Pudendal Nerve Mapping Towards Improved Neuromodulation for Urinary Retention

NCT04236596

Date of IRB Approval: February 4, 2022

Pudendal Nerve Mapping Study

Pudendal nerve mapping towards improved neuromodulation for urinary retention

University of Michigan IRBMED

Protocol HUM00165005

NIH Award OT2OD028191

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1. Study Summary

1.1 Background and Significance

In general, primary bladder complaints include an inability to maintain urine in the bladder or a constant feeling of needing to empty (incontinence and overactive bladder (OAB)) and an inability to effectively empty the bladder (underactivity, voiding dysfunction). A significantly greater focus in healthcare management and bladder study has been placed on problems with maintaining urine in the bladder, likely due to discomfort with and social stigmas of incontinence. However, underactivity affects a similarly high percentage of the population and can lead to significant conditions including urinary tract infections [1] and urinary retention-driven incontinence and OAB, impacting quality of life [2]. Underactive bladder is a symptom often indicating detrusor (bladder muscle) underactivity (DUA) and results in prolonged urination and urinary retention [2]. These effects may also be due to bladder outlet obstruction (BOO), such as for an enlarged prostate, making DUA and BOO challenging to differentiate [3]. The specific prevalence of DUA is not known as a wide range has been reported, including 9-28% of men under 50, up to 48% of older men [2], [3], and 12-45% of older women [3]. DUA is common for cases of damage to or problems with the nervous system, including Parkinson disease, multiple sclerosis, and peripheral neuropathies like Guillain-Barré syndrome [2], [3]. Other factors with an unclear relationship to DUA include reduced mobility, colorectal dysfunction, various medications, and menopause in women [2]. DUA affects tens of millions of Americans, and is expected to increase in prevalence as the population ages.

Overall management of DUA is generally not successful, due to insufficient efficacy and/or poor tolerability of treatments [2]. Patients with moderate to severe cases will often use intermittent catheterization to empty their bladders. While this is a standard approach that has low infection rates with proper training, it is generally not well received by patients, some of whom are not always capable of catheterizing themselves and are candidates for indwelling catheters [2]. There are pharmacological therapies that help with detrusor contractions, such as parasympathomimetics, however evidence for their efficacy is limited and side effects such as cramping and visual effects limit their clinical utility [2]. Sacral nerve stimulation, as discussed further below, is used for non-BOO retention and has yielded the best efficacy to date [4]. It is thought to induce sphincter or pelvic floor relaxation rather than increased bladder contractility [2] and does not provide on-demand control. Electrical stimulation of ventral roots has been used to empty the bladder in spinal cord injured patients [5], however it requires an invasive surgery for electrode placement, limiting its utility in other groups.

Many animal studies have demonstrated bladder excitation in response to electrical stimulation of pudendal nerve fibers [6]–[9]. Initial studies focused on the use of cuff electrodes to stimulate the entire pudendal nerve. Stimulation frequencies within 20-33 Hz are generally micturition-selective while lower frequencies like 3-10 Hz activate the continence circuit, though there can be variation within and across experiments which may depend on nerve activation efficacy. Studies have obtained selective activation of micturition through several means, including stimulating within the urethra [10], [11] or on distal pudendal branches originating from proximal or distal regions of the urethra [12], [13]. Penetrating electrodes within the pudendal nerve [14] or spinal roots [15] have been used to selectively activate micturition-driving neurons. Most of these studies have focused on exciting the bladder. Only a few have reported clinically-relevant bladder emptying [12]. A primary factor in this limited output is the effect of anesthesia, which can depress synaptic transmission in spinal circuits and/or maintain sphincter closure or urethral

tone, depending on the agent used [16]. In general, these studies are performed in rats and cats, although other species like mice, pigs and non-human primates have been used occasionally. Each of these animals has similar lower urinary tract physiology and primary neural control through pudendal, pelvic, and hypogastric nerves [17] and are accepted as models for human anatomy and physiology.

In contrast to animal studies, clinical exploration of pudendal neuromodulation for voiding has been limited. Thanks to the pudendal-driven micturition circuit originating within the urethra, stimulation with catheter-mounted electrodes has been performed in several pilot clinical studies, though the effects are marginal or only explored in a limited fashion [18]–[20]. This catheter stimulation approach is an in-clinic tool that is not feasible for at-home use by patients, though it allows for patient screening. One study has shown that it is possible to elicit bladder-excitation responses with an electrode inserted percutaneously near the pudendal nerve, however the effects were again marginal due in part to the limited opportunity to explore stimulation paradigms and a lack of nerve-electrode visualization [21]. A recent modeling study suggested that it is possible to selectively activate different fascicles with a multi-contact cuff placed on the pudendal nerve [22]. While cadaver dissections suggested the surgical feasibility of cuff electrode placement to accomplish this selective stimulation [23], the invasive nature of the cuff electrode placement surgery has prevented validation of this computational model.

