Evaluation of Implantable Tibial Neuromodulation Pivotal Study (TITAN 2)
Clinical Investigational Plan Version 4.0
18-Jul-2022
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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Evaluation of Implantable Tibial Neuromodulation (TITAN 2) Pivotal Study
Clinical Investigation Plan Identifier	MDT20061
Study Product Name	Tibial Neuromodulation (TNM) System
Sponsor	Medtronic, Inc. Neuromodulation 7000 Central Ave NE Minneapolis, MN 55432 USA
Document Version	4.0
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1. Investigator Statement and Signature Page

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
ADL	Activities of Daily Living
AE	Adverse Event
BTA	Botulinum Toxin-A
CDU	Clinical Data Upload
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRO	Clinical Research Organization
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
EAU	European Association of Urology
eCRF	Electronic Case Report Form
IRB	Institutional Review Board
EDC	Electronic Data Capture
FD	Financial Disclosure
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form

Term	Definition
IDE	Investigational Device Exemption
IUSS	Indevus Urgency Severity Scale
MedDRA	Medical Dictionary for Regulatory Activities
mSv	MilliSievert
MESA	Medical, Epidemiological, and Social Aspects of Aging urinary incontinence questionnaire
MI	Multiple Imputation
[redacted]	[redacted]
OAB	Overactive Bladder
OAB-q	Overactive Bladder Quality of Life
PHI	Protected Health Information
[redacted]	[redacted]
PTNS	Percutaneous Tibial Nerve Stimulation
PTNM	Percutaneous Tibial Neuromodulation
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SR	Significant Risk
SID	Subject Identification
TNM	Tibial Neuromodulation
UADE	Unanticipated Adverse Device Effect
UF	Urinary Frequency
UI	Urinary Incontinence
UPS	Urgency Perception Scale

Term	Definition
USADE	Unanticipated Serious Adverse Device Effect
UUI	Urinary Urge Incontinence

3. Synopsis

Title	Evaluation of Implantable Tibial Neuromodulation (TITAN 2) Pivotal Study
Clinical Study Type	Investigational Pivotal Study
Product Name	Tibial Neuromodulation (TNM) System: ▪ TNM Neurostimulator (4NR040) ▪ Handset with Communicator (TH90 which contains: - Handset (HH90) and Communicator (TM90)) ▪ Ankle Cuff (4NR041) ▪ Wireless Recharger kit (RS5200) which contains: – Wireless Recharger (WR9220) and Charging Dock (CD9000) ▪ Patient and clinician therapy application software (4NR039, 4NR038) ▪ Recharger application software (A90300)
Sponsor	Medtronic Neuromodulation 7000 Central Ave NE Minneapolis, MN 55432 USA
Indication under investigation	The indication under investigation is for the treatment of overactive bladder (OAB) and associated symptoms including urgency, urinary frequency, and/or urinary urge incontinence (UUI).
Investigation Purpose	The purpose of this prospective, multicenter study is to assess the safety and efficacy of tibial neuromodulation using the Medtronic Tibial Neuromodulation (TNM) system.
Product Status	Investigational
Primary Objective	To demonstrate that the percentage of subjects considered a UUI responder after 6 months of tibial neuromodulation exceeds a performance goal of 40%.

Primary Endpoint	Proportion of TNM subjects experiencing a reduction of 50% or more in daily urinary urge incontinence (UUI) episodes (UUI responder rate) at 6 months after device implant.
Secondary Objectives	▪ To demonstrate an improvement from baseline to 6 months in number of UUI episodes in subjects with UUI at baseline ▪ To demonstrate an improvement from baseline to 6 months in number of urinary frequency (UF) episodes in subjects with UF at baseline ▪ To demonstrate an improvement from baseline to 6 months in urinary urgency using the Urgency Perception Scale (UPS) ▪ To demonstrate an improvement from baseline to 6 months in quality of life (QoL) using the Overactive Bladder Symptom Quality of Life Questionnaire (OAB-q)
Secondary Endpoints	▪ Change in UUI episodes at 6 months compared to baseline in subjects with UUI at baseline ▪ Change in daily UF episodes at 6 months compared to baseline in subjects with UF at baseline ▪ Change in urinary urgency assessed through the UPS at 6 months compared to baseline ▪ Change in OAB-q HRQL (health related quality of life) Total Score at 6 months compared to baseline

[redacted]	[redacted]
Study Design	This is a prospective, multicenter, pivotal study to assess safety and efficacy for the implantable TNM device in subjects with overactive bladder. The study is intended to be conducted at up to 30 institutions in the United States. Eligible subjects will sign a study-specific informed consent form (ICF). Subjects will complete an Enrollment/Baseline Visit, a Device Implant Visit, and 7-day, 1-month, 2-month, 3-month, 6-month, 12-month and 24-month Follow-up Visits. A Clinical Events Committee will periodically review adverse events reported during the study to assure appropriate and consistent classification of adverse events, as well as issues regarding individual study subjects and adverse event trend reporting.
Sample Size	Up to 200 subjects will be enrolled. Enrollment will be closed once the number of completed implants reaches 121; all enrolled subjects who meet eligibility criteria may be implanted (not to exceed 130 total implants). Implanted subjects who exit from the study will not be replaced.

Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Subjects 18 years of age or older 2. A 3-day voiding diary demonstrating a minimum of 3 episodes of urinary urge incontinence in 72 hours 3. Have a diagnosis of UUI for at least 6 months 4. No OAB pharmacotherapy for 2 weeks prior to completion of the baseline voiding diary and Overactive Bladder Quality of Life (OAB-q) questionnaire 5. Failed, or are not a candidate for, conservative non-pharmacologic treatment (e.g., pelvic floor training, biofeedback, behavioral modification) 6. Failed and/or are intolerant* to at least 2 overactive bladder medications (antimuscarinics or beta-3 agonist) or contraindicated to all pharmacological therapies for the treatment of overactive bladder 7. Willing and able to accurately complete study diaries, questionnaires, attend visits, operate the system, and comply with the study protocol 8. 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. Severe uncontrolled diabetes 3. History of urinary retention within the previous 6 months 4. Current symptomatic urinary tract infection 5. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component [see enrollment/baseline requirements for use of the Medical, Epidemiological, and Social Aspects of Aging urinary incontinence questionnaire (MESA) questionnaire] 6. Diagnosis of bladder pain syndrome, pelvic pain, or interstitial cystitis 7. Current urinary tract mechanical obstruction (e.g., benign prostatic enlargement or urethral stricture) 8. History of a prior implantable tibial neuromodulation system 9. Knowledge of planned diathermy procedures

	10. Have had treatment of urinary symptoms with sacral neuromodulation in the past 6 months, botulinum toxin therapy in the past 9 months or percutaneous tibial nerve stimulation (PTNS)/percutaneous tibial neuromodulation (PTNM) in the past 3 months 11. Skin lesions or compromised skin integrity (e.g., skin atrophy, thinning, fragility, etc.) which may affect incision healing at the implant site 12. Current or a recent history (within the past 6 months) of a medical condition such as venous insufficiency and/or venous stasis ulcers, clinically significant malnutrition, immunocompromised state, or other relevant chronic disease which may indicate a higher risk for delayed or poor wound healing. 13. Anatomical defects, clinically significant edema or previous surgeries which precludes use of the device (including any metal implant that is within 20 cm of the intended neurostimulator location) 14. Previous pelvic floor surgery in the last 6 months 15. Women who are pregnant or planning to become pregnant during the course of the study 16. Any subject who is considered to be part of a vulnerable patient population.** 17. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements. 18. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.*** *Defined as stopped taking medication due to lack of efficacy or intolerable side effects **See Section 10.6 for the definition of a vulnerable patient population. ***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:** ▪ Enrollment/Baseline Visit ▪ Device Implant Visit ▪ 7-day Post-Procedure Follow-up Visit ▪ 1-month Follow-up Visit ▪ 2-month Follow-up Visit ▪ 3-month Follow-up Visit ▪ 6-month Follow-up Visit ▪ 12-month Follow-up Visit ▪ 24-month Follow-up Visit **Enrollment/Baseline Visit:** The study-specific informed consent form must be signed prior to any study-related activities, at which time a subject will be considered enrolled in the study. 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 and recent OAB medications. The MESA Urinary Incontinence Questionnaire will be used to exclude predominant stress incontinence. Subjects are prohibited from additional OAB treatment until after the 12-month follow-up visit, starting two weeks prior to the baseline voiding diary and completion of the baseline Overactive Bladder Quality of Life (OAB-q) questionnaire. A negative pregnancy test is required for women of childbearing potential. The urinary voiding diary will be explained and given to the subject to be completed for 3 consecutive days. The Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] and Urgency Perception Scale (UPS) questionnaires, will be collected. Between consent and prior to the neurostimulator placement, an ultrasound image to assess measurements related to the tibial nerve may be completed in a subset of patients to summarize the subject's anatomical characteristics. Any adverse events reported following informed consent will be collected.

	Device Implant Visit: It is recommended that the device is implanted within 30 days of the subject's enrollment in the study. The device will be implanted in accordance with the Medtronic TNM Clinician Guide. Motor and sensory thresholds will be assessed during the procedure. During this visit, the device will be interrogated, sensory/motor thresholds assessed, the amplitude will be set, and the subject will be discharged with a compression sock. An ultrasound of the tibial nerve may be completed following the neurostimulator implant procedure. The investigator or delegated personnel may initiate the therapy for the first time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their first therapy session at a time convenient for them within approximately 24 hours of their visit. The subject will receive 30 minutes of stimulation every other day. The subject will be provided instructions which cover post procedure care, activity guidelines, and how to interact with their implanted device. Any adverse events and/or device deficiencies will be collected. **7-Day Post-Procedure Follow-up Visit:** During the 7-day post-procedure follow-up visit, the device will be interrogated, sensory/motor thresholds assessed, and the amplitude will be set. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit. It is recommended that the subject receives 30 minutes of stimulation every other day. The therapy schedule may be adjusted based on symptom control and/or patient preference. Programming data will be collected. Subjects will be trained on neurostimulator recharging which will be recommended weekly starting at the 7-day post procedure follow-up visit. If the wound is not healed, a sterile barrier should be provided by the institution to be placed between the wound and recharger.

	Continued compression may be recommended based on the study-specific guidance. Any adverse events and/or device deficiencies will be collected. **1-Month and 2-Month Follow-up Visits:** The 3-day urinary voiding diary should be started approximately one week prior to the study visit. The device will be interrogated, sensory/motor thresholds assessed, and the amplitude will be set. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit. It is recommended that the subject receives 30 minutes of stimulation every other day. The therapy schedule may be adjusted based on symptom control and/or patient preference. Programming data will be collected. Any adverse events and/or device deficiencies will be collected. **3-Month Follow-up Visit:** The 3-day urinary voiding diary should be started approximately one week prior to the study visit. During the follow-up visit, the Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] Urgency Perception Scale (UPS) [redacted] will be collected. The device will be interrogated, sensory/motor thresholds assessed, and the amplitude will be set. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit. It is recommended that the subject receives 30 minutes of stimulation every other day. The therapy schedule may be adjusted based on

	symptom control and/or patient preference. Programming data will be collected. Any adverse events and/or device deficiencies will be collected. **6-Month Follow-up Visit:** The 3-day urinary voiding diary should be started approximately one week prior to the study visit. During the follow-up visit, the Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] Urgency Perception Scale (UPS) and [redacted] will be collected. The device will be interrogated, sensory/motor thresholds assessed, and the amplitude will be set. The therapy schedule may be adjusted based on symptom control and/or patient preference. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit. Programming data will be collected. Any adverse events and/or device deficiencies will be collected. **12-Month and 24-Month Follow-up Visits:** The 3-day urinary voiding diary should be started approximately one week prior to the study visit. During the follow-up visit, the Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] Urgency Perception Scale (UPS) and [redacted] will be collected. The device will be interrogated, sensory/motor thresholds assessed, and the amplitude will be set. The therapy schedule may be adjusted based on symptom control and/or patient preference. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their

	therapy session at a time convenient for them within approximately 24 hours of their visit. Programming data will be collected. Any adverse events and/or device deficiencies will be collected. The subject will exit the study at the 24-month follow-up visit. The TNM neurostimulator may remain implanted following study exit; the decision whether to explant will be per physician and patient discretion. **System Modification** A system modification may be needed for explant or replacement of the neurostimulator during the study. Prior to neurostimulator removal and/or after a new neurostimulator is placed, an ultrasound image to assess measurements related to the tibial nerve may be completed. During the visit, any relevant medication changes, procedural data, reportable adverse events and/or device deficiencies will be collected. It is recommended that a voiding diary, sensory/motor thresholds, and device data are also collected prior to any system modifications, when possible. For neurostimulator replacement procedures, upon completion of any programming, threshold and programming data will be collected. The therapy schedule will be set based on the timeframe in the study when the system modification was completed, and the therapy session may be initiated during the visit or within 24 hours. Following a system modification, the subject should complete a 7-day Post Procedure Follow-up Visit and the subject will receive a 1-month post-procedure phone call. Further follow-up visits will be based on the original implant date.
Statistics	The primary objective will be met by the percentage of subjects who are considered a UUI responder which is statistically superior to a performance goal of 40%. To determine responder status, the 3-day urinary voiding diary data at baseline and the 6-month follow-up visit will be used to determine daily urinary urge incontinence episodes per subject. Each subject's daily values at baseline and at 6 months will be compared to the UUI responder definition to determine if the subject is a responder. The UUI responder rate, corresponding two-

	sided 95% confidence interval, and p-value from the comparison to the 40% performance goal will be calculated. All p-values will be reported as 2-sided tests with alpha=0.05. The primary objective will be tested with a binomial test or a Z-test, depending on the use of imputation. If the primary objective is passed, the secondary objectives will each be tested using the Hochberg multiple testing strategy using a t-test or Wilcoxon signed-rank test, depending on the normality of the data. The sample size was estimated using a binomial distribution for a one-sided alpha=0.025 test to show a 15% increase for the proportion compared to a performance goal of 40%. Assuming the alternative hypothesis of 55% of subjects who are considered an UUI responder, a minimum of 121 implanted subjects achieves at least 90% power to reject a performance goal of 40%. Sample size was computed in PASS 19. Primary and secondary objectives will be analyzed using the Full Analysis Set (FAS). The FAS includes all subjects, using the intention-to-treat (ITT) principle, who have device implant attempted. All attempts will be made to minimize missing data. If 5% of the data or fewer are missing for the analysis, no imputation will be used, and the data will be analyzed using the Complete Case analysis set. Otherwise, if missing data are observed, multiple imputation will be used for the primary and secondary objectives. In the case of non-normal secondary objective data imputation, last observation carried forward (LOCF) imputation may be needed to test the hypothesis. Sensitivity analyses will be completed for the primary and secondary objectives including using only subjects with outcome data at baseline and follow-up (“Complete Case Analysis”) and using only those complete case subjects who received stimulation (“As Treated Analysis”). [redacted] Comprehensive descriptions of subject accountability and safety will be provided.

