Axonics Sac**R**al Neuromodula**TI**on **S**ystem for Urin**a**ry Urgency Incontinence Treatme**N**t:

ARTISAN-SNM

105-0050 Rev G

REVISION:

Revision G

SPONSOR:

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The signatures below constitutes the approval of this protocol and provide necessary assurances that they have read the protocol, understand it, and will work according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: a guide for manufacturers and notified bodies), MEDDEV 2.12/1 (Guidelines on a Medical Devices Vigilance System), ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), Standards of Good Clinical Practice, or the applicable local and international regulations, whichever provide the greater protection of the individual.

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REVISION HISTORY

Revision Number	Release Date	Change	Reason for Change	DCO #
A	03-Apr-2017	Initial release.	N/A	02749
B	26-Jul-2017	Primary change – Study Population is UUI	To address FDA response to Rev A	03006
C	31-Aug-2017	Primary changes – Revised UUI inclusion criteria, exclusion criteria, and treatment success criteria	To address FDA response to Rev B	03122
D	03-March-2018	Minor updates to clarify Sections on check-in call schedule, study diagram, study schedule, and lead issues	To ensure consistent information across protocol and SAP	03602
E	18-SEPT-2018	Added details of statistical analysis methods from the SAP to the protocol – specifically, primary and secondary endpoints analysis methods, study populations, analysis sets, handling of missing data, sensitivity analysis. Updated language on restarting activation date after lead replacement.	To address FDA response to Rev D	04442
F	06-NOV - 2018	Changed the primary endpoint population to include all implanted subjects per FDA study design consideration Added clarification on the alpha allocation for secondary endpoints	To address FDA study design recommendations and clarify alpha allocation for secondary endpoint analysis	04602
G	11-FEB-2019	Updated MEDDEV version	Used the appropriate MEDDEV version for CE mark approved devices	04940

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STUDY SYNOPSIS

Study Title:	**A**xonics Sac**R**al Neuromodula**TI**on **S**ystem for Urin**A**ry Urgency Incontinence Treatme**N**t: ARTISAN-SNM
Study Device:	Axonics Sacral Neuromodulation System (SNM) System
Study Design:	Single-arm, prospective, multi-center, unblinded pivotal study
Indication for Use:	Axonics Sacral Neuromodulation Therapy for Urinary Control is indicated for the treatment of the symptoms of Urinary Urgency Incontinence (UUI) in patients who have failed or could not tolerate more conservative treatments.
Primary Objective:	To evaluate the safety and effectiveness of the Axonics Sacral Neuromodulation System as an aid in the treatment of the symptoms of UUI designed to gain pre-market approval in the United States.
Secondary Objective:	To evaluate the technical performance and health economics of the Axonics SNM System and the quality of life of patients in the treatment of the symptoms of UUI.
Subjects:	Up to one hundred and forty-five (145) subjects enrolled or at least one hundred and sixteen (116) implanted subjects
Centers:	Up to 20 centers (U.S., Canada, and Western Europe)
Study Duration:	The study duration is expected to be approximately 36 months. The enrollment phase will be approximately 12 months. Subjects will participate in the study for 24 months post activation.
Primary Effectiveness Endpoint:	Proportion of all implanted subjects that are Treatment Responders (i.e. subjects with ≥50% reduction in the number of urgency leaks) is greater than 50% at 6-months post activation.
Secondary Endpoints:	The following secondary endpoints are planned in <u>all implanted</u> subjects at 6-month follow-up • Improvement from baseline in ICIQ-OABqol total score (HRQL)

	• Reduction from baseline in average daily number of urgency leaks • Reduction from baseline in average daily number of large urgency leaks • Reduction from baseline in average daily urgency • Improvement from baseline in average daily number of voids Additionally, the following endpoint is planned in Trial Responders cohort at 6-month follow-up: • Responder rate
Primary Safety Endpoint:	Rate of adverse events (AEs) at 6 months post-activation
Safety Measures:	Adverse device effects (ADEs) Adverse procedure effects (APEs) Serious adverse events (SAEs) Serious adverse device events (SADEs)
Performance Measures:	Device performance metrics Leaks per day with associated urgency and leak magnitude (72-hour voiding diary) Quality of life questionnaires (EQ-5D, ICIQ-OABqol) Subject satisfaction with treatment Bowel function questionnaires (CCF-FIS, CCCS) Medication usage Healthcare utilization
Inclusion Criteria:	Diagnosis of UUI demonstrated on a 72-hour voiding diary defined as: • a minimum of four (4) leaking episodes associated with urgency, • at least 50% of all leaking episodes associated with urgency, and • at least one leaking episode each 24-hour period. Greater than or equal to 6 months' history of UUI diagnosis <u>For male subjects only:</u>

- Peak flow rate > 15 cc/s as verified by uroflowmetry within 6 months prior to enrollment
- Residual bladder volume < 150 cc tested within 6 months prior to enrollment

Positive motor response on at least two (2) implanted electrodes during intraoperative test in the S3 (preferred) or S4 foramen

21 years of age and older

For patients' over 70 years of age, or any patient at the discretion of the Investigator, Edmonton Frail Scale score of 9 or less

Failed conservative therapy and second-line drug therapy and is not a candidate for additional conservative or second-line therapy

No changes to current regimen of medications that affect bladder function for at least four (4) weeks prior to beginning the baseline voiding diary and baseline questionnaires

Willing and capable of providing informed consent

Capable of participating in all testing associated with this clinical investigation

Exclusion Criteria:

More than minimal level of stress incontinence or mixed incontinence with stress component likely to confound study outcome.

Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)

Interstitial cystitis or bladder pain syndrome as defined by either AUA or EAU guidelines

Chronic pelvic pain

History of any pelvic cancer

Uncontrolled hypertension

Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints (e.g. Crohn's disease, moderate to severe fibromyalgia, chronic pain, etc.)

Any psychiatric or personality disorder at the discretion of the study physician

PHQ-15 score of $\geq$15

Current symptomatic urinary tract infection (UTI) or more than three (3) UTIs in past year

Any neurological condition that could interfere with normal bladder function, including stroke, epilepsy, multiple sclerosis, Parkinson's disease, clinically significant peripheral neuropathy, or spinal cord injury (e.g., paraplegia)

Uncontrolled diabetes (A1C > 6.5, documented in the last three (3) months)

Diabetes with peripheral nerve involvement

Treatment of urinary symptoms with botulinum toxin therapy within twelve (12) months prior to SNM implant date

Treatment of urinary symptoms with tibial nerve stimulation within three (3) months prior to SNM implant date

Previously implanted with a sacral neuromodulation device

Underwent an external trial and was deemed a non-responder

Pelvic organ prolapse stage 3 or higher

History of pelvic floor surgery, including surgical treatment for stress incontinence or prolapse, within 6 months prior to SNM implant date

Surgical treatment for stress incontinence (sling, Burch or urethral injection) or pelvic organ prolapse recommended or planned at enrollment

History of allergic response to titanium, zirconia, polyurethane, epoxy, or silicone

Knowledge of planned MRIs on areas other than the head, diathermy, or high output ultrasonic exposure

Any other active implanted devices (e.g., drug delivery pumps, pacemaker, ICD) including neurostimulators whether turned on or off. Passive implants (e.g., prostheses) are allowed, but no implanted metal should be at the Neurostimulator implant site

A female who is breastfeeding

A female with a positive urine pregnancy test

Currently participating in another clinical trial

Sample Size Justification: The study sample size was initially determined considering that

the primary endpoint analysis will be performed in the Trial Responders cohort. The sample size considerations using these assumptions is provided in detail in previous versions of the protocol (Rev A- Rev E).

Based on FDA input, the primary endpoint analysis cohort was changed to all implanted subjects. At this stage (rev F), all subjects have been enrolled and implanted. A justification for why the currently implanted number of subjects is a sufficient sample size is provided below:

The primary effectiveness endpoint hypothesis is that the proportion of all implanted subjects that are Treatment Responders at 6-months is greater than 50% (null proportion).

1. Previous literature on SNM for UUI treatment was used to estimate the expected success rate of all subjects receiving this treatment. These studies[1,2,3] have shown approximately 80-85% of the subjects that receive an external trial proceed to a permanent SNM implant. Long-term (>6 month) clinical success is seen in approximately 80-85% of the subjects with permanent implant. Thus, of all subjects that received SNM therapy, approximately 65-70% are therapy responders at long term follow-up.
2. Assuming that the true proportion of Treatment Responders is 65%, one hundred and sixteen (116) implanted subjects at 6-months provides approximately 90% power to show that the percentage of Treatment Responders is greater than 50%, assuming a one-sided Type I error rate of 0.021. The one-sided Type I error rate of 0.021 is used to account for planned early look analyses (per the Statistical analysis plan).
3. Assuming an attrition rate of 20% between enrollment and the implant procedure due to screen failures and withdrawals, the total number of enrolled subjects will be capped at approximately one hundred and forty-five (145). Therefore, the study will continue to enroll subjects until either:
    - One-hundred and forty-five (145) patients are enrolled

[1] Amundsen CL, Komesu YM, Chermansky C, Gregory WT, Myers DL, et al. Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol. 2018 Jul;74(1):66-73.

[2] Siegel S, Noblett K, Mangel J, Bennett J, Griebling TL, et al. Five-Year Followup Results of a Prospective, Multicenter Study of Patients with Overactive Bladder Treated with Sacral Neuromodulation. J Urol. 2018

[3] White WM, Mobley JD 3rd, Doggweiler R, Dobmeyer-Dittrich C, Klein FA. Incidence and predictors of complications with sacral neuromodulation. Urology. 2009 Apr;73(4):731-5.

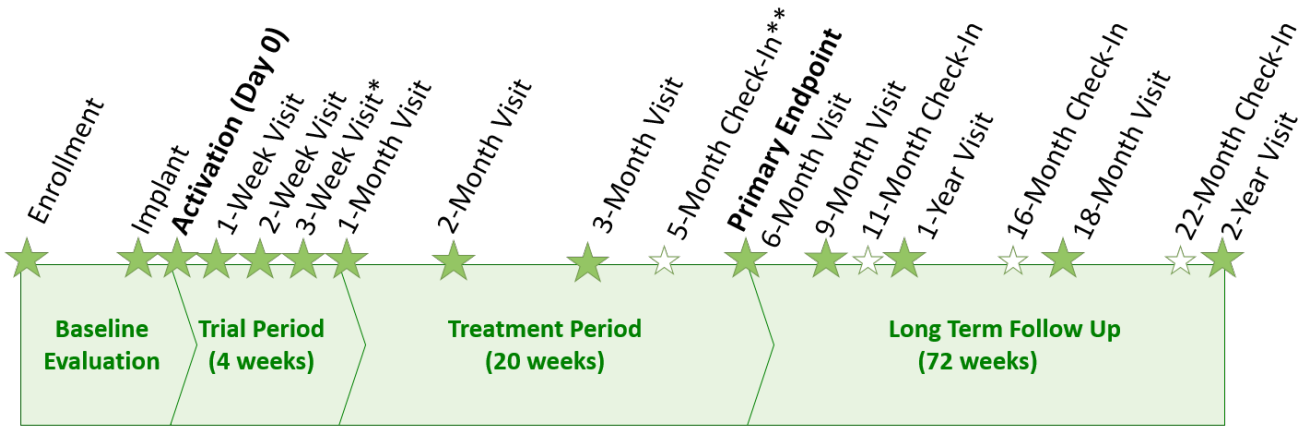
("Enrollment Cap"), or

- There are at least one hundred and sixteen (116) implanted subjects.