Sacral neuromodulation (SNM) is a standard clinical treatment. FDA approval was granted for the Medtronic Interstim implantable neurostimulator over 20 years ago [4], and over 200,000 people worldwide have been implanted. The Interstim system consists of an implantable pulse generator (IPG) and a stimulation lead. The lead consists of helical-coiled, insulated wires that terminate in four ring electrodes near the tip. The Interstim lead has barbs, or tines, along the distal end to provide anchoring and limit migration. For an initial evaluation phase (“stage 1 implant”), the stimulation lead is placed through the third sacral foramen, generally using fluoroscopy, and externalized percutaneously to a stimulator worn on the waist [24]. During implant, anal bellows and/or patient sensations are typically used to determine relative nerve activation for different stimulation amplitudes and electrode combinations. If the patient has had sufficient improvement in symptoms (generally > 50%) after a 2- or 3-week observation period, the IPG is implanted in the lower back and connected to the stimulation lead, leaving a fully-implanted system (“stage 2 implant”). Externally, a programmer can communicate with the IPG to monitor or modulate stimulation. Stimulation can be delivered bipolar between any pair of the four electrodes or monopolar between one electrode and the IPG.

Since 2005, a few clinicians worldwide have started placing the Interstim lead at the pudendal nerve [21], [25], [26]. This is often done in patients who failed traditional SNM or who have concurrent pelvic symptoms [27]. The clinical steps for this pudendal nerve implant procedure follows the steps for SNM, in an off-label use, with fluroscopy and external anal sphincter (EAS) electromyogram (EMG) used to determine the proximity of the lead to the pudendal nerve [28], [29]. Patients at the University of Michigan health system who receive the Interstim at the pudendal nerve offer an opportunity to develop a new computational model of pudendal nerve electrical stimulation. Development of this model and validation of our ability to model the nerve and stimulation lead and will suggest whether it is possible to selectively stimulate the nerve such as to drive bladder excitation and voiding. Thus the goal of this study is to gather imaging data about the location of the nerve and stimulation lead, to create a computational model of the

nerve-lead, and then to validate that model with patients receiving a IPG and lead that target their pudendal nerve as part of their normal clinical care. This study is not studying or establishing the efficacy of the Interstim system at the pudendal nerve. We will collect indicators of patient symptoms at the start and end of study participation to determine whether any factors relate to our ability to model and stimulate the nerve.

Figure 1 shows our overall study design, with example figures of our anticipated study progression as implemented for another neuromodulation approach by our team [30]. Further details on each step are given in Section 2 below. This NIH-funded project is part of the NIH SPARC (Stimulating Peripheral Activity to Relieve Conditions) program. A primary objective of the SPARC program is to enhance knowledge of anatomical and functional neural innervation of autonomic organs towards improved neuromodulation therapies. This project aligns perfectly with this objective, as we will use imaging and electrophysiology techniques to map a key nerve innervating pelvic organs in a relevant clinical population.

