RESET Study
PRospective Study to Evaluate EffectivenesS With the NURO™ PErcutaneous Tibial Neuromodulation System in Patients With OAB
Clinical Investigational Plan Version 1.0
03-Jun-2016
NCT02857816

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	P**R**ospective Study to **E**valuate Effectivenes**S** with the NURO™ P**E**rcutaneous **T**ibial Neuromodulation System in Patients with OAB (RESET)
Clinical Investigation Plan Identifier	1679
Study Product Name	NURO System
Sponsor	Medtronic, Inc. 7000 Central Avenue NE Minneapolis, MN 55432 USA
Document Version	Version 1.0

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Elizabeth Michaud, Sr. Principal Clinical Research Specialist

2. Investigator Statement

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

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3. Glossary

Term	*Definition*
ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MESA	Medical, Epidemiological, and Social Aspects of Aging
OAB	Overactive Bladder
OABq	Overactive Bladder Symptom Quality of Life Questionnaire
PGI-I	Patient Global Impression of Improvement
PPBC	Patient Perception of Bladder Condition
PTNM	Percutaneous Tibial Neuromodulation
PTNS	Percutaneous Tibial Nerve Stimulation
QoL	Quality of Life
Oracle RDC	Oracle Remote Data Capture
Reportable Adverse Events	Serious, device related, procedure related and all device deficiencies will be considered reportable for this study
SAGA	Self-Assessment Goal Achievement Questionnaire
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
TENS	Transcutaneous Electrical Nerve Stimulation
USADE	Unanticipated Serious Adverse Device Effect
UF	Urgency Frequency
UI	Urinary Incontinence
UUI	Urge Urinary Incontinence
UPS	Urgency Perception Scale
US	United States
UTI	Urinary Tract Infection

4. Synopsis

Title	P**R**ospective Study to **E**valuate Effectiveness**S** with the NURO™ P**E**rcutaneous **T**ibial Neuromodulation System in Patients with OAB (RESET)
Clinical Study Type	Post-market, on-label
Product Name	Commercially available External Neuromodulation system ("NURO System", model number 3533)
Sponsor	Medtronic, Inc.
Indication under investigation	The NURO External Neuromodulation system is intended to treat patients with Overactive Bladder (OAB) and associated symptoms of urinary urgency, urinary frequency, and urge incontinence. There are no investigational devices used in this study, all study products will be used in accordance with the product labeling.
Investigation Purpose	To evaluate the NURO system for the treatment of OAB in drug naïve patients.
Product Status	The NURO system is commercially released for the treatment of patients with OAB and associated symptoms of urinary urgency, urinary frequency, and urge incontinence.
Sample Size	Up to 120 subjects consented and qualified to participate in the study.
Primary Objective	To demonstrate a statistically significant reduction, from baseline through 12 percutaneous tibial neuromodulation (PTNM) therapy sessions, in the number of urge urinary incontinence (UUI) episodes per day
Secondary Objectives	• Reduction from baseline through 12 PTNM therapy sessions in number of voids per day • Change from baseline through 12 PTNM therapy sessions in patient reported quality of life outcomes as measured by the Overactive Bladder Symptom Quality of Life Questionnaire (OABq)

Additional Measures	• Incidence of device or therapy-related adverse events
	• Nocturia / Nighttime voiding frequency
	• Urgency including the Urgency Perception Scale (UPS)
	• Patient-reported Outcomes:
	  ○ Self-Assessment Goal Achievement Questionnaire (SAGA)
	  ○ Patient Perception of Bladder Condition (PPBC)
	  ○ Patient Global Impression of Improvement (PGI-I)

Study Design	Prospective, multicenter, single arm study to evaluate changes from baseline in OAB symptoms as measured by voiding diaries and patient reported outcomes through 12 PTNM therapy sessions. Safety will be evaluated by the collection of reportable adverse events and device deficiencies. Subjects will be enrolled that have symptoms of OAB and no prior treatment with anticholinergics/antimuscarinics or beta 3-agonists medications to treat OAB. Each subject will complete: an enrollment/baseline visit, 12 therapy sessions (each approximately 1 week apart), and a final study visit.
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. 18 years of age or older 2. Diagnosis of OAB with associated symptoms of UUI and qualify with at least 3 episodes of mild, moderate, or severe urgency demonstrated on a 3-day voiding diary 3. Experiencing UUI symptoms for at least 3 months 4. No prior treatment with anticholinergics/antimuscarinics or beta 3-agonists medications to treat OAB 5. Willing and able to accurately complete voiding diaries and questionnaires, attend visits, and comply with the study protocol 6. Willing and able to provide signed and dated informed consent Exclusion Criteria: 1. Have received anticholinergics/antimuscarinics or beta 3-agonists medications to treat OAB or advanced therapy treatment options for OAB (botulinum toxin injections, sacral neuromodulation, or percutaneous tibial nerve

	stimulation/neuromodulation) 2. 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] 3. Have implantable pacemakers or implantable defibrillators 4. Use of transcutaneous electrical nerve stimulation (TENS) in pelvic region, back or legs 5. Women who are pregnant or planning to become pregnant during the course of the study (women of child-bearing potential must undergo a pregnancy test, with a clear negative result, prior to first PTNM session) 6. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol 7. Nerve damage that could impact either tibial nerve or pelvic floor function 8. Subjects prone to excessive bleeding 9. Inadequate skin integrity in the area of PTNM needle placement 10. History of diabetes unless the diabetes is well-controlled through diet and/or medications 11. Have symptomatic urinary tract infection (UTI) 12. Participation in any research study involving or impacting gynecologic, urinary or renal function within the 4-week period prior to or plans to participate during study enrollment
Study Procedures and Assessments	Each subject will complete an enrollment/baseline visit, 12 PTNM therapy sessions (each approximately 1 week apart), and a final study visit for a total of 14 study-related visits. **Enrollment/Baseline** Subjects are considered enrolled at the time the study-specific informed consent form is signed. Each subject must meet all of the inclusion and no exclusion criteria to be eligible to participate in this study. At the enrollment/baseline visit, data will be gathered from subjects including