Our primary endpoint analysis will be conducted in **All implanted** subjects.

A secondary endpoint analysis will also be performed in the Trial Responder cohort to be comparable to the published literature and standard clinical practice whereby subjects are only implanted after a successful trial period with an external stimulator.

Figure 1: Study Schematic



*3-week visit is not mandatory if patient is already a Trial Responder
**Check-ins are calls or visits without data collection

Table 1: Study Visit Schedule

Visit	Baseline	Implant	Activation (Day 0)	1-Week Visit (Day 7 ± 4)	2-Week Visit (Day 14 ± 4)	3-Week Visit (Day 21 ± 7)*	1-Month Visit (Day 30 ± 7)	2-Month Visit (Day 60 ± 10)	3-Month Visit (Day 90 ± 10)	6-Month Visit (PEP) (Day 180 ± 20)	9-Month Visit (Day 270 ± 30)	1-Year Visit (Day 365 ± 30)	18-Month Visit (Day 545 ± 30)	2-Year Visit (Day 730 ± 45)	Unscheduled
Informed Consent	X														
Demographics & Medical History	X											X		X	
Inclusion/ Exclusion Criteria	X														
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-15	X														
Edmonton Frail Score	X														
Adverse Event Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Procedure Report		X													
Device Performance			X	X	X	X	X	X	X	X	X	X	X	X	X
72-hour Voiding Diary	X			X	X	X	X	X	X	X	X	X	X	X	X****
EQ-5D	X									X		X		X	
CCCS**	X						X		X	X	X	X	X	X	
CCF-FIS***	X						X		X	X	X	X	X	X	
ICIQ-OABqol	X						X		X	X	X	X	X	X	
Subject Satisfaction with Treatment					X		X		X	X	X	X	X	X	
Medication Usage & Healthcare Utilization	X				X		X		X	X	X	X	X	X	X

*3-week visit is not mandatory if subject is responding positively to programming and does not need reprogramming.
** CCCS survey will only be asked after Baseline for patients that had a qualifying score (15 or greater) at Baseline.
***CCF-FIS survey will only be asked after Baseline for patients that had a qualifying score (6 or greater) at Baseline.
****If unscheduled visit is planned in advance, subject should be asked to complete a diary prior to the visit.

1 STUDY DESCRIPTION

1.1 History/Rationale

SNM is a well-established therapy for subjects with Urinary and Fecal dysfunction. To date, over 200,000 subjects worldwide have received InterStim® SNM implants[4].

In 1994, Medtronic obtained CE Marking for SNM for the management of chronic intractable disorders of the pelvis and lower urinary or intestinal tract and is currently the only company marketing this therapy. The device has proven to be safe and effective (see Section 1.2 below), however, improvement in technology could potentially improve the subject experience, reduce costs to the healthcare system and expand access to the therapy.

Medtronic's implantable neurostimulator employs a primary cell battery that requires the device be explanted and replaced on average, every 3-5 years. Additionally, the InterStim neurostimulator uses constant-voltage therapy that does not provide a fixed amount of current as the tissue impedance changes, requiring an adjustment of stimulation amplitude over time to maintain efficacy.

The Axonics SNM System addresses these shortcomings based on the following innovations and improvements:

- A rechargeable battery: The battery inside the Axonics neurostimulator is qualified to last at least 15 years, obviating the need for recurring surgical explants and replacements.
- A smaller neurostimulator size: The Axonics neurostimulator is 5.5 cc, which is 60% smaller than the InterStim neurostimulator, which may improve patient comfort.
- Current-controlled stimulation: The Axonics neurostimulator automatically adjusts output voltage based on tissue impedance, which may provide a more consistent therapy and may reduce the need for stimulation adjustments by the subject and/or physician.

While none of these advancements are expected to modify therapy, it is hypothesized that they may reduce adverse events, lower the risk profile and improve the patient experience.

1.2 Previous Clinical Studies

A recent guidance document by the American Urological Association provides an extensive and systematic literature review on SNM.[5] The guidance stated, "Given the negative effects on quality of life associated with severe incontinence and frequency, the panel judged that benefits of SNM in the appropriate patient outweighed the risks/burdens and notes that patients should be carefully

[4] Siegel, S., Noblett, K., Mangel, J., Griebling, T. L., Sutherland, S. E., Bird, E. T., Irwin, C. P. (2014). Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourology and Urodynamics.

[5] Gormley, E. A., Lightner, D. J., Burgio, K. L., Chai, T. C., Clemens, J. Q., Culkin, D. J., Vasavada, S. P. (2014). Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. Retrieved from https://www.auanet.org/common/pdf/education/clinical-guidance/Adult-Urodynamics.pdf.

counseled regarding the risk/burdens."

The adverse event profile for SNM therapy has been determined to be acceptable. Moreover, the InSite study[6] shows that improvements in implantation technique and the introduction of a smaller neurostimulator and Tined Lead in recent years have led to lower adverse event rates.

To date, the Axonics SNM System was implanted in fifty-one (51) European subjects with symptoms of Overactive Bladder (OAB), including UUI, and urgency-frequency alone or in combination with UUI, in the RELAX-OAB study, a multi-center, prospective, post-market clinical follow-up study.

The 3-month follow-up results of the study indicate that the outcomes and safety profile of the Axonics SNM System are comparable to the InterStim device.

1.3 **Purpose**

The ARTISAN-SNM study is a pivotal study designed to evaluate the safety and effectiveness of the Axonics Sacral Neuromodulation System as an aid in the treatment of the symptoms of UUI designed to gain pre-market approval in the United States.

The secondary objectives of the ARTISAN-SNM study are to evaluate the technical performance, health economics of the Axonics SNM System, and quality of life of patients as an aid in the treatment of the symptoms of UUI.

Given the Axonics SNM System has CE Mark approval, the ARTISAN-SNM study is considered a post-market clinical follow-up study for the European Union (EU).

1.4 **Safety**

All adverse events will be recorded. All reported adverse events will be graded using the Clavien-Dindo classification of surgical complications or Common Terminology Criteria for Adverse events (CTCAE), and adjudicated by an independent DSMB committee. Adverse events will be classified based on seriousness and relatedness ('related' or 'not related') to the subject's device.

The definition of adverse events classified as Serious adverse events is provided in Section 8.6.1. Specifically, the number of events and subject rates of the following will be tabulated and reported:

- Adverse device effects (ADEs)
- Adverse procedure effects (APEs)
- Serious adverse events (SAEs)
- Serious adverse device effects (SADEs)
- Unanticipated adverse device effects (UADEs)

[6] Siegel, S., Noblett, K., Mangel, J., Griebling, T. L., Sutherland, S. E., Bird, E. T., Irwin, C. P. (2014). Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourology and Urodynamics.

1.5 **Effectiveness Endpoint**

The primary effectiveness endpoint is defined as the percent of all implanted subjects who have 50% or greater reduction in the number of urgency leaks at six (6) months (*Details in Section 5.2.3.1*).

The following metrics will also be measured according to the study schedule in Table 1:

- Device performance metrics
- Leaks and voids per day with associated urgency and leak magnitude (72-hour voiding diary)
- Quality of life questionnaires (EQ-5D, ICIQ-OABqol)
- Subject satisfaction with treatment
- Bowel function questionnaires (CCF-FIS, CCCS)
- Medication usage
- Healthcare utilization

1.6 **Study Justification**

The study will be a prospective, multi-center, single-arm pivotal study. Subject outcomes will be compared to their baseline, with subjects serving as their own control. This study will use a performance goal as the primary endpoint metric.

Based on the evaluation of pre-clinical data, risk analysis and that SNM is a well-established therapy, a single-arm study should be sufficient to evaluate the safety and effectiveness of the device. As noted in a recent review[7], numerous studies have been conducted on SNM therapy, including randomized, controlled studies, and this study is expected to provide clinical data comparable to published results.

The study is anticipated to begin enrollment in the second half of 2017 and is expected to complete enrollment within 12 months. The study will be conducted at a maximum of twenty (20) centers in the United States, Canada, and Western Europe. The scheduled visits are shown in the Study Schematic (Figure 1) and Visit Schedule (Table 1). Subjects will be permitted unscheduled follow-ups as needed.

Study sites and investigators will be selected according to the Axonics Site Selection Standard Operating Procedure. They will be selected based on their experience with SNM therapy and their ability to conduct clinical research. At least half of the study sites will be located in the United States to ensure that the outcomes are reflective of the U.S. patient experience.

Reports will be prepared when all subjects reach the primary endpoint, and after the all study subjects have completed their final study visit.

An independent Data Safety Monitoring Board will assess the safety of the device as the study progresses.

[7] Gormley, E. A., Lightner, D. J., Burgio, K. L., Chai, T. C., Clemens, J. Q., Culkin, D. J., Vasavada, S. P. (2014). Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. Retrieved from https://www.auanet.org/common/pdf/education/clinical-guidance/Adult-Urodynamics.pdf.

1.6.1 Intraoperative Test

Per standard SNM procedure, subjects will undergo an intraoperative test to ensure that good motor thresholds are observed from at least two (2) electrodes. If two (2) electrodes produce a satisfactory response, then the subject will be implanted with the Axonics Tined Lead and Neurostimulator (full system implant).

1.6.2 External Trial in Commercial Setting

In a typical commercial setting, patients undergo a surgical procedure to implant a trial lead, which is externalized through the skin and connected to an external stimulator that is worn on the patient's waist. The external trial period can last up to one month, at the end of which subjects who experience ≥50% reduction in symptoms are determined to be "Trial Responders" and undergo a second surgical procedure to have a full system implanted. Patients that do not respond to external trial stimulation are determined to be "Trial Non-responders", and undergo a second procedure to have the lead surgically removed and the external stimulator disconnected.

1.6.3 *Trial Period in ARTISAN-SNM Study*

In the ARTISAN-SNM study, subjects will <u>not</u> undergo "external trial stimulation".

In the ARTISAN-SNM study, subjects will be classified as Trial Responders or Trial Non-responders based on whether or not they have ≥50% reduction in symptoms during the first one-month Trial period.

As is the case in SNM clinical literature and to allow for clinically relevant interpretation of study outcomes, a secondary effectiveness outcome will be performed for subjects classified as Trial Responders.

Forgoing the external trial stimulation period will reduce the number of procedures for the vast majority of subjects. Because the lead is not externalized for the trial period, it is hypothesized that the infection rate will be decreased.