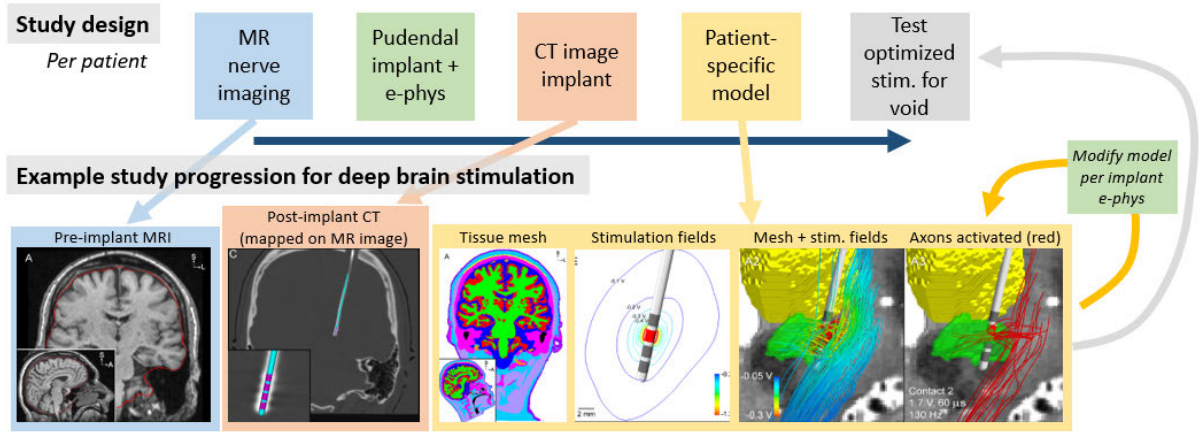

Figure 1. Overall study design. At top, the standard progression of experimental steps for each study participant are shown. At bottom, corresponding images for planned steps are shown, from Dr. Lempka's previous study performing patient-specific modeling of deep brain stimulation [1].

Stimulation of the pudendal nerve is also a promising minimally invasive solution for the mitigation of stress urinary incontinence (SUI). SUI is a form of incontinence in which undesired urination occurs in association with physical exertion. SUI profoundly affects quality of life [31] and is prevalent in approximately 13% of women aged 19-44 years and 22% of women aged 45-64 years [32]. There are a number of therapies and treatments for SUI [33], including conservative measures and minimally invasive options with varying and limited efficacy [34]. Pudendal nerve stimulation may help maintain urethral closure during events that cause SUI, such as coughs, however it has not been studied directly in patients. As described below, in this study we will also perform nerve stimulation during the final test visit when patients simulate conditions that cause SUI, such as with a cough. This study will examine whether nerve stimulation increases urethra pressures during these events. This study is not testing the efficacy of pudendal nerve stimulation against SUI but may provide preliminary support for a future study to examine it further.

1.2 Objective

The goal of this study is to map the pudendal nerve with imaging and electrophysiology, by gathering additional data from patients receiving an implanted neurostimulator as part of their

normal clinical care, and to examine the response of the bladder and urethra to different pudendal nerve stimulation frequencies.

1.3 Specific Aims

The aims of this study are to:

- **Specific Aim 1**: Use pre-implant magnetic neurography to identify and map the path of the pudendal nerve bilaterally.
- **Specific Aim 2**: Examine activation of pudendal nerve paths during unilateral stage-1 implant with pelvic floor catheters and electromyogram sensors.
- **Specific Aim 3**: Create a patient-specific model of the implanted electrode and pudendal nerve and predict stimulation-driven nerve responses.
- **Specific Aim 4**: Evaluate ability of model-derived stimulation paradigms to activate pudendal-nerve controlling bladder pathways during a cystometrogram.
- **Specific Aim 5**: Determine the change in urethral leak point pressure (ULPP) with pudendal nerve stimulation.

1.4 Primary Outcomes

The primary outcome measure in this study are evoked bladder contractions of at least 20 centimeters of water (cmH2O) during the stage-4 test in at least 50% of participants.

1.5 Secondary Outcomes

The secondary outcome measures in this study will be 1) selectivity indices for selective stimulation of pudendal nerve branches for both patient stimulation and simulated model stimulation and 2) selectivity index for selective stimulation of pudendal nerve branches for simulated model stimulation. The SI calculation may be modified in some patients, as necessary, for factors such as the presence of a short urethra that only allows for a single intraurethral pressure measure (female urethras < male urethras) and/or the placement of EMG in the perineal floor between yields one or more additional sensors. 3) Measurement of effect of pudendal nerve stimulation on urethral leak point pressure (ULPP) using stimulation targeted for the external urethral sphincter.

1.6 Investigative team

Tim Bruns, PhD, is an Associate Professor of Biomedical Engineering. He leads a research group that develops interfaces with the peripheral nervous system to restore function while focusing on autonomic organs like the bladder. He has over ten years of experience in studying neuromodulation for bladder control, including preclinical feline studies at the pudendal nerve and dorsal root ganglia and pilot clinical studies investigating intraurethral and genital nerve stimulation. At the University of Michigan, he was PI on a clinical study investigating skin-surface neuromodulation for female sexual dysfunction, which was recently completed (HUM00101713).

Priyanka Gupta, MD, is an Assistant Professor of Urology. She has extensive training in the use of neuromodulation for bladder conditions. In her clinical practice she regularly uses sacral neuromodulation, posterior tibial nerve stimulation, and pudendal neuromodulation to improve the bladder symptoms of her patients.