	relevant medical history. 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 enroll the subject. Subjects will complete the following required questionnaires: OABq, UPS, PPBC, and SAGA at the enrollment/baseline visit. The 3-day urinary baseline voiding diary, pregnancy test (if of childbearing potential) must be completed prior to the initial therapy session. For subjects who have dual incontinence (defined as bladder and fecal incontinence), a 7-day fecal incontinence diary will be recommended at baseline in addition to the 3-day urinary voiding diary. **Weekly PTNM Therapy Session Visits (PTNM Sessions #1-#12)** At the weekly follow-up visits, OAB medication(s) and adverse events will be collected from the subject. Following completion of all visit-specific data collection, subjects will then complete a NURO therapy session in accordance with the NURO System Instructions for Use. Approximately one day after PTNM therapy sessions #1, #4, #8 and #12, subjects will start their 3-day urinary voiding diary. OABq, UPS, and PPBC questionnaires will be completed prior to starting PTNM therapy sessions #2, #5 and #9. Questionnaires must be completed prior to the therapy session. Following completion of all visit-specific data collection, subjects will then complete a NURO therapy session. **Final Study Visit** At the final study visit, the subject's 3-day urinary voiding diary will be collected. For subjects who have dual incontinence, a 7-day fecal incontinence diary will be recommended in addition to the 3-day urinary voiding diary. Any OAB medication(s) and adverse events will be collected from the subject. Subjects will complete the required questionnaires associated with the OABq, UPS, PPBC, SAGA and PGI-I. Subjects will then be exited from study.
Safety Assessments	Safety will be evaluated by the collection of reportable adverse events.
Statistics	The sample size estimate is based on a one-sample t-test, with α=0.05 two-sided, 90% power and an estimated standard deviation of 2.2 UUI episodes/day. If the mean reduction in number of UUI episodes is expected to be .75 per day after 12 PTNM therapy sessions compared to baseline, a sample size of 93 subjects would be required to demonstrate

	a statistically significant reduction from baseline. To account for subject attrition over the period of the study, additional subjects will be enrolled for a sample size of up to 120 consented and qualified subjects.

5. Introduction

This prospective, open-label clinical study using the NURO System will be conducted in approximately 120 subjects with UUI, and will include approximately 15 study sites in the United States (US). The expected study commitment for each subject is approximately 14 weeks, including the baseline and final study visits. The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, all applicable regulatory requirements (21 Code of Federal Regulations [CRF] §50 Protection of Human Subjects, and 21CFR§56 Institutional Review Board [IRB] and 21CFR§803 Medical Device Reporting), and in accordance with Good Clinical Practice (GCP). This study will be posted on ClinicalTrials.gov as part of Medtronic's commitment to full disclosure for ongoing studies that meet the requirements for public posting.

Documentation for this study will be produced and maintained to ensure that a complete history of the study exists. Documents created for this study, including all versions and translations of original documents, will be identifiable and appropriately stored to assure control and traceability of data related to this study.

5.1. Background

The American Urological Association Guidelines for the diagnosis and treatment of OAB in adults provides a clinical framework for the diagnosis and treatment of non-neurogenic OAB. The guidance lists Percutaneous Tibial Nerve Stimulation (PTNS), otherwise known as Percutaneous Tibial Neuromodulation (PTNM), as an acceptable treatment in a carefully selected patient characterized by moderately severe baseline incontinence and frequency and willingness to comply with the PTNM protocol.[1]

The most common therapy protocol is the application of 30 minutes of stimulation once per week for 12 weeks based on early work done by Govier et al. [2] and thus 12 weekly treatment sessions is the duration of the majority of published studies.

The safety of PTNM has been reported extensively in the literature.[2-8] These studies range in size from 35 patients[6] to 110 patients[7] receiving active treatment over a 12 week period. The reported treatment-related adverse events were described as generally mild and transient (such as discomfort at the needle site, minor bleeding, bruising, cramping); none needing surgical intervention to resolve. Published randomized controlled trials have been conducted comparing PTNM to sham[6,7] or PTNM to pharmacological treatment.[4,5,8] Overall, PTNM improved key objective efficacy outcomes of incontinent episodes and voiding frequency[4-8] along with patient's quality of life compared to baseline.[5-8] PTNM was observed to be superior to sham regardless of the endpoint definition (objective or subjective)[6,7]; however, no statistically-significant differences were observed between PTNM and medication in terms of

voiding symptom improvement and Quality of Life (QOL).[5] One study indicated a greater degree of efficacy in PTNM compared to medications.[8]

Multiple systematic reviews have been published on the performance of PTNS for OAB[9-13], and conclude that PTNM is safe and effective for treating OAB. Additionally, PTNM appears in medical treatment guidelines in the United States[1] and Internationally.[14,15] Since the the NURO device delivers identical stimulation therapy as the PTNS device evaluated in the literature, a user can expect similar performance as that reported in the clinical literature.

Published literature has primarily focused on OAB drug refractory populations; however, in a study by Preyer et al. (2015), 36 treatment naïve subjects were randomized between PTNM and pharmacological treatment.[16] In this patient population, PTNM reduced incontinence episodes and improved QOL in patients with OAB to a similar degree to those patients receiving pharmacological treatment. This study provided an initial example of how drug naïve patients may respond to PTNM therapy, however additional clinical work is needed to characterize drug naïve patients and better understand their treatment response to PTNM.

5.2. Purpose

The purpose of this prospective, multicenter, single arm study is to evaluate the NURO system for the treatment of OAB in drug naïve patients. The study will assess change from baseline through 12 PTNM therapy sessions in UUI episodes, voiding episodes, and patient reported outcomes. Safety will be evaluated by the collection of reportable adverse events. The study is expected to last approximately 14 weeks per subject following the enrollment visit. Subjects will be exited from the study after the final study visit is complete.

6. Objectives and Endpoints

6.1. Objectives

6.1.1. Primary Objective(s)

The primary objective of this study is to assess the efficacy of PTNM on UUI episodes in drug naïve patients with OAB.

6.1.2. Secondary Objective

Secondary objectives of this study are to assess the improvement on number of voids per day and QOL measures in drug naïve patients with OAB.

6.2. Endpoints

6.2.1. Primary Endpoint

The primary objective of this study is to demonstrate a statistically significant reduction from baseline through 12 PTNM therapy sessions in the number of UUI episodes per day.

6.2.2. Secondary Endpoints

Secondary objectives include:

- Reduction from baseline through 12 PTNM therapy sessions in number of voids per day
- Change from baseline through 12 PTNM therapy sessions in quality of life as measured by the Overactive Bladder Symptom Quality of Life Questionnaire (OABq)

6.2.3. Additional Measures

Additional measures include:

- Incidence of device or therapy-related adverse events
- Nocturia / Nighttime voiding frequency
- Urgency including the Urgency Perception Scale (UPS)
- Patient-reported Outcomes:
    - Self-Assessment Goal Achievement Questionnaire (SAGA)
    - Patient Perception of Bladder Condition (PPBC)
    - Patient Global Impression of Improvement (PGI-I)

7. Study Design

This is a prospective, multicenter, open-label study evaluating the use of PTNM in OAB drug naïve patients with UUI.