4. Introduction

4.1 Background

4.1.1 Overactive Bladder Syndrome

The medical condition of overactive bladder (OAB) is recognized as a symptom syndrome characterized by the symptoms of urinary urgency (UU), with or without urinary urge incontinence (UUI), usually with urgency frequency (UF) and nocturia (waking at night one or more times to void)[1,2,3]. OAB may be treated with one or a combination of the treatments described in clinical guidelines developed by various professional organizations, including the American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) Guideline for Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) In Adults[4]. Conservative measures are typically recommended as first-line treatment and include simple clinical interventions, lifestyle interventions, and behavioral and physical therapies. When conservative measures fail, pharmacologic management is typically recommended as second-line treatment. Pharmacologic management includes anti-muscarinics, anticholinergics and β3 adrenergic receptor agonists.

For patients who are refractory to pharmacologic treatment or unable to tolerate associated side effects, advanced therapy options may be offered. These include percutaneous tibial neuromodulation (PTNM also known as percutaneous tibial nerve stimulation), botulinum toxin-A (BTA) injections, and implantable sacral neuromodulation (SNM). The AUA/SUFU guidelines note that reported adverse events (AEs) for PTNM are minor; furthermore, the European Association of Urology (EAU) Guidelines recommend PTNM before advancing to surgical options such as BTA injections or SNM[5], and PTNM is considered a conservative or second-line treatment in several other articles[6–9].

4.1.2 Tibial Neuromodulation

Tibial neuromodulation (TNM) devices are designed to deliver electrical pulses that stimulate the tibial nerve that runs posterior to the tibia and extends to the sacral nerve plexus. These pulses are thought to relieve OAB symptoms by modulating communication between the bladder and central nervous system.

PTNM is a Food and Drug Administration (FDA) cleared, in-office procedure that delivers adjustable electrical pulses through a needle to stimulate the tibial nerve. The needle electrode is placed into the lower, inner aspect of either leg, slightly cephalad to the medial malleolus. Treatment usually consists of 30-minute therapy sessions delivered weekly for 12 weeks, followed by maintenance therapy delivered approximately monthly. PTNM is a medical guideline indicated therapy[4] and is accepted as a safe and effective treatment for OAB[10]. Two independent multicenter, randomized controlled 12-week trials demonstrated that PTNM therapy is safe and showed superior efficacy to sham[11] and comparable efficacy to medication[12].

While these results are promising, therapy adherence can be an issue in patients for whom it is a burden to return to the clinic for weekly therapy sessions (or monthly for long-term maintenance therapy). In a large retrospective analysis, Gordon et al. reported that 347 of 1331 patients (26%) completed 12 PTNM sessions while 158 (46%) of these continued with long term PTNM defined as completion of 8 additional sessions[13]. The gap between clinical efficacy and therapy dropout rates suggests that frequent office visits are a barrier to care for both patients and physician offices. The need for frequent, recurrent office visits for therapy delivery may prove to be a significant barrier to care as the global medical community adapts to the need to reduce clinic visits and explores way to treat more patients in their home setting.

In order to eliminate the barrier of frequent clinic visits for PTNM sessions while retaining the efficacy and positive safety profile of tibial neuromodulation, implantable tibial neuromodulation (ITNM) devices have been proposed as an alternative to PTNM. Two feasibility studies and one pivotal study have been published to date with promising results. Clinical success was observed in 69.6% and 68% of UUI patients at 12 weeks and 48 weeks, respectively[14,15] and 70.6% of OAB patients at 6 months[16]. All three studies report significant improvements from baseline in quality of life. Incision site infection, implant site pain and stimulation discomfort were reported[14–16].

This pivotal study is intended to assess the safety and efficacy of the Medtronic TNM system for the treatment of overactive bladder. Early learnings from the TITAN 1 feasibility study provided information about procedural learnings to further inform the pivotal study protocol.

4.2 Purpose

Medtronic, Inc. is sponsoring the Evaluation of Implantable Tibial Neuromodulation (TITAN 2) Pivotal Study, a prospective, multicenter, pivotal clinical study. The purpose of this study is to is to assess the safety and efficacy of tibial neuromodulation using the Medtronic Tibial Neuromodulation (TNM) system.

5. Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objective

To demonstrate that the percentage of subjects considered a UUI responder after 6 months of tibial neuromodulation exceeds a performance goal of 40%.

5.1.1.1 Primary Endpoint

Proportion of TNM subjects experiencing a reduction of 50% or more in daily urinary urge incontinence (UUI) episodes (UUI responder rate) at 6 months after device implant.

5.1.2 Secondary Objectives

- To demonstrate an improvement from baseline to 6 months in number of UUI episodes in subjects with UUI at baseline
- To demonstrate an improvement from baseline to 6 months in number of UF episodes in subjects with UF at baseline
- To demonstrate an improvement from baseline to 6 months in urinary urgency using the Urgency Perception Scale (UPS)
- To demonstrate an improvement from baseline to 6 months in quality of life (QoL) using the Overactive Bladder Symptom Quality of Life Questionnaire (OAB-q)

5.1.2.1 Secondary Endpoints

- Change in UUI episodes at 6 months compared to baseline in subjects with UUI at baseline
- Change in daily UF episodes at 6 months compared to baseline in subjects with UF at baseline
- Change in urinary urgency assessed through the UPS at 6 months compared to baseline
- Change in OAB-q HRQL (health related quality of life) Total Score at 6 months compared to baseline

[redacted]

6. Study Design

This is a prospective, multicenter, pivotal study to assess safety and efficacy for the implantable TNM device in subjects with overactive bladder.

Eligible subjects will sign a study-specific informed consent form (ICF), at which time they will be considered enrolled in the study. All eligible subjects will complete baseline procedures, including a baseline diary and assessment of medical history. Subjects must be consented and meet all inclusion and no exclusion criteria to continue to the neurostimulator implant procedure. Any subject who does

not meet all inclusion/exclusion criteria will be excluded from study participation and exited from the study.

Study requirements, including diaries, questionnaires and safety assessments will be completed as required in Section 10. Subject follow-up is expected to last approximately 24 months following the neurostimulator implant procedure. Subjects will be exited from the study after the 24-month follow-up visit is completed. Any subjects who have the device explanted and not replaced during follow-up will be exited from the study.

The study is expected to be conducted at up to 30 study sites located in the United States. Up to 200 subjects will be enrolled to obtain 121 subjects who have the study device implanted. Enrollment will be closed once the number of completed implants reaches 121; all enrolled subjects who meet eligibility criteria may be implanted (not to exceed 130 total implants).

To ensure a widespread distribution of data and minimize study site bias in study results, the maximum number of subjects to be implanted at a single study site is 24 subjects.

6.1 Duration

The estimated study duration, from first subject enrollment to last subject visit, is expected to last approximately 36 months. The duration of individual subject participation will vary based on timing of study visits; however, participation of an individual subject will be approximately 24 months. Study completion is defined as Sponsor approval of the Final Study Report and closure of all sites.

6.2 Rationale

This pre-market study will collect data in an organized, systematic manner based on product use to assess safety and efficacy of the Medtronic TNM System for tibial neuromodulation. No comparator is required in the study design due to performance goals being based on the literature available on advanced therapy options for OAB. Relevant pre-clinical and clinical testing are outlined in the Report of Prior Investigations.

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 tibial neuromodulation as a potential treatment option.

7. Product Description

7.1 General

The TNM neurostimulator is a rechargeable, implantable pulse generator implanted subcutaneously over the tibial nerve in the lower leg. A recharger is used to recharge the implanted device. An ankle cuff

is used to hold the recharger during recharging sessions. Clinician and patient apps on a handset are used to program the implanted device. A handheld communicator provides a communication bridge between the apps on the handset and the implanted device. The TNM system is investigational, intended to be used for this study, and is not intended to be market-released.

The TNM system is comprised of investigational and market-released components.

The study will be conducted using the products/components described in the table below. There are no anticipated changes to the product expected during the course of the study which are anticipated to impact the conduct of the study outside of possible software or component changes. Instructions for use of the devices used in this study are provided in their respective instruction manuals.

Investigators and subjects will be provided with copies of instructions for the TNM system. Subjects should be given instructions to contact the study doctor or research coordinator if any component of the TNM system is lost, damaged or malfunctions.

The estimated sample size for this study may yield 121-130 implants with the TNM System implantable neurostimulator (INS) and associated system accessory product (see table below). Additional system components will be needed for system modifications.

Table 1: Investigational System component information

Model Number	Component
4NR040	TNM Neurostimulator
TH90	Handset with Communicator which contains: Handset (HH90) and Communicator (TM90)
4NR039	Patient therapy application software (TNM MyTherapy app)
4NR038	Clinician therapy application software (TNM Clinician app)
4NR041	Ankle Cuff
RS5200	Recharger Kit which contains: Recharger (WR9220) and Charging Dock (CD9000)
A90300	Recharger application software (Recharger app)

7.1.1 TNM Neurostimulator

The TNM neurostimulator is a programmable device that delivers stimulation through surface electrodes on the implanted device.

Figure 1: TNM Neurostimulator

The neurostimulator may be set to one of the following Therapy Schedules based on requirements outlined in Section 10.

Table 2: Therapy Schedule Options

Therapy Schedule	Therapy Schedule duration	Therapy Schedule frequency
1	30 minutes	Every other day (every 48 hours)
2	30 minutes	Daily (every 24 hours)
3	30 minutes	Every third day (every 72 hours)
4	1 hour	Every other day (every 48 hours)
5	30 minutes	Once a week (every 168 hours)
6	1 hour	Daily (every 24 hours)
7	4 hours	Daily (every 24 hours)
8	8 hours	Daily (every 24 hours)
9	Custom	Custom

7.1.2 Programming Subsystem

The Medtronic Model 4NR039/4NR038 patient and clinician applications (apps) are intended for use with the HH90 Handset and TM90 Communicator to program, adjust, and troubleshoot the Medtronic Model 4NR040 TNM neurostimulator for tibial neuromodulation therapy.

7.1.3 Wireless Recharger Subsystem

The Wireless Recharger (WR9220) is used to recharge the battery of the neurostimulator device. The Charging Dock (CD9000) is used to recharge the battery of the Wireless Recharger. No changes will be made from the InterStim™ Micro (used for sacral neurostimulation) commercial versions of the Wireless Recharger or Charging Dock for use in the clinical study. Investigational labeling for Wireless Recharger and Charging dock will arrive separately from the system components. Instructions on how to use the Wireless Recharger for the TNM system will be provided to each investigational site and to each study subject.

The Ankle Cuff has an adjustable sleeve that holds the Wireless Recharger in position over the tibial implant location.

7.1.4 Study Aids

Study aids for use in the study will be provided by Medtronic.

Table 3: Study Aids

Component
Army Navy Retractor
Sterile ruler, marker
Sterile Bag
Shower Bag
Compression Sock

7.2 Manufacturer

Medtronic, Inc. is the legal manufacturer of the investigational products used in this study.

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA
www.medtronic.com
Tel. +1-763-505-5000

7.3 Packaging

Copies of investigational product labeling will be provided.

All TNM system components will have labeling which states "CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use". Study aids will not be labeled as an investigational device. No changes will be made to the commercial devices for the Wireless Recharger and Charging Dock.

7.4 Intended Population

The study will enroll patients with symptoms associated with overactive bladder, including urgency, urinary frequency and/or urinary urge incontinence, who meet all eligibility criteria outlined in Section 9 Selection of Subjects.

7.5 Product Use

Investigators must agree not to use any investigational device or system component listed in Section 7.1, on any person except subjects enrolled in this study.

7.6 Equipment

Ultrasound equipment may be used at each study site to support study activities and equipment will be provided by Medtronic.

7.7 Product Training Materials

Principal Investigator and delegated individuals performing the implant/explant procedure and programming activities for the TNM system will be required to undergo training on use of the system prior to completing the delegated activities.

7.8 Product Receipt and Tracking

Distribution of the investigational products to study centers during the clinical study will be managed by Medtronic, can only be ordered by Medtronic personnel and will be labeled in accordance with 21 CFR§812.5. A Device Accountability Log will be used by centers for tracking of all investigational products by unique identifiers, (e.g., by assignment of serial numbers, lot numbers, batch numbers). Logs must be maintained at each study center and updated when investigational product is received, used, explanted, disposed of by the institution/subject, or returned to Medtronic. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site as outlined on the Device Accountability Log. Product accountability of investigational product will be reviewed during monitoring visits.

Subjects will be informed to contact the research coordinator in the event that any study product is lost, damaged or malfunctions.

7.9 Product Storage

Investigational product, once received at the study site, must be stored in a secure location at the study site. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

7.10 Product Return

It is recommended that all explanted devices are returned to Medtronic for analysis when permissible by local laws and regulations. In addition, it is recommended that all external TNM system components are returned to Medtronic at the time of explant. If the products are explanted but not returned, a justification will be reported on the appropriate Device Accountability Log. Contact the Medtronic Study Team for return instructions.

All unused investigational product will be returned to Medtronic upon the completion of the study, unless instructed by Medtronic to dispose of product at the institution.

7.11 Product Accountability

The TNM system is considered investigational. Investigational product will be distributed to a study site only when Medtronic has received all required documentation and has notified the study site of study site activation. Distribution of an investigational product to study sites during the study will be managed by Medtronic and can only be ordered by Medtronic personnel.

The study site is responsible for maintaining tracking of the investigational devices during the study. An electronic device accountability log will be located in the study-specific Electronic Data Capture (EDC) for tracking. The Device Accountability Log must be maintained at each study site and updated when the investigational product is received, used, explanted, disposed of by the institution/subject, or returned to Medtronic. In addition to tracking the date of events, the Device Accountability Log tracks product information which may include, but is not limited to, date, model/serial/lot (as applicable) number, and expiration date for the received product, subject ID of the implanted subject, reason(s) for and method of destruction/disposal for explanted components not returned to Medtronic (if applicable), and name of the person responsible for return or destruction/disposal (if applicable).