2 STUDY DEVICE

Axonics SNM Therapy for urinary control is CE Marked and indicated for the treatment of fecal incontinence, urinary retention and the symptoms of overactive bladder, including UUI and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments. The Axonics SNM System does not have marketing approval in the U.S.

The Axonics SNM System, as illustrated in Figure 2, is comprised of the following devices:

i. Neurostimulator: rechargeable implanted device that provides electrical pulses to stimulate the target sacral nerve.

ii. Tined lead: a tined lead with four (4) electrode contacts to provide stimulation. The distal tip is implanted through the applicable foramen near the S3 sacral nerve with the proximal end connected to the Neurostimulator. Tines on the lead facilitate fixation of the lead just posterior to the sacral foramen.

iii. Remote control (RC): a non-rechargeable battery-powered device that uses radio-frequency (RF) signals to communicate with the Neurostimulator. The RC allows the subject to check and adjust the stimulation level, to check the status of the Neurostimulator battery charge level and to turn stimulation on or off.

iv. Charger: a portable device powered by a rechargeable battery. The Charger is used for transcutaneous charging of the Neurostimulator through RF induction.

v. Dock: a device that connects to a wall outlet and is used to recharge the Charger.

vi. Clinician programmer (CP): a tablet computer used by a clinician or Axonics Representative to program the Neurostimulator.

The following surgical tools that are required for implantation are also part of the Axonics SNM System:

vii. Foramen needle with needle stylet: used for locating the correct sacral foramen for implant and subsequent acute stimulation testing.

viii. Directional guide: a thin metal rod that holds the position in the sacral foramen as determined by using the foramen needle for the subsequent placement of the introducer sheath and dilator.

ix. Introducer sheath and dilator: tool that increases the diameter of the hole through the foramen to allow introduction of the Tined Lead.

x. Lead stylet (straight or curved tip): a stiff wire that is inserted into the lead to increase its stiffness during lead placement.

xi. Torque wrench: a small wrench used to tighten the setscrew that locks the lead with the Neurostimulator.

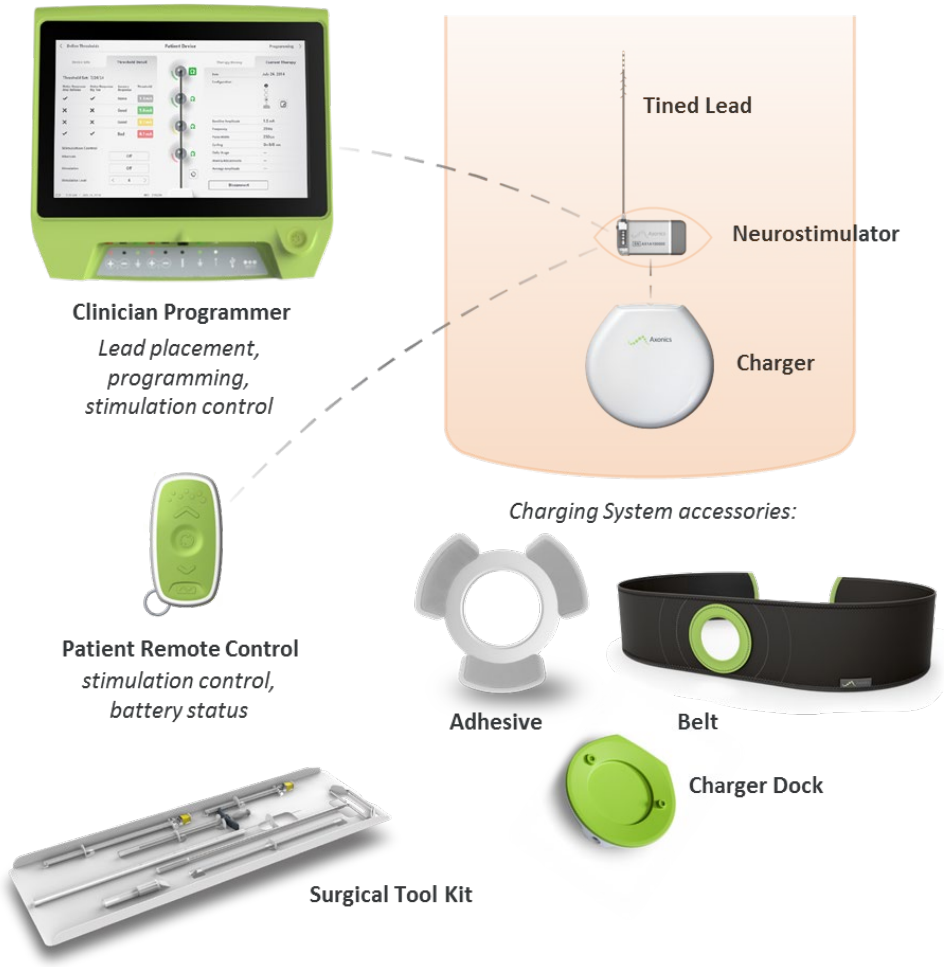
xii. Tunneling tool: a stiff, sharp device that creates a subcutaneous tunnel, allowing the lead to be placed along a path under the skin.

xiii. Needle stimulation cable: a cable provided to connect the CP to foramen needle to

deliver test stimulation during lead placement procedure.

xiv. Lead stimulation cable: cable provided to connect the CP to Tined Lead to deliver test stimulation during lead placement procedure.

Figure 2: The Axonics SNM System



Please see the device manuals for additional information on the device(s) and their use.

All implantable components and surgical tools are single use only. There will be no re-sterilization and no re-use of these components.

3 STUDY POPULATION

Subjects will be recruited from each investigator's patient population. The investigator has the responsibility of screening potential subjects and selecting those who meet the eligibility criteria for the study. A screening form will be filled out by the physician prior to enrolling the subjects, based on the subject's chart review. Candidates will be enrolled in the study only after having met all the inclusion and none of the exclusion criteria, and having given their informed consent.

Subjects who are enrolled in ARTISAN-SNM will be given a subject identification card. The subject should present this card to all active healthcare providers to ensure subject safety and compliance with the ARTISAN-SNM protocol.

3.1 Inclusion Criteria

The following are the inclusion criteria for the study:

Inclusion Criteria:

Diagnosis of UUI demonstrated on a 72-hour voiding diary defined as:

- a minimum of four (4) leaking episodes associated with urgency,
- at least 50% of all leaking episodes associated with urgency, and
- at least one leaking episode each 24-hour period.

Greater than or equal to 6 months' history of UUI diagnosis

For male subjects only:

- Peak flow rate > 15 cc/s as verified by uroflowmetry within 6 months prior to enrollment
- Residual bladder volume < 150 cc tested within 6 months prior to enrollment

Positive motor response on at least two (2) implanted electrodes during intraoperative test in the S3 (preferred) or S4 foramen

21 years of age and older

For patients' over 70 years of age, or any patient at the discretion of the Investigator, Edmonton Frail Scale score of 9 or less

Failed conservative therapy and second-line drug therapy and is not a candidate for additional conservative or second-line therapy

No changes to current regimen of medications that affect bladder function for at least four (4) weeks prior to beginning the baseline voiding diary and baseline questionnaires

Willing and capable of providing informed consent

Capable of participating in all testing associated with this clinical investigation

3.2 Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded from this clinical investigation:

Exclusion Criteria:

More than minimal level of stress incontinence or mixed incontinence with stress component likely to confound study outcome.

Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)

Interstitial cystitis or bladder pain syndrome as defined by either AUA or EAU guidelines

Chronic pelvic pain

History of any pelvic cancer

Uncontrolled hypertension

Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints (e.g. Crohn's disease, moderate to severe fibromyalgia, chronic pain, etc.)

Any psychiatric or personality disorder at the discretion of the study physician

PHQ-15 score of $\geq$15

Current symptomatic urinary tract infection (UTI) or more than three (3) UTIs in past year

Any neurological condition that could interfere with normal bladder function, including stroke, epilepsy, multiple sclerosis, Parkinson's disease, clinically significant peripheral neuropathy, or spinal cord injury (e.g., paraplegia)

Uncontrolled diabetes (A1C > 6.5, documented in the last three (3) months)

Diabetes with peripheral nerve involvement

Treatment of urinary symptoms with botulinum toxin therapy within twelve (12) months prior to SNM implant date

Treatment of urinary symptoms with tibial nerve stimulation within three (3) months prior to SNM implant date

Previously implanted with a sacral neuromodulation device

Underwent an external trial and was deemed a non-responder

Pelvic organ prolapse stage 3 or higher

History of pelvic floor surgery, including surgical treatment for stress incontinence or prolapse, within 6 months prior to SNM implant date

Surgical treatment for stress incontinence (sling, Burch or urethral injection) or pelvic organ prolapse recommended or planned at enrollment

History of allergic response to titanium, zirconia, polyurethane, epoxy, or silicone

Knowledge of planned MRIs on areas other than the head, diathermy, or high output ultrasonic exposure

Any other active implanted devices (e.g., drug delivery pumps, pacemaker, ICD) including neurostimulators whether turned on or off. Passive implants (e.g., prostheses) are allowed, but no implanted metal should be at the Neurostimulator implant site

A female who is breastfeeding

A female with a positive urine pregnancy test

Currently participating in another clinical trial

3.3 **Subject Disposition**

3.3.1 Enrolled Subjects

Subjects who have signed the informed consent form will be considered enrolled in the study and will count towards the Enrollment Cap.

3.3.2 Pre-operative Screen Failures

A subject who has signed the informed consent, is found to not meet the inclusion/exclusion criteria and will not undergo the implant procedure with the device. Subject will be classified as a “Screen Failure.” Any adverse events from the signing of the informed consent to the point of screen failure will be recorded, but no further follow-up will be required. The original signed Informed Consent and any associated adverse event forms will be maintained in the center’s administrative file. All open adverse events should be followed until closed or documented as chronic.

3.3.3 Intraoperative Screen Failures

A subject who has signed the informed consent, in whom the implant procedure is initiated, and does not meet the intraoperative inclusion criteria will not be implanted with the Axonics SNM System. If the subject is not implanted, the subject will be classified as an "Intraoperative Screen Failure" and will be managed according to section 3.3.2.

3.3.4 Implant

A subject who is implanted with the Axonics SNM System as per the study Protocol will be classified as "Implant." These subjects are followed in accordance with the follow-up schedule and included in all study analysis.

3.3.5 Trial Responders/Non-responders

At the end of 1-month Trial period, all subjects will be classified as Trial Responders or Trial Non-responders (Figure 3).

A subject is considered a Trial Responder if at the end of the 1-month of Trial period, they achieve 50% or greater reduction in the number of urgency leaks compared to baseline on the 72-hour diary.

A subject is considered a Trial Non-responder if they did not meet the above criteria for Trial Responder.

3.3.6 Treatment Responders/Non-responders

A subject is considered a Treatment Responder if at a given follow-up visit they achieve 50% or greater reduction in the number of urgency leaks compared to baseline on the 72-hour diary.