All eligible subjects will sign a study-specific informed consent form (ICF). Following qualification using a baseline diary, subjects will undergo 12 PTNM therapy sessions, administered weekly, utilizing the NURO system. Urinary voiding diaries (3-day) to assess efficacy measures and quality of life questionnaires will be completed after therapy sessions as required in Figure 1-1: Study Procedures. The study is expected to last approximately 14 weeks per subject following the baseline/enrollment visit. Subjects will be exited from the study after the final study visit is complete.

The required sample size is 120 consented and qualified subjects; which includes 93 subjects required to meet the study endpoint and approximately 20% to account for potential attrition.

The study will be conducted at approximately 15 sites in the US. Initial site enrollment is not planned to exceed 20% of the total number of subjects enrolled to reduce the possibility that a site with atypical results will be overly influential in the overall study results based on pooled data; however this may be increased based on the Sponsor's discretion.

This is an on-label, post-market study of an FDA-cleared device that is exempt from Investigational Device Exemption (IDE) requirements under 21 CFR 812(c)(2). All subjects enrolled in the study will qualify under the approved indication for the NURO system.

7.1. Duration

Study subjects will be enrolled and will complete enrollment/baseline requirements to determine eligibility. Subjects that do not qualify for the study prior to the first PTNM therapy session will be exited from the study. All enrolled subjects that qualify for the study (meet all inclusion and no exclusion) will receive 12 PTNM therapy sessions, each approximately 1 week apart, prior to completing the final study visit. The visits are expected to occur over a 14 week period.

7.2. Rationale

While there is extensive literature on the safety and efficacy of PTNM, the majority of published literature is on OAB drug refractory patients. The purpose of this study is to understand the effect of PTNM in a OAB drug naïve patient population. The NURO system is cleared by the Food and Drug Administration (FDA) and will be used in accordance with commercially available product labeling.

8. Product Description

8.1. General

The NURO system includes: the NURO External Neurostimulator (model 3533), Therapy Sessions (model 3533S), and single-use Therapy Session Kits (model 3533K) which are provided separately. The Therapy Session Kit includes: two sterile needles, two alcohol wipes, a needle holder, and ground pad. The NURO device is a small and portable pulse generator, and should only be used with the single-use items listed above. The system also includes a wall charger and USB cable. Sites will need to ensure technical compatibility with the NURO e-commerce site in order to activate the device and download and transfer therapy sessions to the NURO External Neurostimulator.

8.2. Manufacturer

The products used in this study, identified in Section 8.1, are manufactured by Medtronic, Inc. and are approved for use in treating patients with OAB.

8.3. Intended Population

The study will enroll OAB drug naïve patients with a diagnosis of OAB and associated symptoms of UUI (see Section 9).

8.4. Product Return

Since all products are commercially available, product associated with a complaint should be returned through commercial processes. Contact your study team member for return instructions.

8.5. Product Accountability

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

9. Selection of Subjects

9.1. Study Population

The intended study population is subjects with UUI who have not tried an OAB medication. In addition, subjects must not have received advanced therapy treatment options for OAB (botulinum toxin injections, sacral neuromodulation or PTNS/PTNM).

9.2. Subject Enrollment

Subjects are considered enrolled at the time the study-specific ICF is signed. Each subject must meet all of the inclusion criteria and no exclusion criteria to be eligible to participate in this study. Any subject meeting an exclusion criterion will be excluded from study participation.

9.3. Inclusion Criteria

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

1. 18 years of age or older
2. Diagnosis of OAB and associated symptoms of UUI and qualify with at least 3 episodes of mild, moderate, or severe urgency demonstrated on a 3-day urinary voiding diary
3. Experiencing UUI symptoms for at least 3 months
4. No prior treatment with anticholinergics/antimuscarinics or beta 3-agonists medications to treat OAB
5. Willing and able to accurately complete voiding diaries and questionnaires, attend visits, and comply with the study protocol
6. 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 received anticholinergics/antimuscarinics or beta 3-agonists medications to treat OAB or advanced therapy treatment options for OAB (botulinum toxin injections, sacral neuromodulation, or percutaneous tibial nerve stimulation/neuromodulation)
2. Primary stress incontinence or mixed incontinence where the stress component overrides the urge component (see enrollment/baseline requirements for use of the MESA urinary incontinence questionnaire)
3. Have implantable pacemakers or implantable defibrillators

4. Use of transcutaneous electrical nerve stimulation (TENS) in pelvic region, back or legs
5. Women who are pregnant or planning to become pregnant during the course of the study (women of child-bearing potential must undergo a pregnancy test, with a clear negative result, prior to first PTNM session)
6. Characteristics indicating a poor understanding of the study or characteristics that indicate the subject may have poor compliance with the study protocol
7. Nerve damage that could impact either tibial nerve or pelvic floor function.
8. Subjects prone to excessive bleeding
9. Inadequate skin integrity in the area of PTNM needle placement
10. History of diabetes unless the diabetes is well-controlled through diet and/or medications
11. Have symptomatic urinary tract infection (UTI)
12. Participation in any research study involving or impacting gynecologic, urinary or renal function within the 4-week period prior to or plans to participate during study enrollment

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 meet the criteria for evaluability. See Table 1-1 for visit requirements. Both paper and electronic case report form (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.

Enrollment/Baseline

Subjects are considered enrolled at the time the study-specific ICF is signed. Each subject must meet all of the inclusion criteria and no exclusion criteria to be eligible to continue participation in this study.

As part of the inclusion/exclusion evaluation, 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 enroll the subject.

Additionally, prior and ongoing conservative therapies for OAB such as physical therapy, pelvic floor muscle training, behavior modification, and dietary programs and relevant medical history will be assessed at baseline tracked throughout the duration of the study. Subjects will be encouraged to continue any conservative therapies for OAB they were on at entry through the duration of the study.

Subjects will complete the following required questionnaires: OABq, UPS, PPBC, and SAGA at the enrollment/baseline visit. The 3-day baseline urinary voiding diary and pregnancy test (women of child-bearing potential must undergo a pregnancy test, with a clear negative result) must be completed prior to the initial therapy session. For subjects who have dual incontinence, an additional 7-day fecal incontinence diary will be recommended at baseline.

