptoms unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. Expected postoperative outcomes include headache, incisional pain, nausea, vomiting, low grade fever, oozing at dressing, dizziness, irritability, sleepiness, nervousness, insomnia, constipation, urinary retention, confusion and similar events.
- Any non-clinically significant, transient (lasting for only a short time) stimulation-related effects that occur during the implant procedure, programming and follow-up period.
- [redacted]

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	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 11-2. IRB/EC reporting must be completed in accordance with the policies of the governing IRB/EC. Governing regulatory 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:

- 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 IRB/EC. Commercial medical device reporting processes will be followed for complaint handling.

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

Medtronic study personnel will promptly review all reported adverse events and if necessary request clarification and/or additional information from the Investigator. If Medtronic disagrees with the Investigator's assessment of the adverse event relationship to device, therapy and/or procedure,

Medtronic study personnel will document the disagreement and report or ensure reporting of both opinions to IRB/EC as necessary. All reported adverse events will be reviewed by a Medtronic Medical Advisor to ensure consistent reporting.

9.1.1. 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

9.1.2. Deaths

All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but no more than 5 working days after learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. If limited information is known, the Adverse Event eCRF must be completed with available information as soon as possible. As information becomes available, the eCRF will be updated. If the death occurs at a location remote from the study site, it is the study site's responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's death summary of the known events surrounding the death to Medtronic or its designee. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system, therapy, and/or procedure. 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

[redacted]

Using PASS 2011, assuming that motor or sensory response is able to be obtained in 95% of subjects who qualify for a BE lead placement, with 100 subjects, this produces a two-sided 95% CI of 88.7-98.4% with a width equal to 9.6%. The confidence interval width will vary slightly depending on the actual proportion of subjects with motor or sensory responses.

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 will be implanted 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.

For the primary objective of motor or sensory response, in case subject's motor or sensory response is not tested or response data are lost during lead placement, a sensitivity analysis will be performed by displaying the full range of proportions on the potential impact of missing data by running an analysis assuming all missing values as not obtaining motor or sensory response to none of the missing values as not obtaining motor or sensory response.

Adjustment for Multiple Endpoints

As there is no hypothesis testing for the primary objective, adjustment for multiple endpoints is not required.

Interim Analysis

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

13.1.4. Reports

A final clinical study report will be generated for this study. Periodic progress reports may also be generated for the study. Reports may be submitted to the regulatory authorities, as required based on applicable local regulations.

13.2. Demographics

Demographics and baseline characteristics will be summarized in the report.

13.3. Primary Objective – Motor or Sensory Response

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

Hypothesis

There is no formal hypothesis. The objective is to estimate the proportion of subjects who demonstrate motor or sensory response(s) during lead placement using the InterStim BE Lead.

Experimental Design

During the lead placement procedure using the InterStim BE lead, subject's motor and/or sensory response will be collected as specified in Section 9.5. Subjects may be implanted with more than one BE lead. In this case subject's motor and/or sensory response from all implanted BE leads will be recorded. In case more than one BE lead is implanted, the subject is considered as demonstrating a response if motor or sensory response is obtained from at least one BE lead.

Analysis Methods

Subjects who had the BE lead placement and provide data (completers) will be included in the primary analysis. The primary analysis will report the proportion of subjects who obtain motor or sensory response and its two-sided exact binomial 95% CI among those who had lead placement.

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

In cases where subject's motor or sensory response is not tested, or response data are lost during lead placement, or other reasons where missing data occur, a sensitivity analysis will be performed by displaying the full range of proportions on the potential impact of missing data by running an analysis assuming all missing values as not obtaining a response to none of the missing values as not obtaining a response.

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

[redacted]

[redacted]

13.5. Safety Assessment

To characterize safety during the Basic Evaluation lead implant and therapy evaluation.

Safety will be evaluated by the collection of reportable adverse events. Reportable adverse events are defined as serious, device, procedure and/or therapy-related events.

Device deficiencies will be collected and reported.

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/ies in which the study is conducted will be followed and in accordance with GCP.

- In the US, the study will be conducted in accordance with 21 CFR§11 Electronic Records, Electronic Signatures, 21CFR§50 Protection of Human Subjects, 21CFR§56 IRB, 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.

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

Medtronic will report AEs and device deficiencies according to post-market vigilance 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 regulatory authority have been obtained, if appropriate.

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

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 will ensure no study-related activities occur prior to regulatory and IRB/EC approval. Any actions taken by the IRB/EC with respect to the investigation will be forwarded to Medtronic as soon as possible. The

Principal Investigator is responsible for submitting all required reports to the sponsor and/or IRB/EC. Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. It is the responsibility of the Investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB/EC responsible for oversight of the study. Investigators should report serious adverse events, device-, procedure- and therapy-related adverse events and device deficiencies to Medtronic after the Investigator learns of the event in accordance with Table 15-1.

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

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

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

Table 15-1 includes minimum reporting requirements for investigators participating in studies in Europe, the US and Canada. Medtronic study personnel will immediately report Adverse Events and Device Deficiencies, related to a CE marked, Canadian licensed or FDA approved device used during the study, to Medtronic's Compliant Handling Unit who will ensure prompt review and appropriate reporting. The Therapeutic Products Directorate is a division of Heath Canada, and is responsible for regulating therapeutic products including Food, Drugs, Medical Devices, Natural Health Products, Cells, Tissues and Organs and Cosmetics. Table 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
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
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
Deaths	
Investigator submit to:	
Medtronic	**All geographies:** All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but no more than 5 working days of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy
EC/IRB	**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
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
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

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
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
Failure to Obtain Informed Consent	
Investigator submit to:	
Medtronic	**US and Europe:** The Investigator must notify Medtronic within **5 working days** upon awareness **Canada:** The Investigator must notify Medtronic within **5 working** days after Procedure
EC/IRB	**US and Europe:** The Investigator must notify the EC/IRB within **5 working days** after upon awareness **Canada:** The Investigator must notify the EC/IRB within **5 working** days after procedure
Final Report	
EC/IRB	**US and Europe:** Study reports must be submitted within **6 months** after termination or completion of the investigation or as required by applicable regulation **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation

15.2. 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.

Contact information for the study monitoring:
Medtronic Core Clinical Solutions Monitor Group
8200 Coral Sea Street, N.E., MVS33
Mounds View, MN 55112

15.7. Source Documentation

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. Data Management

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

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

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

15.8. 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

15.9. Direct Access to Source Data/Documents

Source data is all information, original records (or certified copies) of clinical findings, observations or other activities in a study necessary for the reconstruction and evaluation of the study. Examples of these 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. 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 of Canada, Ltd., Medtronic International Trading SARL, and Medtronic Logistics LLC are wholly owned subsidiaries of Medtronic, which as the parent company of such entities maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC, governing regulatory authority (if applicable) and/or the IRB.

15.11.3. 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 regulatory authority (if applicable); protocol amendment approval and approval of any associated changes to the informed consent document must be obtained prior to implementation of the amendment except:

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

15.13. 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 BE lead, foramen needle, BE kit and therapy evaluation period.
- 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. 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.

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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
- Product performance/product supply issues

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

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

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

16. References

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