A subject is considered a Treatment Non-responder if they have analyzable data at the follow-up visit, but did not meet the above criteria for Treatment Responder.

3.3.7 Withdrawal

A subject who becomes inactive in the study due to, for example, physician recommendation, subject choice, loss to follow-up, or death, will be classified as "Withdrawal."

After a subject has been withdrawn from the study or after a subject has withdrawn his/her consent, for any reason, Axonics will not actively collect any additional data after the point of withdrawal. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used for analysis and all post-withdrawal adverse events will be recorded in the subject file.

For a subject that wishes to withdraw from the study, the investigator must deactivate the device, request return of all external components, and explant the device. Subject decisions must be fully documented on the final case report form. A statement personally signed and dated by the subject

about the decision to withdraw should be filed in the subject binder. The center will use the electronic database to document this decision process.

3.3.8 Subject Lost to Follow-up

If a subject is lost to follow-up, the investigator should make a good faith effort to contact the subject with at least three (3) documented communication attempts (at least one of which must be in writing). The investigator should inform the subject of the option to withdraw.

If a subject relocates during the clinical trial, efforts will be made to maintain the subject in the study if reasonable travel expenses allow continued participation, provided payment of travel expenses by the sponsor is permitted by applicable law. Alternatively, the subject may be transferred to another clinical trial site, if one is available in the new geography. If the subject cannot be transferred to another clinical site, then the investigator will withdraw the subject from the study as described above.

3.4 **Subject Care**

The following sections contain general guidance on dealing with device explant and/or replacement. Axonics does not recommend the removal of the implanted Neurostimulator except in cases of uncontrolled infection, suspected damage to surrounding tissues that may be worsening because of the implant, or intolerable side effects that are not mitigated with inactivating the system.

The decision to explant or replace an implanted device should be made by the subject with appropriate counsel by the physician on procedural risks. A qualified physician who has been trained in the implant/explant of the Axonics SNM System must perform these procedures according to the device manuals.

3.4.1 Implanted Lead Issues

In the event that the implanted Tined Lead fails, migrates, or is implanted in an undesired position such that adequate therapy cannot be provided, Axonics recommends revising or replacing the lead. Tined Lead revision and replacement does not require a Neurostimulator replacement, however, the physician has the option to replace the Neurostimulator at that time. If the subject does not wish to undergo a replacement in the case of lead failure, their device should be deactivated. If a Tined Lead replacement occurs, the original activation date shall remain as Day 0.

3.4.2 Explanting the Neurostimulator

In the event that a Neurostimulator needs to be surgically revised (for example, in the case of infection or significant pain at the Neurostimulator site), the device may be moved or replaced and the original activation date shall remain as Day 0.

3.4.3 Deactivating the Axonics SNM System

In some cases, the subject may elect to leave the device implanted, but no longer activated. Leaving the Tined Lead and/or Neurostimulator implanted does not add significant risk to the subject.

Subjects who elect to leave a device implanted that is not activated must return their external devices to the clinical site.

3.5 **Study Termination**

3.5.1 Study Completion

The study may be closed when the following occurs:

- The Enrollment Cap has been met or eighty-one (81) Trial Responders have reached the 1-month follow-up.
- All the subjects have met one of the following criteria:
  - Subject has completed the final study follow-up visit
  - Subject has a mandated or elective deactivation/explant of the device with completion of required follow-up per protocol
  - Subject is withdrawn from the study or is lost to follow-up

When a subject completes the final study visit, they will be allowed to continue to use the Axonics SNM System and be treated by their physician according to the normal standard of care.

Axonics expects that the study will run to completion prior to being closed. In the case of an unexpected issue, the following contingency plans will be enacted.

3.5.2 Study Closure

If the Data Safety and Monitoring Board (DSMB) determines there is sufficient concern for subject safety and/or there is a logistical reason to discontinue the study (e.g., lack of enrollment), Axonics reserves the right to terminate the study. In the case of a safety concern, devices may be deactivated and/or explanted.

- If the study is terminated, the reasons for this decision will be documented and the information will be provided to the investigator.
- All external components must be returned to Axonics.
- Adverse events will be followed until closure or documented as chronic.

3.5.3 Clinical Site Closure

Axonics, with or without advice from the DSMB, reserves the right to close a clinical site at any stage based on reasonable written notice to the investigator.

The investigator may also discontinue participation in the study with reasonable written notice to Axonics.

Should either of these events occur, the investigator shall:

- return all documents and devices to the sponsor
- provide a written statement as to why the investigator would like to discontinue participation
- notify the Ethics Committee and the regulatory authority (as applicable)
- arrange for continued follow up of already enrolled participants (as applicable)

4 DATA COLLECTION AND MANAGEMENT

4.1 Procedures and Steps

Table 1 lists the assessments required for each visit, as well as the time window for each visit. This section describes the visit requirements and each assessment.

If a subject has temporary illness or an adverse event that is likely to interfere with the interpretation of the data collection (e.g., diarrhea, common cold, urinary tract infection), then the physician may postpone the visit outside the visit window and treat the subject according to the usual standard of care. The physician shall make a determination if stimulation should be active during the temporary illness period. The visit data should be collected as soon as possible once the illness/adverse event has cleared.

If the stimulation was turned off for any reason, then the visit shall be postponed and the diary and other data collected once the stimulation has been on for at least one week. In the case that stimulation was off, it should be reactivated and remain on at all times.

4.1.1 Enrollment & Baseline

The investigator will identify subjects for inclusion in the study using accepted medical practice (e.g. screening subject records).

A pre-screening form that is provided by the sponsor shall be completed by the investigator to ensure that there is the potential for the subject to meet the inclusion and exclusion criteria.

Only information that is available through the standard of care shall be used to complete pre-screening.

The subject must be following a stable regimen of medical/drug therapy with no anticipated changes in therapy for a period of at least six (6) months following implantation. Any changes to medical/drug therapy during the study are highly discouraged unless it becomes a medical necessity.

A urine pregnancy test will be administered if the subject is female and of child-bearing potential. Female subjects of child-bearing potential must remain on adequate contraception, including surgical sterilization, hormonal methods, intrauterine devices, barrier methods, spermicidal methods, or abstinence.

Before signing the consent form, subjects must have the potential to meet all of the inclusion criteria and none of the exclusion criteria. Only subjects identified as eligible and who have consented will be implanted with the Axonics SNM System according to the implant manuals.

Once a subject has signed the informed consent, they will begin the baseline evaluations as listed in Table 1. Baseline questionnaires and the 72-hour bladder diary should be completed and entered into the electronic database at least 7 days prior to the implant procedure date to allow for review for completeness and to ensure that the inclusion/exclusion criteria are met. Axonics reserves the right to require that the implant procedure be postponed if the data is not entered 7 days prior to the implant procedure date.

After signing informed consent, subjects will be given written and verbal instruction and may be shown instruction videos on how to complete their diaries and how to use the Axonics SNM System.

To ensure that the subjects can refer to this information as needed, subjects may be provided with an electronic tablet containing informational videos to use for the duration of the clinical study.

4.1.2 Implant

A qualified physician who has been trained on the Axonics SNM System implantation must perform the implant. In the absence of specific guidance from Axonics on surgical procedures (such as anesthesia, surgical cut-down, post-operative wound care), the physician should follow their usual standard of care.

The following are requirements of the study protocol:

- Subjects must use an antiseptic wash the night before surgery.
- Appropriate intravenous antibiotics must be administered at the time of the surgical procedure.
- Surgical procedure will be performed under general anesthesia, conscious sedation, or MAC anesthesia. Use of muscle relaxants should be avoided to allow for observation of intraoperative motor responses.
- Lead impedance measurements must be obtained and recorded at the time of implant to verify system integrity. Impedances should be within 400 to 6000 ohms. Physicians should refer to the Clinician Programmer Manual for information on troubleshooting impedances that are not within range.
- Intra-operative testing must be performed. Stimulation must evoke motor responses consistent with the S3 sacral nerve at motor thresholds less than 4mA on at least two (2) electrodes to confirm acceptable Tined Lead placement and proceed with the Neurostimulator implant. Motor threshold is defined as the lowest stimulation amplitude that provides a clear anal bellows with or without big toe flexion. Sensory threshold is defined as the lowest stimulation amplitude that provides a feeling of “tapping”, “pulling” or “tingling” in the rectum, extending forward to scrotum or vagina and/or labia. Subjects who do not provide a positive motor response to intra-operative testing will be managed according to Section 3.3.3.
- Tined Lead placement must be verified with lateral and anterior-posterior fluoroscopy. The lead must be in the S3 (preferred) or S4 foramen. An image of the lateral fluoroscopy showing the position of the tined lead must be captured and maintained by the site.
- Neurostimulator implanted no deeper than 3.0 cm below the skin.
- Neurostimulator implanted horizontally with the ceramic side farthest from the midline.
- Wound should be irrigated prior to closure.

4.1.3 Activation (Day 0)

Activation should occur between zero (0) and fourteen (14) days of the implant. On the day of stimulation activation, the following steps should be taken:

- The subject will be instructed on how to use the Remote Control and Charge System.
- Subjects should be instructed to charge the device for approximately one hour every week. Any subject that has difficulty charging the device due to post-operative pain, fluid in the pocket, or difficulty placing the charger in an effective location should be provided further training at the clinical site.
- A study card indicating the subject is enrolled in a clinical trial using an experimental device, as well as an ARTISAN-SNM Subject Therapy Guide that details the charging of the device and safety related information will be given and reviewed with each subject.
- Stimulation should be turned on and programmed to an appropriate level as described in the device manuals.
- A voiding diary should be provided with instructions given to the subject that the diary must be completed within seven (7 days) prior to the next visit.
- The evaluations listed in Table 1 must be completed.
- Subjects should be reminded to continue to take their medications as prescribed and to be consistent with their fluid intake.
- The initial programming should be set to a stimulation frequency of 14 Hz and pulse width of 210μs.
- The amplitude should be set to a level where the stimulation can be felt, but is not uncomfortable.
- Bipolar stimulation is recommended, with the cathode placed so that the stimulation is felt in the areas between the vagina/scrotum and the rectum and the anode placed as far from the cathode as possible.
- The subject should be advised to increase amplitude, as necessary, to ensure that stimulation can be felt.

4.1.4 Scheduled Follow-Up Visits

At each follow-up visit, the following steps should be taken:

- Ensure the evaluations listed in Table 1 are completed.
- A voiding diary completed within seven (7) days prior to the next visit.
- Stimulation should be checked to ensure optimal therapy. If some reduction in symptoms occurred, but the subject no longer feels the stimulation, the stimulation amplitude should be increased. If good results were experienced, but unwanted or uncomfortable stimulation occurs, then stimulation amplitude, pulse width and/or frequency can be adjusted. If the subject did not experience symptom reduction, another electrode configuration should be tried. Refer to Clinician Programmer Manual for more information on ensuring optimal therapy and guidance regarding the stimulator's output limitations.
- A review of the operation of the Remote Control and Charge System use should be given, if

needed.