Gaurang Shah, MD, is a Professor of Radiology, Director of Clinical Functional MRI Service within the Neuroradiology Division, and Director of Medical Student Education within Neuroradiology. He has a record of clinical expertise and research projects in a range of

advanced imaging techniques, including neurography to identify and track peripheral nerves as well as fMRI, resting stage fMRI, diffusion tensor imaging (DTI), and tractography.

Scott Lempka, PhD, is an Assistant Professor of Biomedical Engineering and Anesthesiology. He has more than a decade of experience in modeling nerve stimulation for a variety of clinical applications, including deep brain stimulation and spinal cord stimulation. In these applications, he has implemented a patient-specific modeling approach towards improving neuromodulation efficacy. He also has expertise in clinical neuromodulation studies that combine clinical testing with patient-specific computational models.

2. Research Procedures

We will conduct the proposed study in accordance with the requirements of the University of Michigan Medical School Institutional Review Board (IRBMED). All study visits will be conducted at University of Michigan Health System locations.

2.1 Pre-study surveys

Once enrolled in the study, participants will complete surveys to assess their pre-implant pelvic organ function. The participants will five complete clinically validated surveys on:

1. Bladder health: American Urological Association Symptom Index (AUASI) also called International Prostate Symptom Score (IPSS) [35], [36]
2. Bladder health: Michigan Incontinence Symptom Index (M-ISI) [37]
3. Sexual function: Female Sexual Function Index short form (FSFI-6) for women [38] and the International Index of Erectile Function (IEEF-5) also called Sexual Health Inventory for Men (SHIM) for men [39], [40]
4. Bowel function: Colorectal-Anal Distress Inventory 8 (CRAD-8) [41]
5. Pelvic pain: Female GenitoUrinary Pain Index (FGUPI) for women and Male GenitoUrinary Pain Index (MGUPI) for men [42].

Additionally, some participants (i.e., recruited patients who are in urinary retention with detrusor underactivity and have failed bladder outlet surgery, S3 neuromodulation or PTNS trial as identified by Dr. Gupta) will complete two additional clinically validated surveys as well as a three-question catheterization survey.

6. Quality of Life: Short Form 12-Item version 2 (SF-12v2) quality of life survey [43]
7. Sexual Health: Sexual Quality of Life Questionnaire-Female (SQOL-F) for women [44] and the Sexual Quality of Life Questionnaire-Male (SQOL-M) for men [45]

The AUASI and M-ISI surveys are already part of the normal clinical care for these patients and the F/MGUPI are sometimes also given already. Participants will also complete a questionnaire on demographics. All of these surveys are loaded in section 29 of the IRB protocol. Surveys will be completed over the phone, or on paper either in person and/or mailed to participants before study visits, and/or online, through RedCAP or a similar, clinically-approved interface.

2.2 Visit 1: Pre-implant imaging *(Aim 1)*

Once a patient is consented for study participation, an imaging session will be scheduled as part of the research study. Pre-menopausal women will undergo a urine pregnancy test prior to imaging session. A research staff member (i.e. study investigator/coordinator/research staff) will administer the test by providing participants with a specimen cup. Participants will then provide a urine sample, a research staff member will read the results by placing a dip stick inside the

specimen cup. This test will be covered by research funds and not billed to the patient. We will use magnetic resonance neurography (MRN) to identify the nerve path and surrounding tissue (Figure 2), as it is a structural MRI technique that allows for the identification and characterization of fine structures like peripheral nerves [46], [47]. We may also perform diffusion tensor imaging (DTI), which is a specialized imaging technique used with MR neurography and provides more specific structural information about peripheral nerves such as. DTI can indicate the myelinated fiber density and differentiate between motor and sensory-dominated fascicles in peripheral nerves [48]. This imaging session will be performed at the main University of Michigan hospital, Department of Radiology, or at another University of Michigan Health System location with MRI facilities. The MRN and DTI will be reviewed for planning the stage-1 implant. This imaging session is not part of the patient's normal clinical care, but the procedures performed are often used during other patients' care. Some enrolled patients may have a previously implanted, non-MRI compatible Interstim neurostimulator at the sacral nerve or pudendal nerve that is no longer providing therapeutic benefit and is being removed during the stage-1 surgery of this study. These patients will undergo the MRI at a later point in the study as is convenient for them, after the new MRI-compatible neurostimulator is placed in the stage-1 surgery.