Medtronic will perform periodic reconciliation of the investigational product to ensure traceability.

Non-investigational study aids should be retained for use in the study, but individual component tracking is not required.

8. Study Site Requirements

8.1 Investigator/Investigation 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. Study site personnel training in accordance with the study-specific training plan will be completed and documented prior to participation in this study.

8.2 Study Site Activation

During the activation process (prior to subject consenting), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent (IC), product accountability, data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before participating in the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- Institutional Review Board (IRB) approval (and voting list, as required) of the current version of the Clinical Investigation Plan (CIP) and ICF.
- FDA approval
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure
- Curriculum Vitae (CV) of investigators and key members of the investigation study site team (as required)
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by the IRB and FDA shall be followed

In addition, all participating study site staff must be trained on the current version of the CIP, investigational system, implant procedure, as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, Medtronic representatives may participate in the conduct of the study under supervision of the Principal Investigator to the extent listed below. Medtronic representatives responsible for human factors may observe study activities (e.g., implant procedure).

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 Medtronic equipment, TNM system and components (including software/applications) and/or protocol-related procedures and forms. In addition, Medtronic personnel may perform certain activities to ensure study quality. These activities may include:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Observe implant, follow-up visits and/or medical procedures to provide information relevant to protocol completion
- Review collected data and study documentation for completeness and accuracy

In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following significant trial related duties:

- Provide technical support for setting up investigational product
- Perform device programming or device interrogation under the direction of the investigator(s)
- Perform ultrasound assessments

Any data collection completed by Medtronic personnel will be clearly identified as such.

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 eCRFs or make entries in the subject's medical record

9. Selection of Subjects

9.1 Study Population

The study will enroll patients with overactive bladder, who meet eligibility criteria in Sections 9.3 and 9.4.

9.2 Subject Enrollment

Eligible subjects will sign a study-specific informed consent form (ICF) at which time they will be considered enrolled. Each subject must meet all the inclusion criteria and no exclusion criteria to be eligible to participate in the study. Any subject not meeting eligibility criteria will be excluded from study participation and exited from the study. Site personnel must complete logs related to recruitment and enrollment as required by the study.

9.3 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. A 3-day voiding diary demonstrating a minimum of 3 episodes of urinary urge incontinence in 72 hours
3. Have a diagnosis of UUI for at least 6 months

4. No OAB pharmacotherapy for 2 weeks prior to completion of the baseline voiding diary and Overactive Bladder Quality of Life (OAB-q) questionnaire
5. Failed, or are not a candidate for, conservative non-pharmacologic treatment (e.g., pelvic floor training, biofeedback, behavioral modification)
6. Failed and/or are intolerant* to at least 2 overactive bladder medications (antimuscarinics or beta-3 agonist) or contraindicated to all pharmacological therapies for the treatment of overactive bladder
7. Willing and able to accurately complete study diaries, questionnaires, attend visits, operate the system, and comply with the study protocol
8. Willing and able to provide signed and dated informed consent

9.4 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. Severe uncontrolled diabetes
3. History of urinary retention within the previous 6 months
4. Current symptomatic urinary tract infection
5. Have primary stress incontinence or mixed incontinence where the stress component overrides the urge component [see enrollment/baseline requirements for use of the Medical, Epidemiological, and Social Aspects of Aging urinary incontinence questionnaire (MESA) questionnaire]
6. Diagnosis of bladder pain syndrome, pelvic pain, or interstitial cystitis
7. Current urinary tract mechanical obstruction (e.g., benign prostatic enlargement or urethral stricture)
8. History of a prior implantable tibial neuromodulation system
9. Knowledge of planned diathermy procedures

10. Have had treatment of urinary symptoms with sacral neuromodulation in the past 6 months, botulinum toxin therapy in the past 9 months or percutaneous tibial nerve stimulation (PTNS)/percutaneous tibial neuromodulation (PTNM) in the past 3 months

11. Skin lesions or compromised skin integrity (e.g., skin atrophy, thinning, fragility, etc.) which may affect incision healing at the implant site

12. Current or a recent history (within the past 6 months) of a medical condition such as venous insufficiency and/or venous stasis ulcers, clinically significant malnutrition, immunocompromised state, or other relevant chronic disease which may indicate a higher risk for delayed or poor wound healing.

13. Anatomical defects, clinically significant edema or previous surgeries which precludes use of the device (including any metal implant that is within 20 cm of the intended neurostimulator location)

14. Previous pelvic floor surgery in the last 6 months

15. Women who are pregnant or planning to become pregnant during the course of the study

16. Any subject who is considered to be part of a vulnerable patient population.**

17. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol requirements.

18. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results.***

* Defined as stopped taking medication due to lack of efficacy or intolerable side effects.

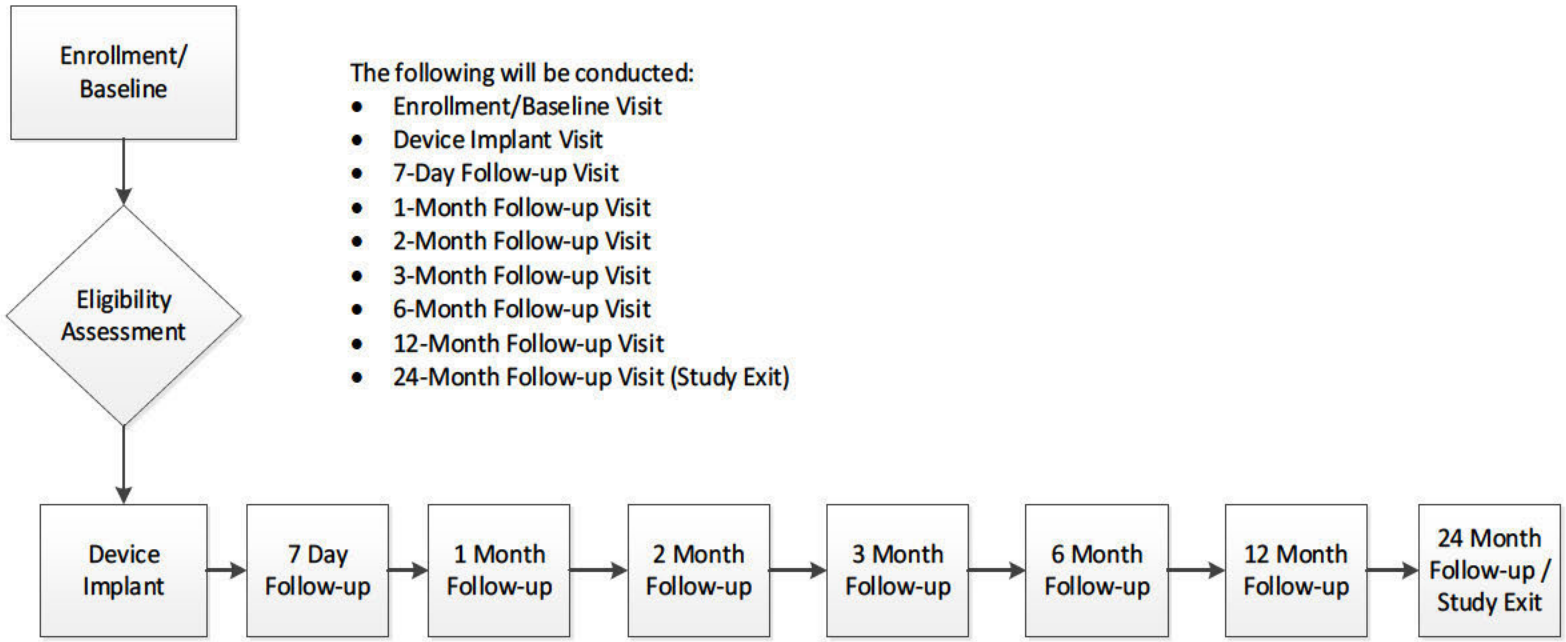
**See Section 10.6 for the definition of a vulnerable patient population.

***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.

10. 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. 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 2: Study Visits



10.1 Schedule of Events

Enrollment/Baseline Visit:

The study-specific informed consent form must be signed prior to any study-related activities. OAB medications must have a washout of 2 weeks prior to starting the baseline voiding diary and the baseline Overactive Bladder Quality of Life (OAB-q) questionnaire. The [redacted] and UPS questionnaires will also be provided for the subject's completion. The urinary voiding diary will be explained and given to the subject to be completed for 3 consecutive days.

Data will be gathered from subjects including relevant medical history and overactive bladder medications. The MESA urinary incontinence questionnaire will be used to exclude predominant stress incontinence. If the Investigator's assessment differs from the results of the MESA questionnaire, rationale must be documented to explain the decision to implant the subject.

Women of child-bearing potential must undergo a pregnancy test (e.g., serum, urine), with a clear negative result, prior to the device implant procedure. During the course of this study, women of child-bearing potential must agree to use a medically acceptable form of birth control. Women who are pregnant or plan to become pregnant during the course of the trial cannot participate in the trial. If unanticipated pregnancy occurs while participating in the trial, the subject should consult with the study physician to determine programming of the device and therapy decisions.

The correct fitting compression sock should be determined prior to the implant procedure. Compression may be used for up to two weeks post-implant, if needed. Reference the compression sock labeling for sizing and study specific recommendation for compression duration.

Prior to the implant procedure, the Investigator should assess the subject's implant site location based on the study eligibility criteria. Each subject must meet all inclusion and no exclusion criteria to be eligible to participate in the study.

Between consent and prior to the neurostimulator (device) placement, an ultrasound image to assess measurements related to the tibial nerve may be completed in a subset of patients to summarize the subject's anatomical characteristics. It is estimated that ultrasound data may be collected on approximately 30 patients.

Any adverse events reported following informed consent will be collected. Subjects should not receive additional OAB treatment (such as OAB medication, tibial neuromodulation, Botox injections, or sacral neuromodulation) during the first 12 months of the study. If additional treatment is added prior to the 12-month follow-up visit, a protocol deviation is required. Throughout the study, a voiding diary is required prior to starting any OAB medication or additional advanced therapies to confirm the patient is a non-responder (< 50% improvement from baseline) to tibial neuromodulation therapy. If additional OAB treatment is added without confirmation of non-response to the therapy based on a voiding diary, a deviation is required.

The following information should be collected at the enrollment/baseline visit:

- Informed Consent details
- Subject demographics, height, weight, ethnicity, & race data
- Diagnoses and medical history
- Pregnancy test (required for women of childbearing potential)
- OAB Treatment History
- Voiding diary
- MESA/OAB-q/[redacted]/UPS Questionnaires
- Eligibility Confirmation (required prior to device implant; once all eligibility information is available)
- Any adverse events

Device Implant Visit:
It is recommended that the device is implanted within 30 days of the subject's enrollment in the study. The implant procedure may occur in a clinic, ambulatory surgical center, or hospital.

A sterile surgical marker and ruler will be provided for use during the implant procedure. The device will be implanted in accordance with the Medtronic TNM Clinician Guide.

During the procedure, amplitude should be increased using 20 hertz, 200 microsecond pulse width stimulation and Therapy Schedule #1 (30 minutes of stimulation every other day) until sensory and motor thresholds are reached:

- Sensory threshold: defined as the lowest amplitude where the subject first perceives sensation in the sole of the foot, heel, or toes during stimulation.
- Motor threshold: defined as the lowest amplitude to elicit movement of the foot or toes.

If the sensory and/or motor thresholds are not observed within a tolerable setting for the subject, this will be documented. The device may also be repositioned, if deemed necessary by the Investigator.

Following Device Implant:
Following device implant, an impedance check should be completed. Perform threshold testing by increasing amplitude using 20 hertz, 200 microsecond pulse width stimulation and Therapy Schedule #1 (30 minutes of stimulation every other day) until the following thresholds are reached without compression, with the foot in a relaxed position:

- Sensory threshold: defined as the lowest amplitude where the subject first perceives sensation in the sole of the foot, heel, or toes during stimulation.
- Motor threshold: defined as the lowest amplitude to elicit movement of the foot or toes.
- Highest acceptable amplitude: defined as the highest amplitude following a sensory and/or motor response where the stimulation level is still comfortable.

An ultrasound of the tibial nerve may be completed following the device implant procedure.

A compression sock will be applied, an impedance check will be completed, and the neurostimulator amplitude will be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed. If no motor or sensory response is observed, the investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If no motor or sensory response is observed, the investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

Programming and device data (e.g., Session Report) will be collected in accordance with device instructions and documented on the programming worksheet at the time of the implant procedure. Use of the handset (TNM My Therapy app) and communicator will be reviewed with the subject. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit. The subject will receive 30 minutes of stimulation every other day.

All subjects must wear a compression sock for at least 72 hours and possibly up to two weeks after device implant. The duration of compression will be determined by the Investigator using the study-specific recommendations which are based on pocket size, motor and/or sensory thresholds and pertinent medical history of the subject.

The subject will be provided post-implant care instructions within the informed consent form and Post-Implant Subject Instructions (outlined below) to explain how to manage their implanted device. Post-implant care and activity guidelines identified below should be reviewed with subjects prior to the end of the visit.

Post-implant Care

To aid healing and minimize the chance for device movement, provide the following guidance to subjects.

Following the implant procedure:

- Subjects should be instructed to consult study physician if they notice any unusual symptoms or signs (for example, swelling, or redness at the incision site).
- Cold packs may be used after implant for comfort. A barrier (for example a towel) may be placed between the cold pack and the compression sock to keep the sock dry.

- Subjects may experience soreness or pain when with walking or flexing the ankle while healing from the implant procedure.
- Subjects must be instructed to wash hands before handling the bandage or compression sock and avoid touching the implant site.

For the first 3 days:

- The implant site must be kept covered with the bandage applied during procedure for 72 hours or based on the physician's instructions.
- The implant site must be kept dry for 72 hours. Shower bags can be used to help keep the site dry.
- A compression sock must be used for at least 72 hours, or longer if the physician advises the subject to. This will aid in healing around the device. If the subject is advised to use a compression sock for longer than 72 hours, a shower bag should be used while showering to keep the site dry for the duration that the subject wears the compression sock.
- If the compression sock gets wet, replace with a dry compression sock.