The baseline urinary voiding diary is to be completed and returned to confirm remaining eligibility criteria. If the subject does not meet eligibility criteria of at least 3 UUI episodes demonstrated on a 3-day voiding diary, the subject must be exited from the study.

Initial PTNM Therapy Session (PTNM Session #1)

The baseline urinary voiding diary must be reviewed to confirm eligibility prior to beginning the initial PTNM therapy session. If the subject does not meet eligibility criteria of at least 3 UUI episodes demonstrated on a 3-day voiding diary, the subject must be exited from the study. Any OAB medication(s), conservative therapies for OAB and reportable adverse events will be collected from the subject.

If the subject meets the eligibility criteria of at least 3 UUI episodes of mild, moderate, or severe urgency demonstrated on a 3-day voiding diary, the subject will then complete a PTNM therapy session using the NURO device. The PTNM therapy sessions will be completed in accordance with the NURO System Instructions for Use.

Weekly PTNM Therapy Sessions: PTNM Sessions #2-#12 (1 Week ± 3 days)

At the weekly follow-up visits, any OAB medication(s), conservative therapies for OAB and reportable adverse events will be collected from the subject. Subjects will then complete a PTNM therapy session with the NURO device used in accordance with the NURO system Instructions for Use.

Three-day voiding diaries will be provided to the subjects to be started approximately one day after PTNM Session #1, PTNM Session #4, PTNM Session #8, and PTNM Session #12.

At PTNM Session #2, PTNM Session #5 and PTNM Session #9, and the final visit subjects will return their completed 3-day urinary voiding diary and complete OABq, UPS and PPBC questionnaires. Subjects are required to complete the questionnaires prior to the PTNM therapy session. Subjects will then complete a PTNM therapy session with the NURO device used in accordance with the NURO system Instructions for Use.

After PTNM Session #12, a 3-day urinary voiding diary will be provided for the subject to start approximately one day after the therapy session. Subjects who have dual incontinence that completed 7-day fecal incontinence diary at baseline be provided with a final 7-day fecal incontinence diary.

Final Study Visit (1 Week ± 3 days)

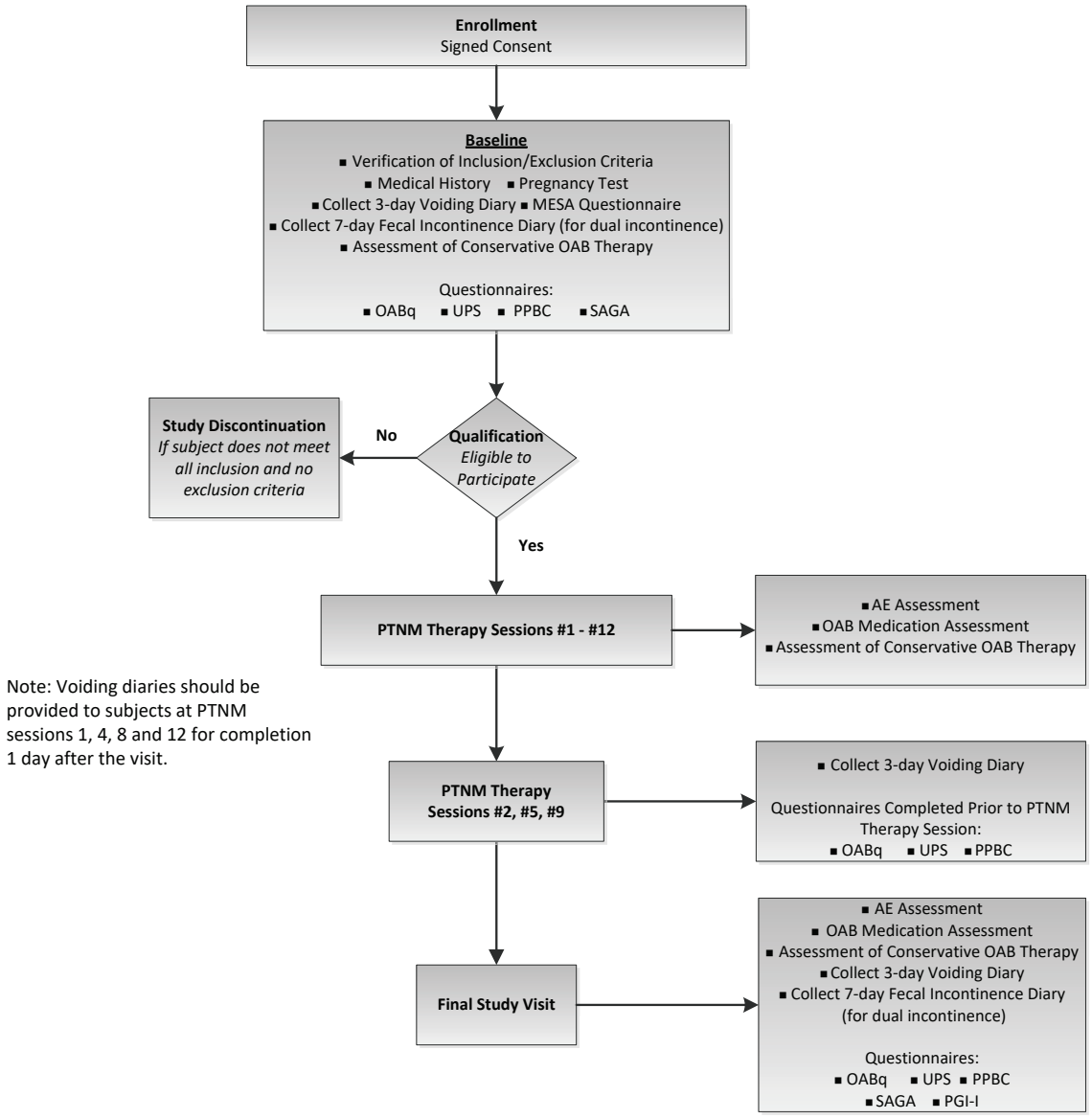
At the final study visit, the completed final 3-day urinary voiding diary, 7-day fecal incontinence diary (if applicable), any OAB medication(s), conservative therapies for OAB and reportable adverse events will be collected from the subject. Subjects will complete the following required questionnaires: OABq, UPS, PPBC, PGI-I, and SAGA. Following collection of all study-related data, the subject will be exited from the study.