- Subjects should be reminded to continue to take their medications as prescribed and to be consistent with their fluid intake.

4.1.5 Unscheduled Follow-Up Visits

Subjects are allowed to make unscheduled follow-up visits as necessary, especially if adjustments to their stimulation are required to improve therapy. At each unscheduled follow-up visit, the following steps should be taken:

- Stimulation should be checked to ensure optimal therapy. If necessary, the clinician or Axonics Representative may adjust the programming parameters to optimize therapy as described in Section 4.1.3.
- A review of the operation of the Remote Control and Charge System use should be given, if needed.
- Subjects should be reminded to continue to take their medications as prescribed and to be consistent with their fluid intake.
- Any new adverse events should be documented.
- If feasible, a 72-hour diary should be completed prior to the visit.

4.1.6 Check-In Visits

Sites will attempt check-in calls or see the subject in the clinic at approximately 5 months, 10 months, 16 months, and 22 months to ensure subjects are adhering to the protocol and to remind them to complete their 72-hour diaries for the next follow-up visit.

4.2 **Data Collection**

4.2.1 Demographics and Medical History

General information about the subject population will be collected. The following items will be collected:

- Gender, Race, Age, Education level
- Secondary diagnoses (stress incontinence, urinary frequency, retention, fecal incontinence, other, none)
- Years since diagnosis of UUI
- Number of voids per day, number of leaks per week, and number of nighttime voids from subject recollection
- Past medical and surgical history, including past UUI treatments and medications
- Gravidity and parity of female subjects

4.2.2 Vital Signs

Subject's blood pressure and temperature must be collected. Height and weight will be collected at

baseline.

4.2.3 Procedure Report

Information pertaining to the implant procedure will be collected, including the following:

- Motor and sensory thresholds (as applicable) obtained on all four electrodes. Thresholds are defined in Section 4.1.2.
- Tined Lead location (S3/S4 sacral foramen, left/right)
- Stylet used (curved or straight)
- Duration of procedure
- Type and amount of antibiotic used

4.2.4 Device Performance Metrics

The following items will be collected to assess performance of the Axonics SNM System, as applicable:

- Impedances on all electrodes. Impedances should be within 400 to 6000 ohms. Physicians should refer to the Clinician Programmer Manual for information on troubleshooting impedances that are not within range.
- Electrode configurations and stimulation parameters at office arrival and upon departure (after programming optimization)
- Charging history from the Neurostimulator
- Number of hours stimulation has been ON since last visit
- Subject's ability to recharge the device

4.2.5 Voiding Diary

A voiding diary will be recorded over 72 consecutive hours (3 days) to record the subject's voiding habits. The information collected includes the following:

- Number of voids
- Number of urinary incontinence episodes with magnitude of leakage
- Number of urgency episodes with severity

A member of the study staff must review all 72-hour diary data with the subject before the subject leaves the clinic to ensure that the data was filled out correctly and accurately.

4.2.6 Quality of Life Assessments

4.2.6.1 EQ-5D

The EQ-5D is a short, generic, validated quality-of-life instrument used to measure health outcomes. It is widely used to calculate health economic benefits of therapies. It takes about five minutes to complete.

4.2.6.2 ICIQ-OABqol

The ICIQ-OABqol is a validated quality-of-life questionnaire designed to provide a robust assessment of the impact of OAB in subjects' lives. It consists of 26 questions and takes about 15 minutes to complete.

4.2.7 CCF-FIS

The Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS) is a five (5) question survey assessing severity of fecal incontinence symptoms. The questions cover incontinence to gas, liquid, solid, need to wear pad, and lifestyle changes. Each question is scored on a scale from zero (absent) to four (daily). The survey takes less than 5 minutes to complete.

4.2.8 CCCS

The Cleveland Clinic Constipation Score (CCCS) is an eight (8) question survey that assesses the severity of constipation symptoms. The questions cover the frequency and difficulty of bowel movements, associated sensations of completeness and pain, and the subject assessment of time, assistance, and failure associated with their attempts to evacuate their bowels. The survey takes less than 5 minutes to complete.

4.2.9 Subject Satisfaction with Treatment

Subjects will be asked to rate how satisfied they are with their treatment. Subjects will also be asked if they were able to successfully charge their device, how easy it is to charge their device, and how they feel about how long and how often they have to charge their device. All responses will be provided on a 7-point Likert scale, ranging either from "Very satisfied" to "Very dissatisfied" or from "Definitely" to "Definitely Not".

4.2.10 Medication Usage

Subjects will be asked about their medication usage and dosages, including any changes from the previous visit (except at baseline).

4.2.11 Healthcare Utilization

Subjects will be asked about their healthcare utilization, including visits to medical specialists, hospital stays, and other healthcare use such as physical therapy and acupuncture. This information will be used to assess the reduction in healthcare costs due to SNM therapy.

4.2.12 Screening Tools

4.2.12.1 PHQ-15

The Patient Health Questionnaire (PHQ) is a diagnostic tool for mental health disorders used by health care professionals that is quick and easy for patients to complete. The PHQ-15 is used to assess somatic symptom severity and the potential presence of somatization and somatoform disorders.

4.2.12.2 Edmonton Frail Scale

The Edmonton Frail Scale is an assessment of subject frailty that is administered by a physician or nurse

and takes 20 minutes to assess the 10 frailty domains including general health, cognition, balance, and mobility.

5 DATA ANALYSIS AND MANAGEMENT

5.1 Data Management Process

Details of the data management process will be specified in the ARTISAN-SNM Data Management Plan.

5.1.1 Source Documents and Source Document Verification

Source documentation related to subjects' participation in this study is required. The investigator must maintain original source documents that are accurate, complete, and current. Source documentation includes, but is not limited to the following:

- Subject consent form
- Electronic and paper data collection forms, including subject diaries and questionnaires
- Subject's medical file
- Programmer printouts and/or reports
- Prescribed medications
- Hospitalization/clinical events

Source documentation is also required for all protocol related-testing and in the occurrence of adverse events.

The details of how the subject diaries and questionnaires will be collected will be included in the Data Management Plan. All other data shall be entered into the database directly by the sites using an electronic data capture system (EDC) using electronic Case Report Forms (eCRFs).

The data entry should be done within 7 working days of each study visit, with the exception of Adverse Events. All applicable adverse events must be reported by all possible means to Axonics as described in section 8.7. These means include entering the adverse event data into the study database or e-mailing the information to the dedicated clinical email address.

5.2 Data Analysis and Statistical Determination

5.2.1 Data Analysis

Axonics, or a designated representative, will be responsible for all data analysis. A detailed statistical analysis plan that details the planned analysis of the data will be created and approved prior to analysis of the endpoints.

Axonics, or a designated representative, will be responsible for compiling and submitting all required reports to governmental agencies.

In support of study conduct, designated Axonics personnel may need to review key data. These personnel will have unrestricted "Read Only" access to the Axonics study database. The DSMB may need to conduct independent verification of the Axonics data analysis and any additional, separate, or independent analysis of data, desired or deemed necessary by the DSMB, will be discussed with Axonics prior to conducting such additional analyses.

Adjustments to the statistical analysis plan and/or protocol will be made as needed and will be documented appropriately with notifications to the competent authorities and IRBs/ECs as required. The primary analysis of the study will be prepared when all subjects reach the primary endpoint and another analysis will be performed at the one-year endpoint. A final report after the study has been completed will also be prepared. The safety related aspects of these analyses and reports will be provided to the DSMB according to the DSMB Charter. The reports will follow ISO 14155: 2011 guidelines. Axonics will be responsible for preparation of the study final report. The report shall be reviewed and signed by all principal investigators and forwarded to IRBs/ECs and FDA/Competent Authorities as required.

5.2.2 Sample Size Justification

The study sample size was initially determined considering that the primary endpoint analysis will be performed in the Trial Responders cohort. The sample size considerations using these assumptions is provided in detail in previous versions of the protocol (Rev A- Rev E).

Based on FDA input, the primary endpoint analysis cohort was changed to all implanted subjects. At this stage (rev F), all subjects have been enrolled and implanted. A justification for why the currently implanted number of subjects is a sufficient sample size is provided below:

The primary effectiveness endpoint hypothesis is that the proportion of all implanted subjects that are Treatment Responders at 6-months is greater than 50% (null proportion).

1. Previous literature on SNM for UUI treatment was used to estimate the expected success rate of all subjects receiving this treatment. These studies[8,9,10] have shown approximately 80-85% of the subjects that receive an external trial proceed to a permanent SNM implant. Long-term (>6 month) clinical success is seen in approximately 80-85% of the subjects with permanent implant. Thus, of all subjects that received SNM therapy, approximately 65-70% are therapy responders at long term follow-up.

2. Assuming that the true proportion of Treatment Responders is 65%, one hundred and sixteen (116) implanted subjects at 6-months provides approximately 90% power to show that the percentage of Treatment Responders is greater than 50%, assuming a one-sided Type I error rate of 0.021. The one-sided Type I error rate of 0.021 is used to account for planned early look analyses (per the Statistical analysis plan).

3. Assuming an attrition rate of 20% between enrollment and the implant procedure due to screen failures and withdrawals, the total number of enrolled subjects will be capped at approximately one hundred and forty-five (145). Therefore, the study will continue to enroll subjects until either:

- One-hundred and forty-five (145) patients are enrolled (“Enrollment Cap”), or

[8] Amundsen CL, Komesu YM, Chermansky C, Gregory WT, Myers DL, et al. Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol. 2018 Jul;74(1):66-73.

[9] Siegel S, Noblett K, Mangel J, Bennett J, Griebling TL, et al. Five-Year Followup Results of a Prospective, Multicenter Study of Patients with Overactive Bladder Treated with Sacral Neuromodulation. J Urol. 2018

[10] White WM, Mobley JD 3rd, Doggweiler R, Dobmeyer-Dittrich C, Klein FA. Incidence and predictors of complications with sacral neuromodulation. Urology. 2009 Apr;73(4):731-5.

- There are at least one hundred and sixteen (116) implanted subjects.

Our primary endpoint analysis will be conducted in **All implanted** subjects.

A secondary endpoint analysis will also be performed in the Trial Responder cohort to be comparable to the published literature and standard clinical practice whereby subjects are only implanted after a successful trial period with an external stimulator.

5.2.3. Analysis Sets

The following analysis sets will be utilized for primary endpoint analyses. All subjects will be included for analysis as defined in the Statistical analysis plan and Study protocol. None of the implanted subjects will be excluded from analysis for reasons such as previous medical history, clinical diagnosis etc.

5.2.3.1 As-Treated

The primary endpoint As-Treated analysis will include subjects implanted with the Axonics SNM that have data available. Additionally, implanted subjects with missing data, or subjects that are intraoperative screen failures, will also be included in this analysis, and their data will be imputed based on the circumstance of the missing data. Details on Missing data imputation are provided in Section 11.4.