For the first 2 weeks:

- Avoid scrubbing the incision site for 2 weeks or until the wound is closed.

For the first 4 weeks:

- Avoid soaking the incision site (e.g., taking a bath, swimming, using a hot tub) for 4 weeks.
- Avoid strenuous, long duration and high impact activities; for example: aerobics, cycling, running, swimming, long walks, recreational sports, and gym exercises involving the foot, leg, or ankle (elliptical, leg press, etc.) during the 4 weeks while the device is encapsulating. Subjects should limit physical activities to short duration (30 minutes) and low intensity activities during this time.
- Wear flat shoes (no heels) for 4 weeks. Avoid wearing shoes or boots that rub or are tight around the implanted device.

In addition to post-implant care, the following guidance will be provided to study subjects:

- Subjects should turn on stimulation for the next therapy session following the instructions (Therapy Schedule #1; stimulation for 30 minutes every other day) during the visit or at a time convenient for them within 24 hours of the visit.
- During recovery it is recommended that subjects receive therapy with their leg is in a relaxed position, or in the position where sensory testing was assessed during the post implant testing.
- Subjects may feel sensation or notice a motor response during their therapy sessions.
- Any changes to the stimulation should be made within the first five minutes of each therapy session.

- Subjects will be reminded they are prohibited from taking overactive bladder pharmacotherapy until after the 12-month follow-up visit.

Any adverse events and/or device deficiencies will be collected.

The following information should be collected at the implant visit:

- Procedure details
- System information (e.g., model number, serial/lot number, etc.)
- Motor and sensory threshold data
- Programming and device data
- Ultrasound images (if applicable)
- Post-operative care (e.g., infection control, compression sock duration, etc.)
- Any adverse events and/or device deficiencies
- Any study deviations

7-Day Post-Procedure Follow-up Visit:
The compression sock will be removed if it was still recommended for the subject.

Following this, the subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold without compression will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude, and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

Continued compression until two weeks following the implant will be determined using the study-specific recommendations based on pocket size, motor/sensory thresholds, and pertinent medical history of the subject.

If continued compression is required, comfort of the programmed amplitude will be verified while the subject is in expected positions with the compression sock worn by the subject.

Subjects will be trained on neurostimulator recharging which will be recommended weekly starting at the 7-day post-procedure follow-up visit. If the wound is not healed, a sterile barrier provided by the institution should be placed between the wound and recharger. The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours of their visit.

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

The following guidance will be provided to study subjects:

- If the subject decides to turn therapy on after the visit, turn on stimulation for the next therapy session following the instructions:
    - It is recommended that the subject will receive 30 minutes of stimulation (Therapy Schedule #1) every other day. The therapy schedule may be adjusted based on symptom control and/or patient preference.
- During recovery it is recommended that subjects receive therapy with their leg is in a relaxed position, or in the position where sensory testing was done during post implant testing.
- Subjects may feel sensation or notice a motor response during their therapy sessions.
- Any changes to the stimulation should be made within the first five minutes of each therapy session.
- Following this visit it is recommended that the device is recharged weekly. If the wound is not healed, subject should be instructed to place a sterile barrier between the wound and recharger.

Any adverse events and/or device deficiencies will be collected.

1-Month and 2-Month Follow-up Visits:
The 3-day urinary voiding diary should be started approximately one week prior to the study visit. If the diary is not able to be completed prior to the visit, it will be completed immediately following the study visit.

The subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or

sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours after their visit.

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

The following guidance will be provided to study subjects:

- You may return to normal activity levels
- If the subject decides to turn therapy on after the visit, turn on stimulation for the next therapy session following the instructions:
    - It is recommended that the subject will receive 30 minutes of stimulation (Therapy Schedule #1) every other day. The therapy schedule may be adjusted based on symptom control and/or patient preference.
- If the subject is comfortable with the stimulation sensation, they can resume normal activities during their therapy sessions.
- Subjects may feel sensation or notice a motor response during their therapy sessions.
- Any changes to the stimulation should be made within the first five minutes of each therapy session.
- It is recommended that the device is recharged weekly.

Any adverse events and/or device deficiencies will be collected.

3-Month Follow-up Visit:

The 3-day urinary voiding diary should be started approximately one week prior to the study visit. If the diary is not able to be completed prior to the visit, it will be completed immediately following the study visit. The Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted], [redacted] Urgency Perception Scale (UPS) [redacted] will be collected.

The subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours after their visit.

Programming and device data (e.g., Session Report, Usage Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

The following guidance will be provided to study subjects:

- If the subject decides to turn therapy on after the visit, turn on stimulation for the next therapy session following the instructions:
    - It is recommended that the subject will receive 30 minutes of stimulation (Therapy Schedule #1) every other day. The therapy schedule may be adjusted based on symptom control and/or patient preference.
- If the subject is comfortable with the stimulation sensation, they can resume normal activities during their therapy sessions.
- Subjects may feel sensation or notice a motor response during their therapy sessions.
- Any changes to the stimulation should be made within the first five minutes of each therapy session.
- It is recommended that the device is recharged weekly.

Any adverse events and/or device deficiencies will be collected.

6-Month Follow-up Visit:
The 3-day urinary voiding diary should be started approximately one week prior to the study visit. If the diary is not able to be completed prior to the visit, it will be completed immediately following the study visit. The Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] Urgency Perception Scale (UPS) [redacted] will be collected.

The subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

Following the 6-month follow-up visit, the programmed therapy session may include any of the following based on symptom control and/or patient preference: remaining on 30 minutes stimulation every other day (Therapy Schedule #1), stimulation for 30 minutes every day (Therapy Schedule #2), stimulation for 30 minutes every third day (Therapy Schedule #3), stimulation for 60 minutes every other day (Therapy Schedule #4), stimulation for 30 minutes once per week (Therapy Schedule #5), stimulation for 60 minutes every day (Therapy Schedule #6), stimulation for 4 hours every day (Therapy Schedule #7), stimulation for 8 hours every day (Therapy Schedule #8) or custom stimulation (Therapy Schedule #9). The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours after their visit.

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

The following guidance will be provided to study subjects:

- If the subject decides to turn therapy on after the visit, turn on stimulation for the next therapy session within 24 hours after their visit.

- If the subject is comfortable with the stimulation sensation, they can resume normal activities during their therapy sessions.
- Subjects may feel sensation or notice a motor response during their therapy sessions.
- Any changes to the stimulation should be made within the first five minutes of each therapy session.
- It is recommended for the device to be recharged weekly. More frequent recharging may be required based on the selected program. A different program may be considered if recharge durations are too long.

Any adverse events and/or device deficiencies will be collected.

12-Month and 24-Month Follow-up Visits:
The 3-day urinary voiding diary should be started approximately one week prior to the study visit. If the diary is not able to be completed prior to the visit, it will be completed immediately following the study visit. The Overactive Bladder Quality of Life Questionnaire (OAB-q), [redacted] Urgency Perception Scale (UPS) [redacted] will be collected.

The subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator or delegated personnel should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator or delegated personnel should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

During annual visits, the programmed therapy session may include any of the following: 30 minutes stimulation every other day (Therapy Schedule #1), stimulation for 30 minutes every day (Therapy Schedule #2), stimulation for 30 minutes every third day (Therapy Schedule #3), stimulation for 60 minutes every other day (Therapy Schedule #4), stimulation for 30 minutes once per week (Therapy Schedule #5), stimulation for 60 minutes every day (Therapy Schedule #6), stimulation for 4 hours every day (Therapy Schedule #7), stimulation for 8 hours every day (Therapy Schedule #8) or custom stimulation (Therapy Schedule #9). The investigator or delegated personnel may initiate the therapy at this time. If the subject would prefer a different time to start therapy, the subject will be instructed to

initiate their therapy schedule for their therapy session at a time convenient for them within approximately 24 hours after their visit.

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

At the completion of the 24-month follow-up visit (along with the final voiding diary), the subject will be exited from the study. All programming completed at the visit will be up to the investigator's discretion. Any adverse events and/or device deficiencies will be collected.

The TNM neurostimulator may remain implanted following study exit; the decision whether to explant will be per physician and patient discretion. [redacted] Subjects should be given instructions to contact the study doctor or research coordinator if any component of the TNM system is lost, damaged or malfunctions following completion in the study.

Follow-up Visit Data Collection:
Table 4 outlines requirements for each follow-up visit, including unscheduled visits. Based on the visit requirements, the following data points may be collected.

For logistical and public safety issues (e.g., global pandemic), remote collection of follow-up data will be allowed along with remote device access/programming with enabling software (as applicable). If available during the study, Medtronic may use remote support to access programming data.

In addition to collection of adverse events, device deficiencies, OAB medications, protocol deviations and study exit data, data points are described, but not limited to, the following sections.

- Post-operative care (e.g., wound healing, compression use, activity level assessment questions, etc.)
- Voiding diary
- Questionnaires: OAB-q, [redacted] UPS, [redacted]
- Motor and sensory threshold data
- Programming/device/recharge data

Periodic Progress Check-in Calls:
Following the device implant, it is recommended that site personnel contact study subjects within approximately 48 hours after each study visit and approximately one week prior to each upcoming visit. In addition to these calls, monthly check-in calls will be recommended to start following the 3-month follow-up visit. The intent of the call will be to verify the handset "stimulation on" slide button is on,

provide recharge reminders for the handset, communicator and wireless recharger and provide any reminders for upcoming visits (e.g., diary completion).

Any adverse events and/or device deficiencies will be collected.

Unscheduled Visits

An unscheduled visit may be needed for any device-related reason. During the visit, any OAB medication changes, adverse events and/or device deficiencies will be collected. A 3-day urinary voiding diary may be completed.

If any programming changes are made during the visit, the subject will have an impedance check and sensory/motor threshold testing done with their foot in the same relaxed position as the time of implant. The subject's sensory and motor threshold will be identified using 20 hertz, 200 microseconds pulse width stimulation and titrating up amplitude until the sensory threshold, highest acceptable amplitude and motor threshold are confirmed. The neurostimulator amplitude should be set to the highest acceptable amplitude. If highest acceptable amplitude is unable to be found, it is recommended to set the amplitude to two times the motor or sensory threshold, whichever is lower. The comfort of the programmed amplitude will be verified while the subject is in expected positions and adjusted for comfort, if needed.

If the sensory threshold, highest acceptable amplitude and/or motor threshold are not observed, this will be documented. The Investigator (or delegated personnel) should try repeating the motor and sensory assessment with the foot in a different position. If the motor and/or sensory response is still not observed, the Investigator (or delegated personnel) should set neurostimulator amplitude to 3 mA unless an alternative amplitude level is recommended by the Sponsor.

The subject should have the appropriate program set based on study requirements.

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with device instructions prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

System Modification:

If the device needs to be explanted or replaced at any time after the implant procedure, a System modification procedure will be scheduled. System modifications will include device replacements and explants. Subjects will be encouraged to complete a voiding diary prior to any system modification procedure. Prior to neurostimulator removal and/or after a new neurostimulator is placed, an ultrasound image to assess measurements related to the tibial nerve may be completed.

During the visit, any relevant medication changes, procedural data, adverse events and/or device deficiencies will be collected. Sensory and/or motor thresholds should be assessed (when possible) prior to the implant procedure. Device programming (e.g., Usage Report, Session Report) will be collected in

accordance with device instructions and documented on the programming worksheet prior to the explant (when possible) and at the time of any new implant procedures. The therapy schedule will be set based on the timeframe in the study when the system modification was completed, and the therapy session may be initiated during the visit or within 24 hours.

Post-operative instructions should be followed for any replacement neurostimulators. Following a system modification, the subject should complete a 7-day post procedure visit. In addition, the subject will receive a 1-month post-procedure call in order to assess compression, wound healing, activity levels, etc. The subject will then continue their follow-up schedule based on the initial device implant date.

Post-operative instructions should be followed for any device explant which is not associated with a device replacement procedure. The subject will receive a 1-month phone call in order to confirm resolution of any ongoing adverse events. It is recommended to follow the subject until all ongoing related AEs are resolved or unresolved with no further actions planned.

No replacement neurostimulators will be provided after participation in the study has ended.

10.2 Data Collection

Data collection and study procedures are outlined in Table 4: Data collection and study procedure requirements at subject visits.

Table 4: Data collection and study procedure requirements at subject visits

Study Procedure	Baseline	Implant	7-Day	1-Month	2-Month	3-Month	6-Month	12-Month	24-Month	Unscheduled	System Modification[a]
Informed Consent[b]	X										
Medical History	X										
Eligibility Assessment	X										
MESA Questionnaire	X										
Pregnancy Test[c]	X										
Neurostimulator Implant		X									X[d]
Ultrasound Images[d]		X									X
Sensory/Motor Thresholds		X	X	X	X	X	X	X	X	X[d]	X
Voiding Diary	X			X	X	X	X	X	X	X[d]	X[d]
OAB-q/ [redacted] /UPS Questionnaires	X					X	X	X	X		
[redacted]											
Programming/Device Data (e.g., Session Reports, Usage Reports)		X	X	X	X	X	X	X	X	X[d]	X
Periodic Check-in Calls[f]		X	X	X	X	X	X	X	X		
Neurostimulator Explant											X[d]
OAB Medication Usage, Study Deviations, Adverse Events, and Deaths	----------As they occur----------										
Device Deficiencies		----------As they occur----------									

[a] 7-day post-procedure visit and 1-month phone call will be completed following any system modification/explant procedures

[b] Informed Consent must be completed prior to any study-related procedures including the Baseline voiding diary.

[c] Females of Child-bearing potential only

[d] If applicable

[redacted]

[f] Calls are recommended approximately 1 week prior to study visits, within 48 hours after each study visit and monthly. Monthly calls are recommended following the 3-month follow-up visit.

10.3 Scheduled Follow-up Visit Windows

Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied with a reported study deviation. Follow-up visit windows are listed in Table 5 and are based on days post-implant.

Table 5: Study Follow-up Visit Windows

Study Follow-up Visit	Window (Calculated calendar days post-implant; implant is Day 0)		
	Window Start (days post-implant)	Target (days post-implant)	Window End (days post-implant)
7-Day Post-Procedure Follow-up Visit	4 days	7 days	10 days
1-Month Follow-up Visit	20 days	30 days	40 days
2-Month Follow-up Visit	46 days	60 days	74 days
3-Month Follow-up Visit	76 days	90 days	104 days
6-Month Follow-up Visit	150 days	180 days	210 days
12-Month Follow-up Visit	330 days	360 days	390 days
24-Month Follow-up Visit	660 days	720 days	780 days

10.4 Subject Screening

Subjects may be recruited through the investigator's practice, referring physicians, and advertisements in the public. Potential subjects may be identified through chart reviews or as new or existing patients attending clinic visits. 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 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 available to track 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 (Subject Identification & Enrollment Log).