10.1. Schedule of Events

The start of the study is defined as the date the subject first signs the informed consent. The completion of the study for each subject is defined as the completion of the final study visit. Subjects that do not qualify for the study prior to the first PTNM therapy session will be exited from the study. The completion of the study is defined as the completion of the Final Study Report and closure of all sites.

Figure 1-1: Study Procedures illustrates required study procedure:

Figure 1-1: Study Procedures



A detailed table of the study procedures, presenting the type of procedure required at each visit, is presented in Table 1-1.

Table 1-1: Study Procedures

Procedures	Enrollment/ Baseline Visit	PTNM Session #1	PTNM Session #2	PTNM Session #3	PTNM Session #4	PTNM Session #5	PTNM Session #6	PTNM Session #7	PTNM Session #8	PTNM Session #9	PTNM Session #10	PTNM Session #11	PTNM Session #12	Final Study Visit
Informed Consent Form	X													
Inclusion/Exclusion	X	X												
Pregnancy Test*	X*													
Reportable Medical History	X													
Distribute Urinary Voiding Diary	X	X			X				X				X	
Distribute Fecal Incontinence Diary**	X												X	
Collect Urinary Voiding Diary		X***	X			X				X				X
Collect Fecal Incontinence Diary **		X												X
OABq Questionnaire	X		X			X				X				X
UPS Questionnaire	X		X			X				X				X
PPBC Questionnaire	X		X			X				X				X
PGI-I Questionnaire														X
SAGA Questionnaire	X													X
Conservative Therapies for OAB	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OAB Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*For women of child bearing potential to be completed prior to the first PTNM therapy session
**Fecal incontinence Diary (7-day) is recommended for subjects with dual incontinence
***Qualification diary must be reviewed to confirm eligibility prior to beginning first PTNM therapy session

10.2. Subject Screening

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

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

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

As part of the inclusion/exclusion evaluation, 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 enroll the subject.

10.3. Prior and Concomitant Medications

Subjects may not be enrolled if they have had any prior treatment with anticholinergic/antimuscarinic or beta 3-agonist medications to treat OAB.

10.4. Subject Consent

The informed consent process will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with 21CFR§50 Protection of Human Subjects.

Prior to entering the study, the Principal Investigator or qualified designee will explain to each subject the purpose and nature of the study, procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. Subjects will be given a copy of the IRB-approved ICF and will have time to review the document and to ask questions and will be informed of their right to withdraw from the study at any time without prejudice; ICFs will be provided in a language understandable to the subject. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date the ICF. Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent and any other written information provided to the subject.

The Principal Investigator or qualified (delegated) designee will document the informed consent process, including the date of consent and name of the person conducting the consent process in the subject's medical record. A copy of the signed ICF will also be placed in the subject's medical record.

10.5. Medication Compliance

Subjects eligible to participate must be OAB drug naïve.

If a subject starts an OAB medication prior to starting the PTNM therapy sessions, they should be considered ineligible for the study and should be exited.

If a subject starts anticholinergic/antimuscarinic or beta 3-agonist medications to treat OAB following their first PTNM therapy session a deviation form will be completed and this medication will be captured on the OAB medication form.

Medications used to treat reportable adverse events will be documented as "interventions" on the adverse event case report form.

10.6. Assessment of Efficacy

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

Medical History and Demographics

Assessments will be completed and reported on the eCRF.

Urinary Voiding Diary

Symptoms related to OAB will be evaluated using paper voiding diaries. Subjects will be trained to complete the urinary voiding diaries for 3-days as part of the baseline procedures and instructed to start the voiding diary approximately 1 day after PTNM Session #1, #4, #8 and #12. These voiding diaries will then be collected at the next following PTNM Session. Every effort should be made to remind subjects of the importance of real-time diary completion.

Voiding diary data will be used to verify study inclusion criteria for UUI episodes at baseline. Diaries will also be used for comparison to baseline for the primary study endpoint of UUI, secondary study endpoint of urgency frequency (UF) and additional measures related to urgency, nocturia and nighttime frequency. As clinically defined, nocturia will be measured as the number of times the subject is woken from sleep to void.[17] Nighttime frequency will be defined as number of voids during nighttime sleep.[17]

Fecal Incontinence Diary

It is recommended that subjects with dual incontinence complete a 7-day fecal incontinence diary during baseline procedures and after 12 PTNM therapy sessions.

PTNM Therapy Sessions

Subjects will receive 12 weekly PTNM therapy sessions following the enrollment/baseline visit.

Assessments for Quality of Life Measures

Subjects will complete the study questionnaires confidentially on paper forms without site personnel consultation and these data will be entered to OC/RDC by site personnel. Questionnaires should be completed prior to the initiation of the PTNM therapy session. Site personnel are encouraged to review forms for completeness.

<u>Overactive Bladder Quality of Life Questionnaire (OABq)</u>

The Overactive Bladder Quality of Life Questionnaire (OABq) is a 33-item 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 1-week recall for symptom assessment.

Urgency Perception Scale (UPS)

The Urgency Perception Scale (UPS) is a single item questionnaire measure of perceived urinary urgency with three response options.[19,20]

Self-Assessment Goal Achievement Questionnaire (SAGA)

Patient attainment goals have been used throughout the literature in order to determine if patients are reaching pre-determined goals.[21,22] The Self-Assessment Goal Achievement (SAGA) questionnaire is a tool designed to help patients with lower urinary tract symptoms assess goal achievement.[23] The SAGA questionnaire allows for the patient to rank, in order of importance for standard urology symptom goals using a scale of 0-5 and allows for other personal goals to be included. After treatment has been completed, the patient then completes the follow-up assessment which includes a scale of -2 to 2 to report on achievement of each symptom goal and personal goal(s). The questionnaire includes an assessment question of "Overall, to what extent have you achieved your goals" on a scale of 0-4.

Patient Perception of Bladder Condition (PPBC)

The Patient Perception of Bladder Condition (PPBC) is a single-item, 6-point scale that asks patients to rate their subjective impression of their current bladder problems.[24,25]

Patient Global Impression of Improvement (PGI-I)

Overall impression for improvement is evaluated using the Patient Global Impression of Improvement (PGI-I)[26-28] which is a single question asking the patient to rate their urinary condition now as compared with prior to beginning treatment on a scale from 1 (very much better) to 7 (very much worse).