Adverse event data will be based on all implanted subjects and intra-operative screen failures. Pre-operative screen failures will be excluded from all analyses, and will be presented separately.

5.2.3.2 Per Protocol

The per protocol analysis set will include all subjects in the As-Treated set that have no major protocol deviations (e.g., failed intraoperative testing but was implanted) that would potentially affect study outcomes.

Screen failures will be excluded from effectiveness analyses, and will be presented separately.

All safety data will be summarized and analyzed based on all implanted subjects and intraoperative screen failures.

5.2.4 *Analysis methods*

5.2.4.1 Primary Endpoint

The primary effectiveness endpoint is that the proportion of all implanted subjects that are Treatment Responders is greater than 50% at 6-months post-activation. If the proportion of Treatment Responders is statistically greater than 50%, the study will be considered to be a success.

As mentioned above , a secondary endpoint analysis analysis will also be conducted in subjects who are ”Trial Responders” to allow for a direct comparison to the published SNM literature where analysis at follow-up visits are performed only in trial responders i.e. subjects that have ≥50% improvement in

symptoms after a one-month trial with an external stimulator.

The primary endpoint will be tested for significance based on a one-sided binomial test (such as Fisher's exact test) at a 2.1% significance level to account for two additional early looks as detailed in the Statistical Analysis Plan.

The primary safety endpoint of the study is the rate of adverse events (AEs) through 6-months.

5.2.4.1.1 Hypothesis Statement – Primary Effectiveness

The null hypothesis states the percentage of all implanted subjects that are Treatment Responders at 6-months is less than 50%. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the percentage of Treatment Responders is greater than 50%.

Therefore, the hypotheses to be tested are:

H_0: $\pi \leq 0.5$

H_a: $\pi > 0.5$

where π is the percentage of all implanted subjects that are that were Treatment Responders at 6 months.

5.2.4.2 Secondary effectiveness endpoints

A total of six (6) secondary endpoints are planned, five (5) of which are in all implanted subjects, and one (1) in Trial Responder subjects. The analysis of all secondary effectiveness endpoints will be based on all available data. Details on handling of missing data are provided in Section 5.2.4.6.

5.2.4.2.1 Responder Rate in Trial Responder Subjects at 6-Month Follow-Up

This secondary effectiveness endpoint is that the proportion of Trial Responder subjects that are Treatment Responders is greater than 50% at 6-months post-activation. The null hypothesis states the percentage of Trial Responders that are Treatment Responders at 6-months is less than 50%. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the percentage of Trial Responders that are Treatment Responders is greater than 50%.

Therefore, the hypotheses to be tested are:

H_0: $\pi \leq 0.5$

H_a: $\pi > 0.5$

where π is the percentage of Trial Responder subjects that are Treatment Responders at 6-months.

5.2.4.2.2 Improvement from Baseline in ICIQ-OABqol Total Score (HRQL)

The null hypothesis states that the improvement from Baseline in ICIQ-OABqol Total Score (HRQL) among all implanted subjects is greater than 0 points at 6-month follow-up visits. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the improvement from baseline in this secondary effectiveness endpoint is no more than 0 points. The hypotheses to be

tested are:

H_0: $\mu \leq 0$

H_a: $\mu > 0$

where μ is the improvement from Baseline in ICIQ-OABqol Total Score (HRQL) at 6-months among all implanted subjects.

5.2.4.2.3 Reduction from Baseline in Average Daily Number of Urgency Leaks

The null hypothesis states that the reduction from Baseline in the average number of daily leaks with urgency is greater than 0 at 6-month follow-up visit for all implanted subjects. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the reduction from baseline in this secondary effectiveness endpoint is no more than 0. The hypotheses to be tested are:

H_0: $\mu \leq 0$

H_a: $\mu > 0$

where μ is the reduction from Baseline in the average number of daily urgency leaks at 6-months in all implanted subjects.

5.2.4.2.4 Reduction from Baseline in Average Daily Number of Large Leaks with Urgency

The null hypothesis states that the reduction from Baseline in the average number of daily large leaks associated with urgency is greater than 0 at 6-month follow-up visit in all implanted subjects. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the reduction from baseline in this secondary effectiveness endpoint is no more than 0. The hypotheses to be tested are:

H_0: $\mu \leq 0$

H_a: $\mu > 0$

where μ is the reduction from Baseline in the average number of daily large leaks with urgency at 6-months in all implanted subjects.

5.2.4.2.5 Reduction from Baseline in Average Daily Urgency

The null hypothesis states that the reduction from Baseline in the average daily urgency is greater than 0 at 6-month follow-up visit for all implanted subjects. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the reduction from baseline in this secondary effectiveness endpoint is no more than 0. The hypotheses to be tested are:

H_0: $\mu \leq 0$

H_a: $\mu > 0$

where μ is the reduction from Baseline in the average daily urgency at 6-months in all implanted subjects.

5.2.4.2.6 Improvement from Baseline in Average Daily Number of Voids

The null hypothesis states that the improvement from Baseline in the average number of daily voids is greater than 0 at 6-month follow-up visit for all implanted subjects who had at least eight (8) average daily voids at Baseline. Rejection of the null hypothesis indicates that the observed data support the alternative hypothesis that the improvement from baseline in this secondary effectiveness endpoint is no more than 0. The hypotheses to be tested are:

H_0: $\mu \leq 0$

H_a: $\mu > 0$

where μ is the improvement from Baseline in the average number of daily voids at 6-months in all implanted subjects who had at least eight (8) average daily voids at Baseline.

5.2.4.3 Analysis of Secondary Effectiveness Endpoints

The secondary effectiveness endpoints that are collected as continuous measures will be tested for significance based on two-sided t-test or paired t-test, as appropriate. If the underlying data distribution is found to be non-normal, a non-parametric method (e.g., Wilcoxon signed-rank test) may be employed. The secondary effectiveness endpoints that are collected as binomial measures will be tested for significance based on a binomial test (such as Fisher's exact test).

After evaluation of the primary endpoint hypothesis, secondary effectiveness endpoints will be evaluated in a serial manner. To control for family-wise error rate, Holm's correction for multiple testing will be utilized. If the null hypothesis of the primary effectiveness endpoint is not rejected, no further testing of any of the other endpoints will occur. If the null hypothesis of the primary endpoint is rejected, the significance testing of the secondary endpoints can commence.

To control for a family-wise error rate among the six secondary effectiveness endpoints, Holm's correction will be implemented with a total α=5%. To account for an early look analysis performed on the 6-month data, Axonics plans to allocate no more than α=2.5% for the early analysis. The final analysis will be allocated alpha of 2.5% along with any remaining alpha from the early analysis.

Therefore, for each analysis (early and final) the unadjusted p-values from the testing of the six secondary endpoints will be ordered from smallest to largest. For the early analysis, the smallest p-value will be compared to the cut-off value of 0.025/6=0.0041, the next one being compared to 0.025/5=0.005, the next one being compared to 0.025/4=0.00625 and so forth. For the final analysis, any alpha remaining from early analysis will be added to 0.025 and will be used for comparing cut off values. The null hypotheses will be rejected for the tests where the unadjusted p-value is smaller than the corresponding cut-off value, and for all sequentially preceding hypothesis tests.

5.2.4.4 Control of Systematic Bias

Several measures are incorporated into the study design to help minimize study bias as follows:

1) This is a multi-center trial to help ensure that investigator or site or subject enrollment bias is minimized. Selection of subjects will be made from the Investigator's usual subject load. Consecutively eligible subjects should be enrolled into the study.
2) This document specifies appropriate statistical methodology to ensure that bias is minimized.
3) Standardized and validated questionnaires will be used to collect data during the study. Although many of the data collected would be considered subjective in nature, the standardization and validation of these metrics helps to remove systematic bias introduction into the study data.

5.2.4.5 Pooling Data across Centers

Up to 20 sites will enroll subjects into the study. The analyses will be presented using data pooled across study centers. Comparability between study sites, and US and non-US sites, will be examined based on the primary endpoint of Treatment Responder rate. Summary statistic for the Treatment Responder rate will be calculated by site and geographical area. A formal assessment of the poolability of subjects across sites will be performed.

5.2.4.6 Handling of Missing Data

5.2.4.6.1 Primary endpoint

The analysis of the primary effectiveness endpoint will be based on all available data. The missing data for implanted subjects will also be included in the analysis, and imputed based on the circumstance of the missing data. The following missing data classes have been identified:

Missing not at Random (MNAR):

Subjects that are intraoperative screen failures or explanted or withdrawn due to adverse event(s) or lack of efficacy will be considered treatment failures and their baseline diary data will be used as the primary endpoint diary data.

Missing at random (MAR):

Primary endpoint data for subjects who are missing at random (e.g., missed visits, incomplete data capture, withdrawals not related to safety or efficacy of device, death, loss to follow-up) will be imputed and analyzed using a multi-stage multiple imputation technique as follows:

- **Preliminary step**: the following variables will be considered in the multiple imputation procedure:
  - Age
  - Gender
  - Secondary diagnoses (stress incontinence, urinary frequency, retention, fecal incontinence, other, none)
  - Years since diagnosis of UUI

    - Average daily number of urgency leaks at Baseline, Month 1, 2 and 3 visits.
- **Step 1**: Given the likely arbitrary missing data pattern, Markov Chain Monte Carlo (MCMC) method will first be used to impute just enough missing values among the variables to create a monotone missing pattern as needed for the monotone logistic regression imputation in Step 2.
- **Step 2**: A logistic regression model will be used to impute the missing values for the binary primary endpoint at Month 6 based on the partially imputed datasets created in Step 1. 200 imputed datasets will be created.
- **Step 3**: Each of the 200 imputed datasets created in Step 2 will be analyzed separately using binomial proportion estimation for the primary effectiveness endpoint at Month 6 to obtain parameter estimates of proportion and standard error.
- **Step 4**: Results obtained in Step 3 will be combined using the usual Rubin's rules for combining the imputed samples to account for variability of different imputations. This allows for a valid hypothesis test of the primary endpoint.

5.2.4.6.2 Secondary and Exploratory endpoints

For secondary and exploratory endpoint analyses that use subject-reported outcomes/ questionnaires, missing data will be addressed by the specific scoring guideline provided by the questionnaires. In the cases where the response does not contribute to a score, no imputation will be performed. Subjects with missing or incomplete diaries at 6 months will be included in the secondary/exploratory endpoint analysis by using their Baseline diary data.

5.2.4.7 Tipping point analysis

A sensitivity analysis of tipping point will be performed to assess the robustness of the primary endpoint results. Tipping point analysis will summarize all possible combinations of missing data, where each missing value is replaced with either Treatment Responder or Non-responder.

6 RISK/BENEFIT ANALYSIS

6.1 Risks

A risk assessment in accordance with ISO14971:2012 was conducted.