10.5 Prior and Concomitant Medications/Therapies

Restrictions related to use of OAB treatments prior to enrollment in the study is outlined in the study-specific exclusion criteria. Subjects will be prohibited from taking overactive bladder medications and starting any additional advanced therapies for OAB during the first 12 months of their study participation. If the subject is consented while taking overactive bladder medications, they must have a washout of 2 weeks prior to starting the baseline voiding diary and the baseline Overactive Bladder Quality of Life Questionnaire (OAB-q). Any overactive bladder medications will be captured on a study-specific medication log, and any new advanced therapies for OAB will be captured within the follow-up visit. If additional treatment is added prior to the 12-month follow-up visit, a protocol deviation is required. Throughout the study, a voiding diary is required prior to starting any OAB medication or advanced therapies to confirm the patient is a non-responder (< 50% improvement from baseline) to tibial neuromodulation therapy. If additional treatment is added without confirmation of non-response to the therapy documented on a voiding diary, a deviation is required.

10.6 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form and an Authorization to Use and Disclose Personal Health Information/Research Authorization as required by law that has been approved by the study site's IRB and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the IC and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be approved by the IRB. The document(s) must be controlled (i.e., versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject,

as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the IC Form and Authorization to Use and Disclose Personal Health Information/Research Authorization must be given to the subject in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the IC must be signed and personally dated by the subject and investigator or authorized designee, as required by the IC, and ensured by the principal investigator or his/her authorized designee. The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

A copy of the IC and the Authorization to Use and Disclose Personal Health Information/Research Authorization, signed and dated as required by law, must be provided to the subject.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

The date the subject signed the IC and Authorization to Use and Disclose Personal Health Information/Research Authorization, as required by law, must be documented in the subject's medical records. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur. All subjects who sign the IC will be considered enrolled for the study.

For logistical and public safety issues (e.g., global pandemic), remote consenting and collection of baseline data will be allowed.

The original of the signed IC must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC and Authorization to Use and Disclose Personal Health Information/Research Authorization as required by law must be available for monitoring and auditing. Any Medtronic Field personnel supporting the implant procedure must be able to review the subject's signed and dated IC and verify its completeness prior to proceeding with the implant/programming data download. In the event the Medtronic Field personnel identifies the IC as being incomplete, the implant procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Consistent with the DoH, vulnerable adults (i.e., those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g., Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. If the IC is signed by an individual other than the subject, the monitor may discuss whether the Investigator believes the subject meets the definition of a vulnerable adult. This protocol defines vulnerable adult as those subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response. For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving IC. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

10.7 Device Programming

Subjects are recommended to be set to Therapy Schedule #1 (30 minutes of stimulation every other day) until the 6-month follow-up visit. Following the 6-month follow-up visit, any of the 9 preset Therapy Schedules may be set.

For visits requiring the collection of programming and device data (e.g., Session Report, Usage Report) starting at the first visit following the device implant, data must be either transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

10.8 Device Explants

If the device is required to be explanted, a system modification visit will be completed. If the subject has the device explanted and a replacement is not anticipated to be implanted, the subject will complete a 1-month phone call. Following the call, the subject will be exited from the study after all related AEs have been resolved or remain unresolved based on the Investigator's determination with no further action planned.

It is recommended that all explanted devices be returned to Medtronic for analysis when permissible by local laws and regulations. See Section 7 for final product disposition details.

In the event that a subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via eCRF as separate system modifications.

10.9 Assessment of Efficacy

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.

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 with diary details collected (such as date, time, type of episode, urgency using the IUSS scale[17] nocturia, etc.) as part of the baseline procedures by appropriately trained, qualified and delegated site personnel. The urinary voiding diaries will be completed for 3 days prior to each subsequent follow-up visit starting at the 1-month follow-up visit (or immediately following if not completed prior). Every effort should be made to remind subjects of the importance of real-time diary completion.

10.10 Assessment of Quality of Life

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 into the EDC by site personnel.

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)[18]. The questionnaire used in the current study includes a 4-week recall for symptom assessment. The questionnaire includes an HRQL Total score (comprised of the 4 domains: coping, concern, sleep, and social) and a symptom bother score.

[redacted]

[redacted]

[redacted]

Urgency Perception Scale (UPS)

The Urgency Perception Scale (UPS) is a single item questionnaire measure of perceived urinary urgency with three response options[22,23].

10.11 Assessment of Safety

All adverse events and device deficiencies (see Section 12) will be collected throughout the study once the informed consent form is signed until the subject is exited from the study.

10.12 Recording Data

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, ultrasound images, subject files, device data and records kept at other departments involved in the study).

In general, eCRFs (or paper copies) may not serve as source documents, unless specified below. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

The CRF may be considered source for the following data collection elements:

- Enrollment Notification: Study site assigned subject identifier
- Baseline: Administrative information
- Device Accountability eCRF: All device accountability data points

- AE eCRF: Date study site became aware of event, Relatedness of adverse event, System modification information, Common Terminology Criteria for Adverse Events Classification
- DD eCRF: Date study site became aware of event
- Deviations: Reason for deviation

Electronic Data Capture (EDC)

The Electronic system which is 21CFR§11 Part E compliant controls user access and ensures data integrity. This system is a fully validated system. The EDC 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. The 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.

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.

Programming and Device Data

Programming and device data (e.g., Usage Report, Session Report) will be collected in accordance with instructions provided prior to the subject leaving the visit and transferred to Medtronic using the application on the handset and/or collected on the programming worksheet provided.

Urinary Voiding Diaries

Symptom data for this study will be collected using paper voiding diaries.

The paper voiding diary collects details associated with symptoms for each episode. Diaries are to be completed only by the subject. The data will be entered to the EDC database by center personnel. Center personnel may not make entries to the diaries or questionnaires except for data fields confirmed by the subject as documented within source documentation.

10.13 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP.

Prior approval is not required when a deviation is necessary to protect the safety, rights, or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on a single form in the database.

In the event the deviation involves a failure to obtain a subject's consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or Regulatory Authority requirements. Refer to Table 11: Investigator reports applicable per Medtronic requirements for deviation reporting requirements and timeframes for reporting to Medtronic and/or FDA.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

Examples of study deviations include but are not limited to:

- Failure to obtain proper IC
- Failure to collect required study data (e.g., required study diary)
- Inclusion/exclusion criteria not met

10.14 Subject Exit, 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 24-month follow-up visit, unless withdrawn from the study. Withdrawn or exited subjects will be followed by the Investigator (if still implanted with the study

device) or any physician in accordance with standard of care if the subject has been explanted and is seeking other treatments for OAB.

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. When subjects are lost to follow-up the investigator will make efforts to confirm the vital status of the subject. 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 subjects are lost to follow-up the investigator will make efforts to confirm the vital status/health status of the subject as described in the informed consent

When a subject is withdrawn (exited) 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).

If the subject has the device explanted and a replacement is not implanted, the subject must be exited from the study after all related AEs have resolved. Withdrawn subjects will not be replaced. All components of the investigational system should be returned unless instructed by Medtronic to dispose of product at the institution.

Once a subject completes participation in the study, the subject will be given guidelines for continued therapy use. Any device, procedure and/or therapy related adverse events and all product complaints should continue to be reported until the product is explanted.

10.14.1 Study Exit

A Study Exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing related AEs are resolved or unresolved with no further actions planned. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject was not implanted with an investigational device
- Subject did not provide consent or data use protection authorization
- Subject chose to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deemed withdrawal necessary (e.g., medically justified, failure of subject to maintain adequate study compliance)
- Device explant with no planned replacement.

The following information should be collected at study exit:

- Date of exit
- Reason for exit

10.14.2 Study Completed

At the completion of the 24-month follow-up visit, subjects will be exited from the study. The 24-month follow-up visit and exit visit should be combined, and both a 24-month follow-up visit eCRF and a Study Exit eCRF need to be completed.

11. Risks and Benefits

11.1 Potential Risks

The Clinical Study Risk Management process for the TITAN 2 Study is being performed in accordance with the Code of Federal Regulations for Investigational Device Exemptions (IDE) (21 CFR 812), FDA guidance, and elements of ISO 14971 applicable to clinical research studies to ensure that the level of risk is acceptable prior to starting the study.

The Medtronic TNM Clinician Guide and MRI Guidelines for the TNM Neurostimulator and associated TNM system labeling include system contraindications, precautions, warnings, adverse events, directions for use and other system specific details. In addition to the risks normally associated with a procedure, the following adverse events may occur with the use of an implantable neurostimulation system for tibial neuromodulation. Certain adverse events may necessitate surgical intervention.

Risks (potential adverse events) related to the tibial neurostimulator implant or explant procedure:

- Implant site pain
- Infection

- Reaction to local anesthetic (e.g., redness, irritation at the injection site)
- Wound complications (e.g., swelling, hematoma, bruising, bleeding, seroma)

Risks (potential adverse events) after implantation of the tibial neurostimulator:

- Adverse change in bowel and/or urinary function
- Allergic or immune system response to the implanted materials
- Device site pain
- Infection
- Neurostimulator migration or erosion
- Uncomfortable stimulation sensations

There may be technical device problems with the investigational system which could impact therapy delivery.

There is a possibility of risks to an unborn child. These risks are unknown. Women who are pregnant or expect to become pregnant during the course of the study are excluded from participating.

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.

11.2 General Study Risk/Inconveniences

Subjects may find completing the urinary voiding diary and questionnaire embarrassing and/or an inconvenience.

As with all clinical research, there may be additional risks related to this study that are not yet known.

11.3 Risk Minimization

The potential risks associated with the TNM system and tibial neuromodulation were identified and have been successfully mitigated which include mitigations of selecting qualified investigators, training study personnel on the CIP and providing adequate instructions and labeling.

In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the TNM device. Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the TNM system.

The subject will be informed of any potential study risks.

After implantation, subjects in the TITAN 2 Pivotal study will be followed at regular intervals to monitor the condition of the implanted device.

The Clinical Events Committee and Sponsor will review all related and serious adverse events and/or implantation at any time, if necessary, to protect the safety and well-being of subjects. The study will pause enrollment and implantation after 7 study subjects experience device migration that results in a device explant. This criterion corresponds to a rate of 6% (7/121) of the total planned implanted subjects and ensures that the final 90% confidence interval lower bound (2.7%) for the observed rate exceeds the previously reported rate of adverse events related to migration that led to device explant (2.2%)[14].

Due to lack of reported data regarding adverse events related to erosion in this therapy space, a similar pausing criterion will also be applied for erosion that results in a device explant. That is, the study will pause enrollment and implantation after 7 study subjects experience device erosion that results in a device explant.

Should enrollment and/or implantation pause due to either of these rules (for device migration or erosion), the FDA will be notified. The study will not continue implanting until approval is obtained from the FDA.

11.4 Potential Benefits

The TNM system may offer no medical benefit. The potential benefits of having the TNM system may include an improvement in overactive bladder symptoms. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies), future clinical studies, and/or product labeling.

11.5 Risk-Benefit Rationale

Residual risks of the TNM system have been characterized as acceptable per Medtronic clinical procedure for risk management. No further risk mitigation is required at this time. Medtronic will continue to evaluate the risk/benefit profile, safety, and performance of the product as data becomes available.

The following measures will also be taken to minimize risk to participants as part of this clinical investigation plan:

1. Physicians and staff will receive appropriate training prior to using the study devices. Training will include instruction on the implant and explant procedure, TNM system and protocol requirements
2. Instructions are provided with the TNM device and study aids to ensure consistent use of the device within pre-tested parameters.
3. Subjects will be closely monitored by appropriately trained personnel during the procedure and at regularly scheduled intervals for the duration of the study where their comfort, any potential adverse events and satisfaction will be assessed.
4. Physicians will employ usual and customary clinical technique (e.g., sterile technique during implant use and aseptic wound care procedures).

5. Stimulation will be set in clinic with feedback from the study subject
6. All subjects will have the ability to turn off or adjust stimulation at any time using the provided handset and communicator.

In addition to the potential benefits to the subjects of the study in terms of an improvement in overactive bladder symptoms, the benefit of the study also lies in the knowledge to be gained from the TITAN 2 results and the potential to improve future TNM therapies. Based on the risk acceptance criteria for the TITAN 2 study outlined in the risk management documentation, the study-specific residual risk is determined to be acceptable given the expected benefits.

11.6 Risk Determination

The TNM system used in the TITAN 2 Pivotal study meets the definition for a significant risk (SR) investigational device exemption (IDE) study in 21CFR§812.3(m), because it is an implanted device and presents a potential for serious risk to the health, safety, or welfare of a subject.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

All adverse events 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 14155:2020 definitions. The term “investigational device” refers to any device used in the study including market released devices.

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 TNM system
- Procedure Related: An adverse event that occurs due to any procedure related to the implantation or explant of the TNM system. The procedure is defined as the neurostimulator implant and/or explant procedures
- Study Aids Related: An adverse event that results from the presence or performance (intended or otherwise) of any study aids related to the TNM system
- 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. Reporting of adverse events to Medtronic will occur on an AE eCRF. Each event must be reported separately. For AEs that require immediate reporting (see Table 10: Reporting Requirements), initial reporting may be done by phone or on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.

Subject deaths are also required to be reported in accordance with Table 10: Reporting Requirements.

All non-subject AEs (users or other persons as defined in Table 6) will be collected throughout the study duration.