10.7. Assessment of Safety

Subjects will be assessed for potential reportable adverse events that are reportable under the study protocol at each study visit.

10.8. Recording Data

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

taken from source documents and directly entered into the study database via the CRFs by the site personnel, in accordance with applicable regulations.

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

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

10.9. Deviation Handling

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

The sponsor may choose to terminate the study at a site for failure to follow the written protocol and investigator agreement. If this occurs, the Investigator and IRB will be notified in writing of the reasons for the termination.

10.10. Subject Withdrawal or Discontinuation

Subjects are free to voluntarily withdraw from the study at any time and for any reason. The investigator can withdraw a subject from the study at any time and for any reason. Withdrawn or exited subjects will be followed under normal medical practice.

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

- If the subject does not meet eligibility criteria of at least 3 UUI episodes of mild, moderate, or severe urgency demonstrated on a 3-day urinary voiding diary
- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- Subject becomes pregnant
- Investigator terminates the subject's participation in the study due to lack of compliance, violation of/change in eligibility criteria

- Any clinical laboratory abnormality, inter-current illness, or other medical condition or situation occurs such that continued study participation would not be in the best interest of the subject.
- Subject is not a candidate for PTNM therapy
- Normal study completion

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

When a subject is withdrawn from the study, the Study Discontinuation 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). There is no further medical care provided under the study after a subject exits from the study.

11. Risks and Benefits

11.1. Potential Risks

11.1.1. Health Risks

The following are known potential health risks associated with the NURO system and PTNM therapy:

- Discomfort and pain (including throbbing pain) at, or near, the stimulation site, including the patient's lower leg and foot
- Bleeding at the needle site
- Redness/inflammation at, or near, the stimulation site
- Numbness of toes
- Stomach ache

11.1.2. NURO System Warnings

To avoid risks to study subjects and system users, Investigators and site personnel should be aware of the following.

1. The provided Instructions for Use is NOT a comprehensive reference to therapeutic techniques for the indications noted for the NURO system. Section 11.1 will only be revised based on significant new safety information added to the Instructions for Use. Refer to the current Instructions for Use for complete contraindications, warnings and precautions.
2. Investigators and site personnel should be familiar with appropriate application and techniques involved in the use of the NURO system and needle in the delivery of Percutaneous Tibial Neuromodulation.
3. Do not use the NURO system or needle if the skin in the area of use is inflamed, infected, or otherwise compromised. Monitor subjects during therapy session for pain or skin irritation/inflammation. Discontinue use of the NURO system if the subject complains about these symptoms or any other discomfort.

4. Do not use any part of the NURO system to apply stimulation across or through the head, directly on the eyes, covering the mouth, on the front of the neck (especially the carotid sinus), or on the chest, upper back or crossing over the heart. The application of the ground pad near the thorax may increase the risk of cardiac fibrillation.
5. Subjects should not spend more than 30 minutes in therapy mode during a single therapy session.
6. The subject should remain comfortably seated, or in a supine position, for the duration of the therapy session. The subject should not rise or walk until the therapy session is complete, because mobility during therapy session has not been assessed.
7. Do not use the NURO system if any component or accessory is loose or damaged, including the rear electrode snap or internal battery.
8. Do not use the NURO system if its packaging has been opened or altered. If packaging has been opened or altered, contact Medtronic.
9. Do not reuse the single-use needle, needle holder, or ground pad.
10. Dispose of used needle, needle holder, and ground pad accessories in bio-hazardous material disposal container.
11. Simultaneous connection of a patient to high frequency surgical equipment may result in burns at the site of the ground pad and/or needle and possible damage to the NURO device.
12. Device operation in close proximity (e.g. 1 meter) to short wave or microwave therapy equipment may produce instability in the NURO device output.
13. The NURO device has electric shock protection, type "Internally Powered Equipment" per IEC 60601-1.
14. The NURO device enclosure is type IPX0 and does not protect against the ingress of water. Do not use the NURO device in or around water.
15. For recharging, only use the wall charger provided with the NURO device. Use of a different charger could result in electrical shock or damage to the device.
16. Do not operate the NURO device with anything plugged into the USB port. Do not insert the needle into the micro USB port.
17. The following are known potential health risks associated with this type of device and therapy: discomfort and pain near needle site, bleeding near needle site, redness/inflammation near needle site, numbness in toes, and stomach ache.
18. The NURO device has no serviceable parts. No modification is allowed. Opening the case could lead to electrical shock, device damage, or other risks.
19. Do not exceed the recommended therapy session time of 30 minutes per session.
20. Do not excessively bend or kink the device cable. Always inspect device cable for signs of wear or damage before use. If wear or damage is found, discontinue use and return the NURO device to Medtronic.
21. No modification of this equipment is allowed.
22. Use only the ground pad listed in the IFU. This pad is sized to not to exceed 2 mA/cm2 for the NURO device.

11.1.3. NURO System Contraindications

In order for therapy to be effective and to avoid any possible problems or complications, the NURO system is contraindicated for use on patients who have the following history or conditions (see study exclusion criteria):

1. Subjects prone to excessive bleeding
2. Subjects with pacemakers or implantable defibrillators
3. Subjects with nerve damage that could impact either percutaneous tibial nerve or pelvic floor function
4. Subjects who are pregnant or planning to become pregnant while using this product
5. The NURO system is not intended for intra-cardiac or trans-thoracic use.
6. Concurrent use of medical monitoring equipment during stimulation is not recommended.
7. The NURO system is not suitable for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

11.1.4. NURO System Precautions

- Prior to using the NURO system, read and understand all instructions.
- Caution should be used for patients with suspected or diagnosed heart problems, especially those relating to the pacing or electrical functioning of the heart.
- Medical electrical equipment needs special precautions regarding electromagnetic compatibility (EMC) and needs to be installed and placed into service according to EMC guidelines provided.
    - a. Portable and mobile radio frequency (RF) communications equipment can affect medical electrical equipment.
    - b. Investigators and site personnel should assure the NURO system is used in an appropriate environment.
        - i. Portable and mobile RF Communications equipment (i.e. cell phones) should not be used at close distances.
        - ii. Power frequency magnetic fields should be at levels characteristic of a typical commercial, hospital or clinic environment.
- Always start and restart stimulation at the lowest settings and adjust as necessary. Do not return to any previous setting without observing the patient's responses.

Reporting of adverse events and device deficiencies should follow the requirements outlined in the adverse event assessment section of the study protocol.

There may be risks or side effects which are unknown at this time.