The risks of complications associated with implanting the Axonics SNM System are comparable with general risks associated with any standard surgical procedure. The following risks and discomforts have been identified in relation to the SNM therapy:

- Worsening of bladder and/or bowel function
- Allergic or immune system response to the implanted materials
- Change in sensation or magnitude of stimulation which has been described as uncomfortable by some subjects
- Infection
- Pain or irritation at Neurostimulator and/or Tined Lead site
- Seroma, hemorrhage, and/or hematoma
- Tined Lead or Neurostimulator migration or erosion
- Nerve injury (including numbness)
- Technical device malfunction
- Transient electric shock or tingling
- Unintended nerve activation
- Heating or burn at Neurostimulator site

The risks of the procedure include exposure to anesthesia and exposure to radiation from fluoroscopy. These risks are the same as expected from the procedure of the commercially available SNM system.

The risks associated with participation in this study will be similar to those associated with commercially available SNM therapies. The risks of participation in this study will be minimized by careful subject and site selection, as well as by implementing monitoring procedures to ensure proper conduct and management of the study.

Consult the device manuals for additional information regarding the risks associated with the Axonics SNM System. Any safety directive from Axonics to the ARTISAN-SNM investigators will be reported according to applicable regulations.

In case of any unexpected Adverse Device Effect or Serious Adverse Device Effect, investigators will be informed. Investigators shall forward this information to their IRBs/ECs as per local requirements. Any unexpected Adverse Device Effect or Serious Adverse Device Effect will be reported by Axonics in accordance with applicable US FDA regulations.

6.2 Risk-Benefit Analysis

As noted in Section 1.2, the commercially available InterStim device has been shown to have a favorable risk-benefit profile, especially given the low incidence of adverse events and significant improvements in quality of life with SNM therapy.

The Axonics SNM System has been thoroughly tested to ensure that the device will perform as anticipated, and the benefits of the system are expected to be similar to the InterStim device.

Results from the RELAX-OAB post-market follow-up study indicate that the Axonics SNM System has a similar safety and effectiveness profile to the InterStim device.

The use of the device is designed to protect the health and safety of the patient, user, and environment. Therefore, the device is appropriate for the intended use, the potential benefits of the device outweigh the risks, and all the applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the patient.

7 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

7.1 Investigator Responsibilities

This study will be conducted in accordance with ISO 14155: 2011 guidelines, which provides a detailed description of the investigators' responsibilities. The investigator is responsible for conducting the study in accordance with the Protocol, the signed Investigator Agreement and other agreements, applicable laws and regulations, and any conditions of approval imposed by the reviewing IRBs/ECs and/or FDA/Competent Authority (where applicable). To ensure compliance with the guidelines, the sponsor, an independent body, or a regulatory agency may audit the study. By agreeing to this Protocol, the investigators and their institutions accept to allow monitoring, audits, IRBs/ECs review, and regulatory inspections that are related to the study. They also agree to provide authorized individuals with access to source data and documentation as well as the right to copy records, provided such activities do not violate subject consent and subject data confidentiality.

If the subject or investigator refuses to follow the Clinical Trial Protocol, the study device(s) should be deactivated or explanted, and the subject(s) withdrawn from the study. Axonics will formally communicate with the Investigator in an attempt to maintain compliance. This communication should consist of at least three documented communication attempts including a certified mail. Continued non-compliance by a subject may result in withdrawal from the trial. Continued non-compliance by the investigator may result in removal of the investigator from the trial. Escalation to the IRB/EC and/or Competent Authority may also be necessary.

7.1.1 Investigator Experience

In accordance to ISO 14155: 2011, the clinical investigator in this study will be:

- An appropriately qualified practitioner legally entitled to practice
- Experienced in the field of application and trained in the use of the device under consideration
- Familiar with the background and requirements of the clinical study methodology, and
- Trained in the proper method of obtaining informed consent

7.1.2 Specific Responsibilities

The principal investigators and their co-investigator(s) are responsible for the following:

- Subject well-being
- Strictly adhering to the Protocol which includes all testing and follow-up requirements
- Providing the subject with comprehensive information about the study and documenting subject consent and data during the study
- Addressing medical questions that might be asked, either by Axonics or by external Regulatory Agencies, during or after the study
- Notifying Axonics of any deviation from the Protocol with an explanation for the deviation. This notice shall be given as soon as possible, but in a timely manner after the deviation occurred.

Axonics will review and classify all deviations from the Protocol

In case several co-investigators are taking over certain responsibilities, the principal investigator remains responsible for the proper conduct of the clinical study. Axonics must approve co-investigators before taking over responsibilities. The study is not transferable to other centers attended by the investigator unless prior approval is obtained from the appropriate IRB/EC and Axonics.

In addition to certain other documents, an Investigator Agreement must be executed by the parties before subjects are enrolled into the study.

7.2 Sponsor Responsibilities

Axonics will serve as the sponsor of this clinical study and takes responsibility and assumes liability for the initiation of the study; however, Axonics does not actually conduct the study.

Axonics will ensure proper monitoring of the study and that all clinical requirements are met.

In addition, Axonics representatives may participate in the conduct of the trial to the extent described in the following section 7.2.1.

In this study, Axonics personnel are not blinded to the study results. Participation in the study will be limited to Axonics personnel who are appropriately qualified and trained. All Axonics personnel will be trained on the appropriate clinical study regulations and guidelines for medical device trials.

It is the responsibility of Axonics to ensure appropriate training regarding the Axonics equipment and study protocol procedures of all individuals involved in the ARTISAN-SNM trial. This includes investigators and other health care professionals at the investigational sites, Axonics personnel, and contractors, if applicable.

7.2.1 Role of Axonics Representatives

Axonics personnel will provide support to the health care professionals involved in the study as needed during implant, device programming, and follow-up visits.

Support may include device programming, training, answering questions, or assisting with the operation of the Axonics equipment or the procedures and forms related to the Protocol.

While under the supervision of the clinical investigator, Axonics personnel may operate Axonics SNM equipment during implant or follow-up visits and interact with subjects to accomplish necessary activities. Typical tasks may include:

- Interrogating the device or programming device parameters to physician requested settings
- Clarifying device behavior, operation or diagnostic output as requested by the clinical investigator or other health care personnel
- Entering data on study worksheets, if applicable. This applies to technical data collected during the study procedures or data that is entered into the programmer as long as the responsible clinician verifies and signs the completed worksheet. Worksheets may be used to capture data prior to entry into the EDC system. Medical assessments shall only be completed and signed by a physician.

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

- Observing testing or medical procedures relevant to Protocol compliance or device function
- Reviewing collected data and study documentation for completeness and accuracy
- Performing source data verification when that individual was not directly involved in the collection of the data under review

Axonics personnel will not:

- Practice medicine
- Provide medical advice, diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of a clinician
- Independently collect critical study data or enter data into the electronic database

7.3 **Insurance**

Axonics will obtain insurance to adequately cover costs in the event of clinical-investigation related injuries.

7.4 **Monitoring**

Study monitors are individuals who are designated to oversee the progress of a clinical study. They are appropriately trained and qualified to monitor a clinical study.

7.4.1 Monitoring Visits

Prior to initiating enrolling any subjects, Axonics personnel will confirm that the investigator understands and accepts the obligation to conduct the research study according to the Protocol and applicable regulations and his/her staff have sufficient subjects, time and facilities to conduct the study.

Monitoring will be performed during the study to ensure that compliance with the Protocol and applicable regulations is maintained, that data are collected in a timely, accurate and complete manner, and that the investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. During the monitoring visits, the monitor may review case report forms for timeliness, adequacy, and accuracy and compare to source documents. The monitor may also check the study binder. A final monitoring visit will be conducted before study closure. This final visit will ensure that any pending study issues are resolved. In order to ensure effective monitoring, the investigator must permit the monitor direct access to the case report forms and clinical records.

Additional monitoring details will be described in a separate monitoring plan.

7.4.2 Review of Submitted Data

The eCRFs submitted by the investigators will also be reviewed by Axonics personnel or designates. The following activities will occur:

- All case report forms will be reviewed for completeness and accuracy upon receipt at Axonics or after entry into the electronic data capture system.
- The site staff and/or the assigned Axonics personnel will be contacted regarding any missing or unclear data.
- Study data will be analyzed by Axonics or delegates and may be transferred to locations outside of the United States and/or be sent to the FDA or any other worldwide regulatory authority in support of a market-approval application.

7.5 Independent Data Safety Monitoring Board (DSMB)

To ensure subject safety, qualified physicians, not otherwise engaged in the study, will from time to time, convene either in person or via teleconference to discuss the conduct of the study from the standpoint of subject safety.

The DSMB will be composed of three (3) physicians: a chairman and two additional physicians.

The DSMB will review the aggregate safety data and evaluate any safety issues that may arise during the conduct of study.

The DSMB will review and adjudicate individual adverse events.

The DSMB Charter will describe further details of the DSMB activities.

8 REGULATORY AND COMPLIANCE REQUIREMENTS

8.1 Statement of Compliance

The study will be conducted according to the stipulations of the Declaration of Helsinki, ISO 14155: 2011 and all other applicable regulations as determined by the US FDA.

8.2 Informed Consent

Informed Consent is mandatory from all subjects prior to the subject's participation in the study. Axonics will provide the Informed Consent template to investigators participating in this study.

The process of obtaining Informed Consent shall comply with the Declaration of Helsinki, ISO 14155:2011 and applicable national regulations (local IRBs/ECs and/or Regulatory body, as applicable).

The process of obtaining informed consent shall:

- avoid any coercion of or undue influence of subjects to participate
- not waive or appear to waive subject's legal rights
- use native language that is non-technical and understandable to the subject
- provide ample time for the subject to consider participation and ask questions
- be personally signed and dated by the subject and the investigator

It is the investigator's sole responsibility to have the original signed Informed Consent retained on file and a copy given to the subject.

8.3 Subject Data Confidentiality

Throughout the study, subject confidentiality shall be observed at all times by all parties involved, including in reports and publications. All data will be secured and stored according to country-specific requirements.

The participating sites shall ensure that data (e.g. worksheets, files, programmer printouts, etc.) forwarded to Axonics does not contain any subject identifying data (such as name, birth date, etc.) other than the subject ID.

Only authorized Axonics personnel or designated representatives will have access to these confidential files. Subject data may be made available to foreign Regulatory Agencies, Health or other Governmental Authorities, but under strict confidentiality.

8.4 Control of the Study Devices and Equipment

Axonics will control the availability of the Axonics SNM System and ship products only to Axonics representatives or study investigators.

Axonics will keep records that indicate the destination and date of shipment.

The disposition of all devices will be tracked. Upon request, unused devices must be returned to Axonics.

8.5 Out-of-Service Product

Any implantable product (such as a Neurostimulator or Tined Lead) that has been removed from a subject is considered an out-of-service product. For example, out-of-service product shall include explanted product and devices that do not function appropriately at time of implant. Any out-of-service product should be returned to the Sponsor for analysis. In the event of a subject death, every effort should also be made to retrieve and return product to the Sponsor.