Special considerations for adverse events and device deficiencies reporting:

- Normal expected complaints or symptoms reported during or following the procedure which are related to ordinary procedure or post-procedure care will be reported as adverse events; however, they will not be analyzed as device, procedure, therapy, or study aid-related adverse events unless there is a clinically significant change in severity or duration of symptoms, or the event requires clinical intervention that is different from ordinary procedure or post-procedure care.
  - Includes headache, incisional pain, nausea, vomiting, low grade fever, oozing at dressing, dizziness, irritability, sleepiness, nervousness, insomnia, constipation, confusion, skin irritation/redness, and similar events.
  - The Clinical Events Committee will review these events to confirm agreement with the decision made by the study investigator.
- Any non-clinically significant stimulation-related effects that occur during the implant procedure, programming, and follow-up period will not be considered a reportable adverse event.
- Worsening of OAB symptoms (including questionnaire outcomes) will be collected as part of the efficacy objectives and will not be considered a reportable adverse event.
- Device movement should be assessed and reported as an adverse event if there is clinically significant pain, loss of nerve capture resulting in loss of efficacy, or device explant
- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.
- It is recommended that additional diagnostic information be collected to evaluate reported adverse events, such as suspected infections. It is recommended that cultures are obtained prior to antibiotic treatment for any suspected infections with discharge or that result in device explant procedures. Additional diagnostic information should be reported on the Adverse Event eCRF.

12.2 Device Deficiency

The Device Deficiency (DD) definition is provided in Table 6: Adverse Event and Device Deficiency Definitions. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 10: Reporting Requirements).

12.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD eCRF. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to their completion in the study, it is recommended to continue following the subject until all unresolved related AEs, are resolved or unresolved with no further actions planned

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4 Definitions/Classifications

Where the definition indicates “device”, it refers to any investigational device or system component used in the study. Table 6: Adverse Event and Device Deficiency Definitions contains adverse event and device deficiency definitions.

Table 6: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE) (ISO 14155:2020, 3.2)	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 and whether anticipated or unanticipated 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 the use of investigational medical devices or comparators
Adverse Device Effect (ADE) (ISO 14155:2020, 3.1)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs 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. NOTE 3: The includes 'comparator' if the comparator is a medical device. STUDY SPECIFIC NOTE: These are considered device related, therapy related, study aid related and/or procedure related.
Device Deficiency (DD) (ISO 14155:2020, 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Seriousness	
Serious Adverse Event (SAE) (ISO 14155:2020, 3.45)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. STUDY SPECIFIC NOTE: For this study, all adverse events will be collected; however, adverse events related to infections and neurostimulator explants will be considered non-serious unless the investigator deems that clinical sequala is present which meets the seriousness definition outlined in the CIP.
Serious Adverse Device Effect (SADE) (ISO 14155:2020, 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3(s))	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2020, 3.51)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.
Serious Health Threat (ISO 14155:2020, 3.46)	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Table 7: Adverse Event Relatedness

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.

Relatedness	
Term	**Definition**
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 where 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 be 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 might not be diagnosed with the correct disease or condition.

Table 8: Common Terminology Criteria for Adverse Events (CTCAE)[24]

Grades	Definition
Grade I	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to an AE

*Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.5 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

12.5.1 Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) for Regulatory Activities, to assign a MedDRA term for each AE/DD based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 10: Reporting Requirements for a list of required investigator and Medtronic reporting

requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

Section 11.1 contains a list of AEs related to the use of an implantable neurostimulation system for tibial neuromodulation. For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately.

AEs, including Subject Deaths, will be classified according to the standard definitions as outlined below:

Table 9: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness*	Investigator	Device, Therapy, Procedure, Study Aid
	Sponsor	Device, Therapy, Procedure, Study Aid
	Clinical Events Committee	Device, Therapy, Procedure, Study Aid
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Severity	Investigator	Common Terminology Criteria for Adverse Events Classification Scale (See Table 8: Common Terminology Criteria for Adverse Events (CTCAE))

*Review of reported adverse events will be completed to determine if the event is a normal expected complaint or symptom reported during or following the procedure which are related to ordinary procedure or post-procedure care.

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB.

Table 10: Reporting Requirements

SAEs	
Investigator shall submit to:	
Medtronic	Report to the sponsor, without unjustified delay (recommended within 10 calendar days), all serious adverse events.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
ADEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the effect.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
SADEs	
Investigator shall submit to:	
Medtronic	Immediately (no later than 10 calendar days) after the investigator learns of the event or of new information in relation to an already reported event.
FDA	Submit to FDA per local reporting requirement
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Investigators	Submit per local reporting requirement.

UADE / USADE	
Investigator shall submit to:	
Medtronic	As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
FDA	Submit to FDA per local reporting requirement
IRB	As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
Sponsor shall submit to:	
FDA	As soon as possible, but in no event later than 10 working days after the sponsor first learns of the effect.
IRB	As soon as possible, but in no event later than 10 working days after the sponsor first learns of the effect.
Investigators	Submit per local reporting requirement.
All other reportable AEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit or report as required per local reporting requirements.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.

12.6 Subject Death

All subject deaths must be reported to Medtronic and the IRB 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 eCRFs.

Regulatory reporting of Subject Deaths will be completed in accordance with FDA requirements.

12.7 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse, or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify FDA of events as determined to be reportable based on FDA requirements outlined in 21 CFR 812.150(b).

13. Data Review Committees

13.1 Clinical Events Committee Review

At regular intervals, an independent CEC will conduct a medical review of all reported related and/or serious adverse events for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At least three CEC members must adjudicate, at a minimum, all deaths and serious AEs related to any component of the system under investigation. All other AEs must be adjudicated by at least one physician member of the CEC.

In addition, the CEC will periodically review trending of reported adverse events to make recommendations to the Sponsor whether to continue, modify or stop the study based on pre-specified pausing rules defined in the clinical investigational plan.

The CEC Charter will define the CEC processes for member selection, meeting frequency, roles and responsibilities, procedures, and record keeping.

Medtronic personnel may facilitate and participate in an CEC meeting but will be non-voting members.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to IRBs and regulatory authorities, if required.

13.2 CRO

No CRO(s) will be used in the TITAN 2 Pivotal study.

14. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan that will be approved before data freeze or lock. Any deviation to the pre-specified statistical analyses will be noted in the study report.

14.1 General Aspects of Analysis

The study will be considered successful when the primary objective is met.

For each of the objectives, the available data will be summarized, and missing data will be discussed. The main analysis of the study objectives will be intention-to-treat, meaning that the analysis will use the Full Analysis Set (FAS). The FAS includes all subjects, using the intention-to-treat (ITT) principle, who have an attempted device implant. Additional information on missing data plans are found in section 14.1.2.

Analyses of all data will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables. The primary objective will be tested as described in section 14.4.1. If the primary objective is passed, the secondary objectives will each be tested as described in section 14.5 following the Hochberg multiple testing strategy. All p-values will be reported as 2-sided tests. Additionally, 95% Confidence intervals will be supplied for selected measures.

Safety data will be summarized as the count of events, count of subjects, and percentage of subjects who experienced the event. Subject disposition will be illustrated in a flow diagram. Subject visits will be

tabulated and compliance to the visit schedule and visit windows will be summarized. Attrition will be identified and summarized.

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.4 or higher) will be used to analyze the study results. PASS 2019 sample size calculation software was utilized for determination of sample sizes and associated statistical power calculations.

14.1.1 Analysis Sets

All Enrolled analysis set: Includes subjects who completed the informed consent process.

Full Analysis Set (FAS): Includes subjects with an attempted implant. If all implant procedures are successful, this will be equivalent to the All Implanted Analysis set.

All Implanted Analysis set: Includes subjects who are implanted.

Complete Case analysis sets: Includes subjects who are implanted and provide outcome measures at both baseline and follow-up visits. This set is defined for each outcome measure at each follow-up visit.

The study requires subjects to have UUI to be implanted. UUI subjects are those who have ≥1 urinary urge incontinence episode per day at baseline. For analysis purposes, Urinary Frequency (UF) subjects are those who have ≥10 urinary frequency episodes per day at baseline and all subjects will be considered to have urinary urgency since all eligible subjects have UUI. Some supportive, secondary objective, and additional measure analyses may use different definitions or subsets of the analysis sets listed above (e.g., changed assumptions for those subjects considered to have either UUI or UF).

14.1.2 Handling Missing Data

Primary and secondary objectives will be analyzed using the FAS. The FAS includes all subjects, using the intention-to-treat principle, who have an attempted device implant. All attempts will be made to minimize missing data. For diary-based metrics, missing is defined as any diary which has a total length of less than 48 hours, as defined in section 14.1.5. The OAB-q may be missing if the HRQL Total cannot be calculated; scoring details are found in section 14.5.4. If 5% of the data or fewer are missing for the analysis, no imputation will be used and the data will be analyzed using the Complete Case analysis set[25]. Otherwise, if missing data are observed, imputation will be used for the primary and secondary objectives.

The primary objective imputation will be done using multiple imputation (MI). Predictive mean matching multiple imputation will be used for each variable. First, multiple imputation will be applied to impute missing values in average daily UUI episodes. Unless model errors dictate otherwise, each model will consider Baseline and Month 1, Month 2, Month 3, and Month 6 variables for the UUI episodes variable and demographic variables of age, gender, history of pregnancy, and BMI. The fully conditional specification (FCS) method within SAS (version 9.4 or higher) with 30 repetitions and 100 burn-in

iterations will be used for imputation. No limits will be defined for imputed values. Following imputation, the 6-month outcome data will be converted to the appropriate endpoint (i.e., change from baseline/UUI responder). The estimate and variance of the mean proportion of subjects considered a UUI responder will be determined for each imputation dataset. For the primary objective, the mean and variance for the proportion will be determined using MI analysis methods and the objective will be tested using a Z-test comparing the observed responder rate to the primary objective performance goal of 40%.

For the secondary objectives, the following imputation steps will be taken:

- For secondary objectives related to UUI episodes, the imputation datasets created for the primary objective will be used. For OAB-q HRQL, UF episodes, and urgency, a new set of imputation datasets will be created following the same methods as the primary objective but replacing UUI episodes with OAB-q HRQL, UF episodes, or urgency score.
- After imputation, the normality for the outcome metric will be checked through Shapiro-Wilk test for each imputation dataset. If p-value>0.05 for at least 15 imputed datasets (half of the total), it will be considered that the data are normally distributed. In this case, the mean and standard error of the outcome metric will be calculated within each imputed dataset, and then combined using MI analysis methods. The mean and standard error of the outcome metric will be reported, and the objective will be tested with a t-test.
- If the distribution of outcome metric is non-normal (p-values ≤0.05 in more than 15 of the imputed datasets), MI will not be used. Instead, last observations carried forward (LOCF) will be applied, with the imputed dataset tested using the Wilcoxon signed-rank test.

Sensitivity analyses will be completed for the primary and secondary objectives including subjects who received a TNM implant ("All Implanted Analysis"), using only subjects with outcome data at baseline and follow-up ("Complete Case Analysis"), and using only those complete case subjects who received stimulation ("As Treated Analysis").

[redacted] Comprehensive descriptions of subject accountability and missing data will be provided.

14.1.3 Multiplicity Adjustments

The primary objective is the percentage of subjects considered a UUI responder at 6 months. Four secondary objectives will also be assessed, all of which will be assessed 6 months after implantation of tibial neuromodulation.

To support an indication for OAB, device effectiveness will be demonstrated for the symptoms associated with OAB, including UUI, UF, and urgency. UUI therapy effectiveness will be demonstrated if the primary objective proportion of subjects with UUI response is greater than the performance goal (40%). UF therapy effectiveness will be demonstrated if the secondary UF objective demonstrates an

improvement from baseline to 6 months in number of UF episodes. Urgency therapy effectiveness will be demonstrated if the secondary urgency objective demonstrates an improvement from baseline to 6 months in urinary urgency.

The p-values for the primary and secondary objectives will be calculated according to the methods outlined in their respective analysis sections. The p-values will be reported unadjusted and two-sided; however, declarations of statistical significance will follow the procedures laid out in this section.

The primary objective will be tested separately from the secondary objectives. If the one-sided primary objective p-value is <0.025, then the null hypothesis will be rejected, and the test will be declared statistically significant.

The Hochberg method for the multiplicity adjustment will be used to test the four secondary objective hypotheses, thereby maintaining an overall two-sided type I error rate at 0.05 for these objectives. Each p-value for the four secondary objectives will be calculated. If all p-values are less than 0.05 (two sided), all will be declared significant. If not, the p-values will be ordered from largest to smallest (identified as p1-p4 in this section). If p1 is greater than 0.05, the remaining p-values (p2, p3, p4) will be compared against an alpha of 0.025 (0.05/2). If the three remaining p-values are all less than 0.025, they will all be declared significant. If p2 is greater than 0.025, the remaining p-values (p3, p4) will be compared against an alpha of 0.017 (0.05/3). If p3 and p4 are both less than 0.017, they will both be declared significant. If p3 is greater than 0.017, p4 will be compared against an alpha of 0.013 (0.05/4). If p4 is less than 0.013, it will be declared significant.

The multiplicity adjustment will be performed for evaluations of the secondary endpoints only. No multiplicity adjustment will be performed for supporting, sensitivity, or subset analyses or for evaluations of the additional study measures.

14.1.4 Study Site Pooling

The investigators of this study will conduct the study according to this protocol and use the study-specific eCRFs to collect study data. The study site personnel will be trained prior to the study initiation at each study site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements. Therefore, there is no a priori provision to exclude any study sites from the analysis. The data from all study sites will be pooled for analysis. To reduce the possibility of atypical results from a study site overly influencing the combined results, no more than 24 subjects will be implanted at each study site. The per-study site enrollment cap may be increased upon Sponsor approval.

As an exploratory analysis to assess if treatment effect differs by study center, Freeman and Halton's extension of Fisher's exact test will be conducted using UUI responder as the response variable. This analysis will be based on the Complete Case analysis set for the primary objective. If the p-value approaches statistical significance (defined as ≤0.15), the percentage of subjects who are considered a UUI responder will be presented by site. If center(s) causing the significance are identified, variables

relating to patient characteristics and other factors will be analyzed to try to identify why this center is showing a different treatment effect.

To increase the power of the test for treatment-by-center interaction, all study centers that are too small (fewer than four implanted subjects) to be reliably analyzed alone or to have a noticeable impact on overall study results will be combined into one "virtual" study center. All other study centers with four or more implanted subjects will stand alone in the analysis. If the virtual study center is larger than 30 implanted subjects (~25% of the required sample size), the virtual study center will be split into 2 virtual study centers defined by ordering the study centers alphabetically and splitting the study centers as near the midpoint as possible. In the case that the midpoint is within an individual study center, that study center will be included with the study centers from earlier in the alphabet.