If a subject becomes pregnant while using the NURO system, there may be risks to her or her unborn baby. These risks are currently unknown. If the Investigators becomes aware that a subject is pregnant during the course of the study, the subject should be exited from the study.

11.2. Potential Benefits

Subjects may not receive any direct medical benefit from participation in this study but subjects will receive additional medical oversight of treatment. Participation in this study will not provide greater benefit than if the subject was receiving PTNM therapy with the NURO system outside of the study. Information from this study might help researchers further understand PTNM therapy. The benefit to subjects participating in this study, and to future patients, resides in the knowledge gained from this study related to the safety and efficacy of this therapy when used in OAB drug naïve patients.

11.3. Risk-Benefit Rationale

Participation in this study will not expose the subject to greater risks than if he/she were receiving PTNM therapy with the NURO system outside of the study. There might be other discomforts and risks related to PTNM and/or this study that are not foreseen at this time.

Subjects may find that some of the questionnaires or completing the urinary voiding and fecal diaries are embarrassing.

12. Adverse Event Assessments

12.1. Definitions/Classifications

Any adverse event meeting the definition of: serious, device related, and/or procedure related as well as all device deficiencies will be considered reportable for this study. Adverse events and device deficiencies are defined as follows:

Term	General
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.
Adverse Device Effect (ADE)*	Adverse event related to the use of the medical device under investigation.
Device Deficiency (DD)*	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling. ▪ Malfunctions: Failure of the medical device under investigation to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigational Plan (CIP) ▪ Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

SERIOUSNESS	
Serious Adverse Event (SAE)*	An adverse event that a) led to a death, b) led to a serious deterioration in the health of the subject, that either resulted in: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. c) led to fetal distress, foetal death or a congenital abnormality or birth defect. ***Note:*** *A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.*
Serious Adverse Device Effect (SADE)*	Adverse device effect that resulted in any of the consequences characteristic of a serious adverse event
Unexpected Serious Adverse Device Effect (USADE)*	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified.
RELATEDNESS	
Relationship of Adverse Events	The relationship of the adverse event to the study treatment (device, therapy) will be described using the following terms: • Not related • Unlikely • Possible • Probable • Causal relationship

*Reportable event categories that will be collected during this study

12.2. Reporting of Adverse Events

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

Worsening of OAB symptoms will be collected as part of the efficacy measures and are not considered a reportable adverse event.

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

Event Classification Responsibilities

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

All reportable adverse events must be recorded in the subject's medical record and on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic. IRB reporting must be completed in accordance with the policies of the governing IRB.

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

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

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

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

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

Medtronic study personnel will promptly review all reported adverse events and device deficiencies and if necessary request clarification and/or additional information from the Investigator. If Medtronic

disagrees with the Investigator's assessment of the adverse event relationship to device and/or procedure, Medtronic study personnel will document the disagreement and report or ensure reporting of both opinions to IRB as necessary. All reported adverse events and device deficiencies will be reviewed by a Medtronic Medical Monitor to ensure consistent reporting.

13. Data Review Committees

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

14. Statistical Design and Methods

14.1. General Statistical Considerations

14.1.1. Study Sample Size Justification

This study is to evaluate the reduction from baseline in the number of UUI episodes per day after the 12th PTNM therapy session. The OrBIT trial by Peters et al (2009)[5] compared the effectiveness of PTNS to extended-release tolterodine. This study reported an average reduction of UUI at 12 weeks compared to baseline in the PTNS arm was 1 episode per day with a standard deviation of 2.2. The following assumptions were used for the sample size calculations: reduction of 0.75 UUI episodes/day from baseline, one-sample t-test with two-sided α=0.05, 90% power, and an estimated standard deviation of 2.2 incontinence episodes/day. Based on these assumptions, a sample size of 93 subjects would be required to demonstrate a statistically significant reduction from baseline. To account for an attrition of approximately 20% during the course of the study, a sample size of up to 120 subjects is required for this study.

The sample size requirement of 93 for the primary objective is also adequate to assess the secondary objectives of number of voids per day and quality of life measured by OABq. In the OrBIT trial by Peters et al (2009)[5], the average reduction of voids at 12 weeks compared to baseline in the PTNS arm was 2.4 voids per day with a standard deviation of 4.0. Based on a one-sample t-test, with α=0.05 two-sided, 90% power, 44 subjects with UF are required to demonstrate a statistically significant reduction from baseline if using a conservative estimate of a reduction of 2.0 voids per day with a standard deviation of 4.0. In the InSite study, among all implanted subjects 63% of the urinary incontinence (UI) subjects had both UI and UF at baseline.[29] Therefore, 93 subjects should ensure the sample size needed for the secondary objective of UF based on this assumption.

In the OrBIT trial by Peters et al (2009)[5], the average improvement from baseline of HRQL from OABq for PTNS at 12 weeks was 25.3±21.5. Based on a one-sample t-test, with α=0.05 two-sided, 90% power, 15 subjects are required to demonstrate a statistically significant reduction from baseline when using a conservative estimate of average improvement of 20 points at 12 weeks with a standard deviation of 22. Therefore, 93 subjects should ensure the sample size need for the secondary objective of OABq.

14.1.2. Description of Baseline variables

Summary statistics will be provided for baseline variables.

14.1.3. Center Pooling

Data from all study centers will be pooled for the analysis. There are no planned statistical methods to test for treatment differences among centers. The study will be conducted at approximately 15 sites in the US. Initial site enrollment is not planned to exceed 20% of the total number of subjects that are qualified for the study; however this may be increased based on the Sponsor's discretion. This is intended to reduce the possibility that a site with atypical results will be overly influential in the overall study results.

14.1.4. Special Considerations

No adjustments for multiple analyses will be made for this study.

14.1.5. Interim Analyses

No interim analysis is intended for this study.

14.1.6. Reports

Periodic reports will be provided to each site's IRB. A final report will be generated for this study. Relevant tables of statistical results and graphs will be generated for inclusion in the final report. Any change from the original statistical plan will be summarized.

14.2. Demographics

Summary statistics for demographic variables will be presented.

14.3. Primary Objective

This study will assess the efficacy of PTNM on UUI episodes collected using a voiding diary. The primary objective is to demonstrate a statistically significant reduction between baseline and following the 12th PTNM therapy sessions in the number of UUI episodes per day.

Hypothesis

Ho: μ12th PTNM therapy session = μbaseline

Ha: μ12thPTNM therapy session ≠ μbaseline

Where μbaseline and μ12th PTNM therapy session are average UUI episodes per day at baseline and following the 12th PTNM therapy session respectively.