8.6 Adverse Events

All Adverse Events reported to the Sponsor during the study will be reviewed and adequately reported and classified to comply with applicable regulations (ISO 14155:2011) and vigilance requirements.

Investigators will be asked to classify whether an adverse event is considered serious or non-serious and whether it is considered device or procedure related.

Axonics will determine whether a reported Adverse Event is anticipated or unanticipated.

8.6.1 Adverse Event Classification

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 investigational medical device. This definition includes events related to any procedure in the protocol. The following are NOT considered AEs:

1. Any event expected to occur during the normal course of treatment that is not untoward.
2. Usual aches and pains following the surgical implant procedure. (Pain that is unusually intense or prolonged may be an AE.)
3. Unusual or uncomfortable sensations during the programming of the device or when the Remote Control is used to change stimulation settings. These occurrences are part of the usual standard of care. If the sensation is not resolved by reprogramming then the event may be considered an AE.
4. Change in the effectiveness of the SNM therapy may change over time, possibly requiring changes in programming parameters.
5. Underlying diseases, recorded at baseline, unless there is an increase in severity or frequency during the course of the investigation.
6. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE.

Any AE experienced by the study subject after informed consent, whether before, during or subsequent to the procedure, must be recorded in the eCRF.

Adverse Device Effect (ADE) – adverse event related to the use of an investigational medical device.

a) This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the

investigational medical device.

b) This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE) – An effect that has resulted in any of the consequences characteristic of a serious adverse event related directly to the investigational medical device.

Serious Adverse Event (SAE) – adverse event that:

1. Led to death
2. Led to serious deterioration in the health that either resulted in
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
NOTE 2: Hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Adverse Device Effect (UADE) - 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 nature, severity, or degree of incidence in the clinical trial protocol 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.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device Deficiency - inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error or inadequate labeling.

Malfunction - failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

8.7 Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 3.

Table 3: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	*Description*
Unrelated	The adverse event is determined to be due to a concurrent illness or other effect that is not related to the investigational device.
Related	The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or There is no other reasonable explanation for the event.

8.8 **Relationship to Study Procedure**

The Investigator must assess the relationship of the AE to the study procedure as related or unrelated. See criteria in Table 4.

Table 4: Criteria for Assessing Relationship of Study Procedure to Adverse Event

Classification	*Description*
Unrelated	The adverse event is determined to be due to a concurrent illness or other effect that is not related to the study procedure.
Related	The adverse event is determined to be potentially related to the study procedure, and an alternative etiology is equally or less likely compared to the potential relationship to study procedure, or There is a strong relationship to study procedure, or recurs on re- challenge, and another etiology is unlikely, or There is no other reasonable explanation for the event.

8.9 **Pain-related Adverse Events**

Adverse events associated with pain should be consistently assessed and classified across Investigators. The following guidance should be followed in assessing pain-related adverse events:

- All device-related AEs associated with pain should be assessed on a numeric rating scale. The subject should be asked to rate his or her pain in the last 24 hours from 0 to 10 (11-point scale) with the understanding that 0 is equal to “no pain” and 10 is equal to “worst possible pain.“
- Pain encountered within thirty (30) days of the implant procedure that is associated with the lead or Neurostimulator implant sites should be considered as procedure-related pain and not as device-related pain.
- Pain encountered after thirty (30) days post-implant that is associated with the

Neurostimulator implant site should be classified as follows:

- Transient Lead site pain: pain at the lead implant site that persists for less than thirty (30) days and is resolved without surgical intervention,
- Persistent Lead site pain: pain at the lead implant site that persists for thirty (30) or more days or any lead implant site pain requiring surgical intervention.
- Transient Neurostimulator site pain: pain at the Neurostimulator site that persists for less than thirty (30) days and is resolved without surgical intervention,
- Persistent Neurostimulator site pain: pain at the Neurostimulator site that persists for thirty (30) or more days or any Neurostimulator pain requiring surgical intervention.

8.10 Tined Lead Migration

Tined lead migration is an adverse event often reported in sacral neuromodulation studies. To standardize the reporting of lead migration events this study will utilize imaging to assess lead migration. If a patient has an unexpected loss of efficacy or emergence of pain or discomfort associated with their implant that cannot be resolved with reprogramming, an x-ray or fluoroscopic image of the lead may be acquired to assess whether or not the lead has migrated. Criteria for confirming migration include:

- The ability to produce and compare images of the lead location at the implant procedure and at a timepoint following report of the unwanted outcome (loss of efficacy or discomfort)
- Clear evidence on the images that the lead has been displaced at least 2 cm from the initial lead placement position

8.11 Investigator Reporting Requirements

The communication requirements for reporting to Axonics are as shown in Table 5.

The Investigator will monitor the occurrence of adverse events and adverse device effects for each enrolled subject. Adverse events or adverse device effects reported by the subject to the investigator, confirmed by the investigator, and documented in medical records must be reported on the adverse event form.

AEs must be reported on the AE eCRF. Serious adverse events may be reported by any means available.

Table 5: Investigator Reporting Requirements

Event Classification	Communication Timeline
Unanticipated Adverse Device Effect/ Unanticipated Serious Adverse Device Effect	Within one (1) business day of first becoming aware of the event.
Serious Adverse Event including Serious Adverse Device Effects	Within two (2) business days of first becoming aware of the event
Adverse Event	Within ten (10) business days of first becoming aware of the event and as per local/regional regulations
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)	Within two (2) business day of first becoming aware of the event and as per local/regional regulations

8.12 **Reporting to Regulatory Authorities / IRBs / ECs / Investigators**

Reporting to the reviewing EC/IRB/REB will be conducted in accordance with the local requirements or by the investigator or designated to a third party such as the Study Monitor or Axonics.

The sponsor will ensure the reporting of all reportable adverse events to the appropriate European Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations, and to the FDA according to federal law and FDA guidance.

Axonics (or its representative) is responsible for reporting adverse event information to all participating investigators.

8.13 **Axonics Device Deficiencies**

Device deficiencies are not to be reported as adverse events. However, if a device deficiency leads to an adverse event, the adverse event should be recorded as per section 8.6.

Device deficiencies (including, but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) shall be documented and reported to Axonics and the device should be returned to Axonics for analysis. Instructions for returning the investigational device will be provided by Axonics personnel.

If it is not possible to return the device, the investigator should document the reason the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

8.14 **Subject Death Reporting**

Subject death during the study should be reported to Axonics and per local country regulation. Notification of death should include a detailed statement (death letter) of the pertinent events and be signed by the investigator or co-investigator. A death letter in the local language is acceptable, if accompanied by a translation in English (signed by translator with details about function) with respect to subject data confidentiality.

The death letter should include all of the following, if available:

- Date and time of death
- Place death occurred
- Whether or not the death was witnessed
- The device status and/or activity at the time of death, if applicable
- Immediate cause of death
- Any other circumstances surrounding the death
- Whether death was device or procedure related
- The approximate time interval to death from the initiating event and from the start and end of the research procedure, if applicable.

8.15 **Protocol Deviations**

A protocol deviation is any instance in which the Clinical Trial Protocol was not followed. Following the notification of protocol deviations by the investigator or any Axonics or site personnel, Axonics will review and classify all deviations from the protocol. Axonics will take appropriate action, depending on the classification of each deviation.

8.15.1 Deviation Classification

Axonics will classify protocol deviations according to Table 6 below.

Table 6: Classification of Deviations

Type	**Circumstance or rationale**
A	Deviation to protect the life or physical wellbeing of a subject in an unforeseen emergency
B	Deviation based on medical judgment to prevent harm to a subject in a non-emergency situation
C	Deviation due to a misunderstanding of protocol
D	Deviation due to a situation that is beyond control
E	Deviation due to an oversight, error, or protocol non-compliance

8.15.2 Deviation Reporting

Any deviation from the protocol shall be recorded together with an explanation for the deviation. The investigator shall notify the Sponsor, who is responsible for analyzing all deviations and assessing their significance. The Sponsor shall ensure that all deviations from the protocol are reviewed with the appropriate clinical investigator(s) and reported in the case report forms and the final report for the clinical investigation. Deviations will be reviewed and evaluated on an ongoing basis, and the Sponsor will ensure appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) are put in place, as necessary.

8.16 **Protocol Amendments**

Except where necessary to protect the well-being of a study subject, all items in this Protocol must be followed exactly.

All amendments to the Protocol shall be agreed upon between the sponsor and the investigators and be recorded with a justification for the amendments.

The amendments will be submitted to regulatory body for review and approval (when applicable and as required by local regulatory authorities).

8.17 **Documentation and Records Filing**

The investigator should maintain the study records in a designated study center administrative binder including the following:

1. Correspondence with the Sponsor, IRB/EC and other investigators
2. The signed Protocol with any and all amendments
3. The approved template of the Subject Informed Consent form
4. IRB/EC approval of the Protocol and any amendment (if applicable)
5. The investigator's agreement and the fee agreement (separate or combined)
6. The Investigator's Brochure
7. The insurance certificate
8. The device manuals and all training materials
9. Blank case report forms
10. Current curricula vitae for the principal investigator and all co-investigators
11. Regulatory Approval documents
12. Monitoring letters (if applicable)
13. Study reports
14. Study initiation forms

15. Study closure documents

In addition to the study administrative documents, subject records shall be appropriately filed, including the following:

- Signed informed consent forms
- Relevant source data
- Records of subject death

Study records must be kept for the maximum period of time required by the hospital and any relevant national regulations, but no less than two (2) years after the study completion date. All data and documents should be made available to the relevant authorities on request.

The Sponsor will archive and retain all documents pertaining to the study indefinitely.

8.18 **Ethical Information**

This study is intended to discover valuable information about a medical device. Nonetheless, the safety and health of the subjects is of primary concern.

In all respects, this study shall be conducted pursuant to the latest version of the "Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects."

Ethical approval to participate in this study is required from each participating institution.

9 PUBLICATIONS

The results of this study may be submitted in the form of abstracts to international and/or national congresses and/or in the form of publications to scientific journals.

No abstract(s) or article(s) can be submitted for publication without prior authorization from Axonics.

10 ABBREVIATIONS

Abbreviation	*Full Word*
ADE	Adverse Device Effect
AE	Adverse Event
APE	Adverse Procedure Effect
AUA	American Urological Association
CE	European Conformity
CP	Clinician Programmer
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EAU	European Association of Urology
EU	European Union
FDA	Food and Drug Administration
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
ISO	International Standards Organization
MRI	Magnetic Resonance Imaging
OAB	Overactive Bladder
PEP	Primary Effectiveness Endpoint
PI	Principal Investigator
RC	Remote Control
REB	Research Ethics Board
RF	Radiofrequency
S3/S4	3rd, or 4th Sacral Foramen/Nerve
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SNM	Sacral Neuromodulation
UADE	Unanticipated Adverse Device Effect
UF	Urgency Frequency
UUI	Urinary Urgency Incontinence
USA	United States of America
UTI	Urinary Tract Infection