14.1.5 Diary Data Analysis

The primary and several other objectives and additional measures are based on the analysis of voiding diary data. The diary will be collected for 3 days prior to or after each study visit. The site will assign each diary to the corresponding visit in the eCRF. In some cases, the diary might be completed for slightly less or more than 3 days (e.g., for 68 or 75 rather than the expected 72 hours). All diaries which are greater than 48 hours will be used for analysis. For UI, UUI, and UF, the total number of episodes will be determined for each subject's diary collection period at each visit. The actual total length of the diary for each visit will be determined by using the subject-specific diary start and end time reported by the site. The number of episodes will be divided by the total length of the diary for that subject at the visit and reported as a daily (24 hour) rate (i.e., 'per day'). The change will be determined by subtracting the baseline value per day from the follow-up value per day. Percentage change will be determined by dividing the change in episodes per day by the baseline value. Negative values for change and percentage change represent an improvement. Responder rate for UUI is defined as the proportion of TNM subjects experiencing a reduction of 50% or more in daily urinary urge incontinence (UUI) episodes. Responder rate for UF is defined as the proportion of TNM subjects experiencing a reduction of 50% or more in daily urinary frequency (UF) episodes or a return of voiding to <8 voids per day. Responder rate for UI is defined as the proportion of TNM subjects experiencing a reduction of 50% or more in daily urinary incontinence (UI) episodes. Responder rate for urinary urgency (UU) is defined as the proportion of TNM subjects with an improvement of at least 1 point on the UPS. OAB responder rate is defined as the proportion of TNM subjects who are considered either a UUI, UF, or UU responder.

[redacted]

[redacted]

14.2 Analysis Execution

Study progress reports will be submitted annually. Analysis for the purposes of supporting pre-market approval applications will occur once all subjects have completed the 6-month follow-up visit and will include the primary and secondary objectives and detailed safety summaries. Additional measures will be addressed based on available data at time of the pre-market approval application. A final report will be prepared once all data collection has ended and all subjects have completed the 24-month follow-up visit or have been exited. The inferential analysis for the primary and secondary objectives will not be updated for the final report.

14.3 Interim Analysis

No interim analyses are planned for this study.

14.4 Primary Objective

14.4.1 Primary Objective – UUI Responder Rate

To demonstrate that the percentage of subjects who are considered a UUI responder after 6 months of tibial neuromodulation exceeds a performance goal of 40%.

Hypothesis: The percentage of subjects who are considered an UUI responder 6 months after tibial neuromodulation implantation is greater than 40%.

H_0: $p \leq 40\%$

H_A: $p > 40\%$

Where p = the percentage of subjects who are UUI responders

Endpoint Definition and Derivation: A 3-day urinary voiding diary be used to collect bladder symptoms, including UUI episodes. The primary objective endpoint is the proportion of tibial neuromodulation subjects considered a UUI responder at 6 months after device implant. A subject is considered a UUI responder if they meet the UUI responder criteria as defined in the voiding diary analysis section 14.1.5.

Performance Requirements: The null hypothesis will be rejected if the two-sided p-value is less than 0.05.

Rationale for Performance Criteria: The proposed study design includes a primary objective performance goal of 40%. The performance goal defines an active historical control for this study and

was defined to position the outcome between the expected performance for medications and the more complex SNM treatment.

Sample Size Justification: The sample size justification for the primary objective is provided in section 14.7.

Analysis Methods: The analysis for UUI responder rate will be summarized at 6 months after implant. If 5% of the data or fewer are missing for the primary analysis, no imputation will be used and the objective will be tested using a binomial test for the Complete Case analysis set. Otherwise, missing data will be imputed for the Full Analysis Set as specified in section 14.1.2, and the objective will be tested using a Z-test. The two-sided 95% confidence interval will also be provided.

Determination of Subjects/Data for Analysis: The primary objective analysis will include all subjects from the Full Analysis Set (i.e., all implant attempted subjects) as defined in section 14.1.1.

Supportive and Sensitivity Analyses: There are no requirements or expectations for the results of the supporting and sensitivity analyses. They are meant to investigate the robustness of the study results and/or to provide further details on the therapy effects.

Additional supporting analyses to further understand the primary objective will be completed through analyses of the change in UUI (secondary objective) and percentage change in UUI (additional measure).

To assess the robustness of the primary objective results under the influence of missing data, sensitivity and subgroup analyses will be conducted using alternative missing data methods and by including different subsets of subjects. The first sensitivity analysis will be completed including subjects from the Primary Objective Complete Case analysis set. This analysis set will be used for a second sensitivity analysis which will be completed including only subjects who received stimulation ('As treated analysis') at the 6-month follow-up visit. An analysis will also be completed to evaluate UUI responder rate differences between different programs. A tipping point sensitivity analysis will also be completed. A final sensitivity analysis will be conducted on the Primary Objective Complete Case analysis set assigning response failure for all subjects who took OAB medication or received an advanced therapy from implant to the 6-month follow-up visit.

Complete Case analysis set subgroup analyses will be done for the following subject groups: sex, age (divided by median age; divided by age 65), race, and ethnicity. Subjects on the demographic cut point will be added to the adjacent group containing fewer subjects. Any subgroup with less than 10 subjects will not be reported.

As an exploratory analysis to assess if treatment effect differs by study center, a supporting analysis will be completed, as described in 14.1.4. This analysis will test whether the treatment effect is homogeneous between study centers for the UUI responder rate at 6 months.

UUI responder rate will be assessed over time through 24 months as part of the additional measures.

14.5 Secondary Objective(s)

The following secondary objectives have specific hypotheses to be tested. After the primary objective is met, these four secondary objectives will be tested as described in 14.1.3.

14.5.1 Secondary Objective – UUI Change

To demonstrate an improvement from baseline to 6 months in number of UUI episodes in subjects with UUI at baseline

Hypothesis: The change from baseline in UUI episodes is not 0.

H_0: $\mu = 0$

H_A: $\mu \neq 0$

Where μ = the change in UUI episodes

Endpoint Definition and Derivation: A 3-day urinary voiding diary will be used to collect bladder symptoms, including UUI episodes. Calculation of change in UUI is defined in the voiding diary analysis section 14.1.5. A negative change in UUI episodes represents an improvement.

Performance Requirements: The null hypothesis will be rejected if the two-sided p-value is determined to be significant, as described in section 14.1.3.

Sample Size Justification: Data from published studies or studies presented at conferences on TNM outcomes at 3, 6, and 9 months were used as starting points to estimate expected reduction in UUI episodes as well as expected patient-to-patient variability. Assumption on the expected mean difference (-2.0 episodes per day) and standard deviation (3.5 episodes per day) was used to assess statistical power. Presuming a two-sided, one-sample t-test with alphas ranging from 0.013 to 0.05, power is calculated to be no less than 99% for any of the scenarios examined with a sample size of 121 subjects. Additionally, the minimum detectable change in mean episodes was calculated to be as low as -1.0.

Analysis Methods: The analysis for change in UUI will be summarized for baseline, at 6 months after implant, and for the change from baseline. If 5% of the data or fewer are missing for the analysis, no imputation will be used, and the objective will be tested using a paired t-test following the multiple testing strategy described in section 14.1.3. If more than 5% of the data are missing, missing data will be imputed as specified in section 14.1.2. If non-normality of the data is detected via a significant ($p<0.05$) Shapiro-Wilk test, a Wilcoxon signed-rank test will replace the t-test.

Determination of Subjects/Data for Analysis: The change in UUI analysis will include all subjects from the Full Analysis Set (i.e., all implant attempted subjects) as defined in section 14.1.1.

Supportive and Sensitivity Analyses: There are no requirements or expectations for the results of the supporting and sensitivity analyses.

Additional supporting analyses to further understand the UUI secondary objective will be completed through analyses of the percentage change in UUI (additional measure).

To assess the robustness of the objective results under the influence of missing data, sensitivity analyses will be conducted using alternative missing data methods. The first sensitivity analysis will be completed including subjects from the Secondary Objective (UUI Change) Complete Case analysis set. This analysis set will be used for a second sensitivity analysis which will be completed including only subjects who received stimulation ('As treated analysis') at the 6-month follow-up visit. A final complete case sensitivity analysis will be performed comparing the change in UUI episodes to a performance goal of 1 episode/day.

UUI change from baseline will be assessed over time through 24-months as part of the additional measures.

14.5.2 Secondary Objective – UF Change

To demonstrate an improvement from baseline to 6 months in number of UF episodes in subjects with UF at baseline

Hypothesis: The change from baseline in UF episodes is not 0.

H_0: $\mu = 0$

H_A: $\mu \neq 0$

Where μ = the change in UF episodes

Endpoint Definition and Derivation: A 3-day urinary voiding diary will be used to collect bladder symptoms, including UF episodes. UF episodes include all urinary voids. Calculation of change in UF is defined in the voiding diary analysis section 14.1.5. A negative change in UF episodes represents an improvement.

Performance Requirements: The null hypothesis will be rejected if the two-sided p-value is less than 0.05.

Sample Size Justification: Data from published studies on TNM outcomes at 6 months were used as a starting point to estimate expected reduction in UF episodes as well as expected patient-to-patient variability. Assumption on the expected mean difference (-2.0 episodes per day) and standard deviations (3.0 episodes per day) were used to assess statistical power. Presuming a two-sided, one-sample t-test with alphas ranging from 0.013 to 0.05, power is calculated to be no less than 98% for any of the scenarios examined with a sample size of 51 subjects (as only 42% of the total 121 subjects in the study are expected to have UF with 10 episodes per day at baseline). Additionally, the minimum detectable difference in mean daily episodes was calculated to be as low as 1.4.

Rationale for Clinical Relevance: No published data are available defining minimum clinically meaningful improvement for the change in UF episodes. In the absence of published definitions, assessment of effect size can be used to determine the level of effect. As published by Cohen (1988)[27], an effect size of 0.2 indicates a small effect, 0.5 a modest effect, and 0.8 a large effect. A modest effect size would correspond to a change of -1.5 episodes per day. The assumed mean ± standard deviation difference of 2.0 ± 3.0 UF episodes per day (i.e., an effect size = 0.67) for implantable tibial therapy is considered a medium to large effect.

Analysis Methods: The analysis for change in UF will be summarized for baseline, at 6 months after implant, and for the change from baseline. If 5% of the data or fewer are missing for the analysis, no imputation will be used, and the objective will be tested using a paired t-test following the multiple testing strategy described in section 14.1.3. If more than 5% of the data are missing, missing data will be imputed as specified in section 14.1.2. If non-normality of the data is detected via a significant ($p<0.05$) Shapiro-Wilk test, a Wilcoxon signed-rank test will replace the t-test.

Determination of Subjects/Data for Analysis: The change in UF analysis will include all subjects from the Full Analysis Set (i.e., all implant attempted subjects) who have UF as defined in section 14.1.1.

Supportive and Sensitivity Analyses: There are no requirements or expectations for the results of the supporting and sensitivity analyses.

To assess the robustness of the objective results under the influence of missing data, sensitivity analyses will be conducted using alternative missing data methods. The first sensitivity analysis will be completed including subjects from the Secondary Objective (UF Change) Complete Case analysis set. This analysis set will be used for a second sensitivity analysis which will be completed including only subjects who received stimulation ('As treated analysis') at the 6-month follow-up visit. A final complete case sensitivity analysis will be performed comparing the change in UF episodes to a performance goal of 1 episode/day. A Complete Case supporting analysis will be provided assessing the UF change from baseline using different definitions of UF (UF defined as ≥8 and UF defined as ≥12).

UF change from baseline will be assessed over time through 24 months as part of the additional measures.

14.5.3 Secondary Objective – UPS Change

To demonstrate an improvement from baseline to 6 months in urgency using the Urgency Perception Scale (UPS)

Hypothesis: The change from baseline in UPS is not 0.

H_0: $\mu = 0$

H_A: $\mu \neq 0$

Where μ = the change in UPS score

Endpoint Definition and Derivation: The UPS will be used to collect OAB urgency. The UPS was developed to assess urgency associated with overactive bladder (OAB). The UPS is a single question assessed at each visit and has 3 options for responses: 1, 'I am usually not able to hold urine'; 2, 'I am usually able to hold urine until I reach the toilet if I go immediately'; and 3, 'I am usually able to finish what I am doing before going to the toilet'. Change from baseline is calculated by subtracting the baseline value from the follow-up value. Therefore, the change can range from -2 to 2 (with positive change indicating an improvement)[23].

Performance Requirements: The null hypothesis will be rejected if the two-sided p-value is determined to be significant, as described in section 14.1.3.

Sample Size Justification: Internal data from TNM outcomes were used as a starting point to estimate expected change in UPS as well as patient-to-patient variability in that change. Assumptions on the expected mean difference (0.50) and standard deviation (0.80) were used to assess statistical power. Presuming a two-sided, one-sample t-test with alphas ranging from 0.013 to 0.05, power is calculated to be at least 99% for any of the scenarios examined with a sample size of 121 subjects. Additionally, the minimum detectable change in UPS was calculated to be as low as 0.24 points.

Rationale for Clinical Relevance: No published data are available defining minimum clinically meaningful improvement for UPS. In the absence of published definitions, assessment of effect size can be used to determine the level of effect. As published by Cohen (1988)[27], an effect size of 0.2 indicates a small effect, 0.5 a modest effect, and 0.8 a large effect. A modest effect size would correspond to a change of 0.4 in the mean UPS. The assumed mean ± standard deviation change of 0.5 ± 0.8 in the UPS (i.e., an effect size = 0.63) for tibial therapy is considered a medium to large effect.

Analysis Methods: The analysis for UPS will be summarized for baseline, at 6 months after implant, and for the change from baseline. If 5% of the data or fewer are missing for the analysis, no imputation will be used, and the objective will be tested using a paired t-test following the multiple testing strategy described in section 14.1.3. If more than 5% of the data are missing, missing data will be imputed as specified in section 14.1.2. If non-normality of the data is detected via a significant ($p<0.05$) Shapiro-Wilk test, a Wilcoxon signed-rank test will replace the t-test.

Determination of Subjects/Data for Analysis: The UPS analysis will include all subjects from the Full Analysis Set (i.e., all implant attempted subjects) as defined in section 14.1.1 as all subjects are expected to have urgency.

Supportive and Sensitivity Analyses: There are no requirements or expectations for the results of the supporting and sensitivity analyses.