Endpoint definition

The average UUI episodes per day collected at baseline and following the 12th and final PTNM therapy session will be used as the endpoint for the primary objective.

Sample size methods and assumptions

This details the sample size justification.

Data collection and analysis methods

Diary data collected at baseline and after the 12th PTNM therapy session will be used for the primary endpoint analysis. The paired t-test or the Wilcoxon signed-rank test will be used to evaluate the changes after testing for data normality. A statistical test is deemed significant if the P value is less than 0.05. Primary analysis method will be completers (with no imputation of missing data). Sensitivity analyses will be conducted with the adjusted worst-case method and per protocol analysis.

Determination of subjects for analysis

Subjects with diary data from both baseline and the 12th PTNM therapy session will be included in the primary analysis for this objective.

In additional to the primary analysis, two sensitivity analyses will be performed:

- Adjusted worst-case analysis, in which,
    a. For subjects who received the study therapy and withdrew early due to device-related adverse events, or treatment unsuccessful, the 12th PTNM therapy session data point will be set to subject's baseline assessment.
    b. For subjects who received the study therapy and exit the study early due to all other reasons (i.e. adverse events not related to the device), and for subjects who missed the 12th PTNM therapy session or fail to provide the relevant data for 12th PTNM therapy session, the Last Observation Carried Forward (LOCF) method will be used to impute the missing data.
    c. Subjects who exit the study prior to the initial NURO PTNM therapy session will be excluded from this sensitivity analysis
- Per protocol sensitivity analysis which will be based on the completers dataset, but will exclude those subjects who take OAB medications in the study. Use of OAB medications will be captured as a protocol deviation.

Reduction in number of UUI episodes from baseline will be summarized for each follow up visit when the diary data is collected with no imputation of missing data (completers analysis).

14.4. Secondary Objectives

Secondary objectives are to assess:

- Reduction from baseline through 12 PTNM therapy sessions in number of voids per day
- Change from baseline through 12 PTNM therapy sessions in quality of life as measured by the OABq Questionnaire

14.4.1. Secondary Objective #1

To assess the reduction in number of voids per day from baseline through 12 PTNM therapy sessions. This objective will be assessed in subjects with ≥ 8 voids per day at baseline. Number of voids collected from baseline and the 12th PTNM therapy session will be used for analysis of this objective. Subjects with diary data from both baseline and 12th PTNM therapy session will be included in the analysis. A paired t-test or the Wilcoxon signed-rank test will be used to evaluate the changes after 12 PTNM therapy session from baseline after testing for data normality.

In additional to the primary analysis which includes subjects with diary data from baseline and 12th PTNM therapy session, the same sensitivity analyses as described in primary objective will be performed for secondary objective #1.

Reduction in number of voids per day from baseline will also be summarized by the PTNM session when the diary data is collected.

14.4.2. Secondary Objective #2

To assess the change from baseline through 12 PTNM therapy sessions in quality of life as measured by the OABq Questionnaire. This objective will be assessed in subjects with OABq data at baseline and after 12th PTNM therapy session. The paired t-test or the Wilcoxon signed-rank test will be used to evaluate the changes after the 12th PTNM therapy session from baseline after testing for data normality.

In additional to the primary analysis which includes subjects with diary data from baseline and 12th PTNM therapy session, the same sensitivity analyses as described in primary objective will be performed for secondary objective #2.

Improvement in OABq from baseline will also be summarized at by the PTNM session when this data is collected.

14.5. Additional Measures

Additional measures include:

- Incidence of device-related and therapy-related adverse events
- Nocturia / Nighttime voiding frequency
- Urgency including the Urgency Perception Scale (UPS)
- Patient-reported Outcomes:
    - Self-Assessment Goal Achievement Questionnaire (SAGA)
    - Patient Perception of Bladder Condition (PPBC)
    - Patient Global Impression of Improvement (PGI-I)

Nocturia, nighttime voiding frequency and urgency are collected through voiding diaries and patient reported outcomes. Reductions in nocturia, nighttime voiding frequency and urgency from baseline will be summarized by the PTNM session when the data is collected.

Additional quality of life measures including PPBC, UPS, PGI-I and SAGA are collected in this study. These data will be summarized by the PTNM session when data is collected.

Reportable adverse events will be summarized for all subjects who receive the therapy.

Fecal incontinence diaries will be collected for subjects with dual incontinence. No analysis is pre-specified for dual incontinence data. The intent of collecting this information is to inform future study designs.

15. Ethics

15.1. Statement(s) of Compliance

The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, all applicable regulatory requirements (21CFR§50 Protection of Human Subjects, 21CFR§56 IRB, and 21CFR§803 Medical Device Reporting), and according to GCP. The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent process, IRB approval, risk benefit assessment, study training, clinical trial registration, and publication policy. Study Investigators will be required to sign an Investigator Agreement stating their intent to adher to applicable regulations.

The study will not begin at any site until an IRB letter approving the protocol and the ICF is received by Medtronic.

Details related to stipends provided to study subjects are outlined in the subject ICF.

16. Study Administration

16.1. Monitoring

Medtronic is responsible for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on CRFs. The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data (eg, paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the CRFs as well as other documentation supporting the conduct of the study. The monitor will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed. The monitoring plan contains the strategy for frequency of monitoring visits and source data verification to be performed for this study.

16.2. Medtronic Representative Role

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

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

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

- Observing testing or medical procedures to provide information relevant to protocol completion
- Reviewing collected data and study documentation for completeness and accuracy

Medtronic personnel will not:

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

16.3. Data Management

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

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

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

16.4. Direct Access to Source Data/Documents

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

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

16.5. Confidentiality

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

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

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

16.6. CIP Amendments

Protocol amendments may be initiated by Medtronic to address changes to the conduct of the study. Protocol amendments must be approved by Medtronic and submitted to the IRBs; protocol amendment approval and approval of any associated changes to the informed consent document must be obtained prior to implementation of the amendment except:

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

16.7. Record Retention

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

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

The Principal Investigator is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years following completion of the study. The Principal Investigator will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic. Medtronic will be notified in writing of any transfer of study documentation.

16.8. Publication and Use of Information

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

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

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

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

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

16.9. Suspension or Early Termination

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

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

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

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

Investigators are required to notify the IRB of study suspension/termination. Subjects will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

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18. Appendices

None