To assess the robustness of the objective results under the influence of missing data, sensitivity analyses will be conducted using alternative missing data methods. The first sensitivity analysis will be completed

including subjects from the Secondary Objective (UPS) Complete Case analysis set. This analysis set will be used for a second sensitivity analysis which will be completed including only subjects who received stimulation ('As treated analysis') at the 6-month follow-up visit. A third sensitivity analysis will be performed excluding those subjects who report limited problems with urgency, as reported by a baseline score of 3 on the UPS. A final complete case sensitivity analysis will be performed comparing the change in urgency to a performance goal of 0.4.

A supportive analysis will be completed summarizing the percentage of subjects in each category at each visit.

UPS change from baseline will be assessed over time through 24 months as part of the additional measures.

14.5.4 Secondary Objective – OAB-q Change

To demonstrate an improvement from baseline to 6 months in quality of life (QoL) using the Overactive Bladder Symptom Quality of Life Questionnaire (OAB-q)

Hypothesis: The change from baseline in OAB-q HRQL is not 0.

H_0: $\mu = 0$

H_A: $\mu \neq 0$

Where μ = the change in OAB-q HRQL total score

Endpoint Definition and Derivation: The OAB-q will be used to collect quality of life. The OAB-q was developed to assess symptom bother and the impact of overactive bladder (OAB) on health-related quality of life (HRQL). The Health-Related Quality of Life (HRQL) total score is calculated by summing the four subscale scores (coping, concern, sleep, social). For each subscale, if <50% of the items are missing, the subscale is retained with the mean of the items present used to impute the missing items in that subscale. If ≥50% of items in any subscale are missing, the HRQL Total will be missing. A positive change in OAB-q HRQL score represents an improvement.

Performance Requirements: The null hypothesis will be rejected if the two-sided p-value is determined to be significant, as described in section 14.1.3.

Sample Size Justification:

Data from a published study on TNM outcomes at 6 months were used as a starting point to estimate expected change in OAB-q HRQL score as well as patient-to-patient variability in that change.

Assumptions on the expected mean change (20 points) and standard deviation (30 points) were used to assess statistical power. Presuming a two-sided, one-sample t-test with alphas ranging from 0.013 to 0.05, power is calculated to be no less than 99% for any of the scenarios examined with a sample size of

121 subjects. Additionally, the minimum detectable change in OAB-q HRQL score was calculated to be as low as 9 points.

Analysis Methods: The analysis for OAB-q HRQL total score will be summarized for baseline, at 6 months after implant, and for the change from baseline. If 5% of the data or fewer are missing for the analysis, no imputation will be used, and the objective will be tested using a paired t-test following the multiple testing strategy described in section 14.1.3. If more than 5% of the data are missing, missing data will be imputed as specified in section 14.1.2. If non-normality of the data is detected via a significant ($p<0.05$) Shapiro-Wilk test, a Wilcoxon signed-rank test will replace the t-test.

Determination of Subjects/Data for Analysis: The OAB-q total score analysis will include all subjects from the Full Analysis Set (i.e., all implant attempted subjects) as defined in section 14.1.1.

Supportive and Sensitivity Analyses: There are no requirements or expectations for the results of the supporting and sensitivity analyses.

To assess the robustness of the objective results under the influence of missing data, sensitivity analyses will be conducted using alternative missing data methods. The first sensitivity analysis will be completed including subjects from the Secondary Objective (OABq HRQL score) Complete Case analysis set. This analysis set will be used for a second sensitivity analysis which will be completed including only subjects who received stimulation ('As treated analysis') at the 6-month follow-up visit. A final complete case sensitivity analysis will be performed comparing the change in OAB-q HRQL to a performance goal of 10.

OAB-q HRQL total score change from baseline will be assessed over time through 24 months as part of the additional measures. In addition, the symptom bother score and OAB-q HRQL domains will be analyzed over time through 24 months.

[redacted]

14.7 Sample Size Determination

The sample size for the primary objective was estimated using a binomial distribution for a one-sided alpha=0.025 test to show a 15% increase for the proportion compared to a performance goal of 40%. Assuming the alternative hypothesis of ≥55% of subjects who are considered an UUI responder, a minimum of 121 implant attempted subjects achieves at least 90% power to reject a performance goal of 40%. The primary objective will have at least 88% power for any alternative hypothesis that is at least 15% larger than a performance goal. Secondary objectives are also expected to be adequately powered based on this sample size.

Assuming a ~40% attrition rate before implant, up to 200 subjects will be consented to achieve at least 121 subjects with implant attempted. Enrollment will be closed once the number of completed implants reaches 121; all enrolled subjects who meet eligibility criteria may be implanted (not to exceed 130 total implants). Implant attempted subjects who exit from the study will not be replaced.

14.8 Minimization of Bias

Potential sources of bias that may be encountered in this study have been considered and minimized by careful study design. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- To ensure a widespread distribution of data and minimize site bias in study results, the maximum number of subjects to be implanted at a single study site shall not exceed 20% (24 subjects) of the total implanted subjects
- A statistical analysis plan will be developed prior to analyzing data which will document all prespecified analyses and analysis methods
- Well justified performance goals, defined based on historical controls from multiple sources, are applied for each objective
- All study investigators will be trained on and required to follow the CIP
- All study investigators and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All sites will use the same version of the CIP and standardized case report forms
- All study investigators will be required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- Monitoring will be conducted to verify adherence to the CIP

In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

14.9 Safety Evaluation

All AEs and DDs will be collected throughout the study once the informed consent form is signed. AEs and DDs will be coded and summarized using the most recent version of Medical Dictionary for Regulatory Affairs (MedDRA). Severity will be assessed by the Investigator. Relatedness and seriousness of the events will be classified by the Investigator, CEC, and the Sponsor. Cases where the Investigator's classification does not match the CEC's classification will be displayed within the final report; however, the CEC's adjudication will be used for data analysis.

Adverse events and DDs that occur prior to implant will be summarized. Adverse events and DDs that occur on or after tibial neuromodulation implant date through study discontinuation will also be summarized; summaries specific to the timeframe from implant to the 6-month follow-up visit will be included. The denominator will be the number of subjects in the All Implanted analysis set. Adverse events in subjects with implant attempted but without full implant will also be summarized. Events that occur in subjects with an unsuccessful implant procedure will be included in the summaries. AEs and DDs will be summarized with number of events, number of subjects who experienced the event, and percentage of subjects who experienced one or more events.

15. Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with this clinical investigation plan (CIP) and good clinical practice (GCP) according to the US CFR on Electronic records (21 CFR§11), Protection of human subjects (21 CFR§50), Financial disclosure by clinical investigators (21 CFR§54), Institutional review boards (21 CFR §56), Medical Device Reporting (21CFR§803), Investigational Device Exemptions (21CFR§812), the ethical principles that originate from the Declaration of Helsinki, and applicable local regulatory requirements and laws in the states in which the study will be conducted.

The TITAN 2 Study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below, except no coordinator principal investigator or institution will be identified for the study. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. AE and DD handling in the TITAN 2 Study is ISO 14155:2020 compliant for all participating geographies.

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, IRB approval, regulatory authority approval, study training, and risk benefit assessment.

The study will be publicly registered prior to the first enrollment in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)).

Study investigators will be required to sign and date an investigator agreement stating their intent to adhere to applicable regulations.

Prior to consenting any subjects in this clinical study, FDA approval and each investigation center's IRB will be required to approve the current CIP, the subject ICF, including any other written information to be provided to the subjects and, if applicable, the materials used to recruit subjects. The IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. Sponsor written approval is required prior to the initiation of subject activities. Investigators and their delegated staff are required to be adequately trained and delegated prior to being activated on the study. If action is taken by an IRB with respect to the investigation, the investigator must ensure this information is forwarded to the sponsor.

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. Medtronic will provide funding for the study and will be funding all study procedures costs.

16. Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring either onsite or remotely in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator must make every effort to meet with the monitor during or at the end of each monitoring visit.

16.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance with the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs in accordance with the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

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

16.2 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 EDC 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 data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data from transmissions will be uploaded to secure servers. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

Ultrasound images are to be retained by the site with a deidentified copy submitted to Medtronic via a secure file transfer method (e.g., Box, encrypted USB) and stored at Medtronic in a secured access location.

The Principal Investigator, or delegated personnel, 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.

16.3 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 eCRFs 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, study specific source worksheets, laboratory reports, etc. Site personnel should clearly indicate the subjects participate in the study within the medical records.

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRBs and RAs direct access to source data and documents during monitoring, audits, and regulatory inspections.

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

16.4 Confidentiality

Subject confidentiality is assured through the use of subject identification (SID) numbers, and the de-identifying of photocopied or records obtained by the Sponsor with the exception of data reviewed during remote monitoring visits conducted through a secure system (e.g., BOX). 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.

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each

subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 along with any regional requirements. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the IC and Subject Identification & Enrollment Log. This scenario will be covered in the IC. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable laws and customs concerning specific insurance coverage.

16.6 CIP Amendments

Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be submitted to FDA and governing IRBs, according to applicable regulations. Approval by FDA (as applicable) and IRB must be obtained prior to implementing a CIP revision at the study site.

16.7 Record Retention

The principal investigator is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years after the date the investigation is completed or terminated or the records are no longer required to support a pre-market approval application, whichever date is later. Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. Electronic CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date the investigation is completed or terminated or the records are no longer required to support a pre-market approval application, whichever date is later.

- All correspondence between the IRB, sponsor, monitor, FDA, and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC signed by subject
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Implant and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation study sites
- Financial Disclosure
- Subject Identification & Enrollment Log
- Device Disposition Logs containing information similar to model and serial numbers of devices delivered to the study site, subject IDs of the subjects implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used, or disposed each device, and method of disposal/destruction
- All approved versions of the CIP, IC, Report of Prior Investigation Summary
- Signed and dated CTA
- CV of principal investigators and key members of investigation study site team
- Documentation of delegated tasks
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process.
- FDA notification, correspondence, and approval
- Study training records for study site staff

- Any other records that FDA requires to be maintained
- Final Study Report including the statistical analysis

16.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Investigational device traceability record containing information similar to model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements, Financial Disclosure and current signed and dated CV of principal investigator and key members of the investigation study site, delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- FDA correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, Report of Prior Investigations summary and study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements are listed in Table 11: Investigator reports applicable per Medtronic requirements. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section. Table 12: Additional Investigator reports applicable to the United States per FDA regulations lists Additional Investigator reports applicable to the United States per FDA regulations.

Table 11: Investigator reports applicable per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and FDA	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs and FDA	This report must be submitted within 3 months of study completion or termination.

Table 12: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such an emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB, and the FDA. If the deviation does not affect these issues, then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of FDA, provide accurate, complete and current information about any aspect of the investigation. Medtronic reporting requirements are listed in Table 13: Sponsor reports for the United States.

Table 13: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Investigators, IRB, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, IRB, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at six-month intervals, a current list of the names and addresses of all investigators participating in the investigation. (21 CFR 812.150(b)(4)) unless a waiver is granted by FDA.
Progress Reports	IRB and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)
Recall and device disposition	Investigators, Head of Institution, IRB, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Final report	Investigators, IRB and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this clinical study. (21 CFR 812.150(b)(7))
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the eCRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))

Report	Submit to	Description/Constraints
Premature termination or suspension of clinical study	IRB, Investigators, and FDA	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB and FDA.

16.9 Publication and Use of Information

Publications from the Evaluation of Implantable Tibial Neuromodulation (TITAN 2) Pivotal Study will be handled according to Standard Operating Procedures and as indicated in the CTA.

16.9.1 Publication Committee

Medtronic intends to publish the results from the study in a timely manner upon study completion.

[redacted]

16.10 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 and FDA (as 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.

17. References

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18. Appendices

18.1 Informed Consent Materials

Copies of all informed consent materials will be provided to the site under a separate cover.

18.2 Participating Investigators, Institutions & Institutional Review Boards

At the time of completion of the Clinical Investigation Plan, site selection is not yet complete. Therefore, a complete list of names and addresses of the clinical investigators and institutions will be distributed within the Current List of Investigators Report. The complete list of Institutional Review Boards will be provided with the Annual Progress Report.

18.3 Labeling

Copies of the TNM system labeling will be provided to the site under a separate cover.

19. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	• 'Not Applicable, New Document'	Not Applicable	Not Applicable	Not Applicable	[redacted] Clinical Study Manager, Senior Clinical Research Program Manager [redacted] Sr. Principal Biostatistician
2.0	• Administrative change in wording in "Indication under investigation" in section 3. Synopsis	Not Applicable	None	None	[redacted] Clinical Study Manager, Principal Clinical Research Specialist [redacted] Sr. Principal Biostatistician

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
3.0	• Inclusion criteria update to require "Failed and/or are intolerant* to at least 2 overactive bladder medications (antimuscarinics or beta-3 agonist) or contraindicated to all pharmacological therapies for the treatment of overactive bladder" • Restriction of OAB medications and advanced therapy treatments through the 12-month follow-up visit • Addition of the 1-month post-explant phone call • Clarification of urinary urge incontinence throughout the document • Additional clarification of missing data handling and the study definition of success, and the addition of sensitivity analyses • Clarification of the power calculations • Modifications to the special considerations for adverse event and/or device deficiency reporting section • Added "Adverse change in bowel and/or urinary function" to Section 11.1 Potential Risks • Clerical and administrative updates	Implementation of FDA feedback, including study design considerations along with ongoing review of risk management documentation	None; study enrollment has not started	IC CRFs	[redacted] Clinical Study Manager, Sr. Clinical Research Program Manager [redacted] Sr. Principal Biostatistician

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
4.0	• Increased sample size from 170 subjects to 200 subjects enrolled (consented) to account for the assumed up to ~40% attrition after consent but prior to the implant procedure (screen failures). • Clarifications made to the highest acceptable amplitude the subject should be set to (e.g., ensuring this level is comfortable for the subject) and when the highest acceptable amplitude cannot be found. • Removal of reference to legally authorized representatives due to protocol requirements for subject's ability to sign consent. • Clarification that no Contract Research Organization(s) will be used for the study. • Further definition of the responder rate for OAB. • Definition provided for clinical relevance of statistical analysis results. • Recommendation included for cultures (when applicable) for suspected infections. • Clerical and administrative updates	Ongoing monitoring of screen failure rate, administrative clarifications, and implementation of FDA feedback, including study design considerations	None	IC	[redacted] Clinical Study Manager, Sr. Clinical Research Program Manager [redacted] Sr. Principal Biostatistician