2.3 Bladder diaries

Prior to each of the stage-1 and stage-2 procedures, patients complete a bladder diary for three days as part of their normal clinical care. They bring this diary with them to the clinic on procedure days (included as Medtronic Daily Diary in section 44.1). Observations in these diaries will be added to the research data set for each participant. After the stage-1 implant procedure, one or more representatives of Medtronic regularly touch base with the patient to see whether they are responding to the stimulation. This is normal clinical practice. In these conversations, the Medtronic representatives use a Patient Management Worksheet. Data collected in these worksheets (e.g. bladder urgency score, daily voids, bladder retention) will also be collected for this study.

2.4 Visit 2: Stage-1 implant electrophysiology *(Aim 2)*

Participants will undergo normal surgical steps during the standard stage-1 implant of their

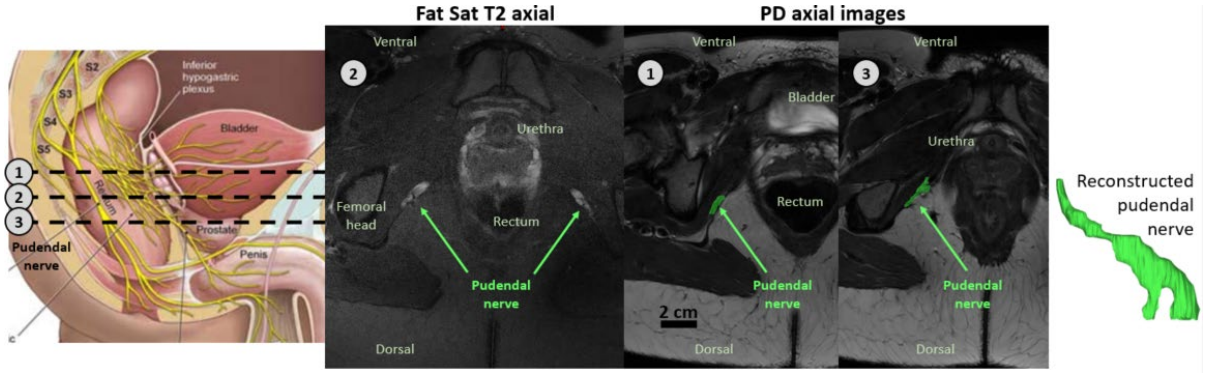

Figure 2. Preliminary, unoptimized pudendal nerve MR neurography and nerve reconstruction from a male volunteer under a different IRB protocol. At left, approximate axial locations for three scans are shown on a diagram of the pelvis. The fat saturation (Fat Sat) T2 scan, shown at location 2 here, clearly visualizes the pudendal nerve bilaterally in Alcock's canal. In the Fat Sat images, the pudendal nerve can be segmented and copied on to higher-definition proton density (PD) images. Here PD images at locations 1 and 3 are shown, with 3 showing separation of pudendal branches. At right, the imaged nerve path is reconstructed for a series of 3-mm interval scans.

neurostimulator lead at the pudendal nerve, as part of their normal clinical care. This is the first stage of a full implant system, in which the stimulation lead is inserted and connected to an external stimulator. If a patient responds positively to this stage-1 implant, then a following stage-2 surgery will be performed as part of their normal clinical care to implant the pulse generator (described below). These surgical procedures are typically done at the main University of Michigan hospital but may be performed at another UMHS facility as scheduling requires. Dr. Gupta regularly performs these procedures as part of her clinical practice. Prior to the stage-1 and stage-2 surgeries, pre-menopausal women will undergo a urine pregnancy test. This is part of their normal clinical care as pregnancy is also an exclusion for clinical care. Once the patient is prepared for surgery, the clinical team will place up to 3 standard clinical catheters in the urethra, positioned with the pressure-sensing ports in the distal urethra, proximal urethra, and/or bladder (See Figure 3). The primary catheter will be a standard clinical-use Covidien Manoscan manometry catheter, to provide high-resolution urethra pressure data, as has been done previously [50], [51]. Other catheters will only be used to infuse some fluid into the bladder (2 catheters in total) or if the manometry catheter is unavailable (up to 3 catheters in total). A standard clinical abdominal catheter may also be placed in the rectum. The standard external anal sphincter electromyogram needles will be placed on either side of the anus for normal clinical monitoring. A pair of standard clinical electromyogram needles may also be placed in the perineal region. These catheters and electromyogram sensors will be recorded from continuously during the implant procedure. The sensors cannot transmit energy to the patient. During the surgical placement of the neurostimulator lead, if a location is identified that may be the final position then a pre-planned, structured set of stimulation parameters will be applied through each lead contact. We will vary the amplitude and pulse width of the applied stimulation pulses through the stimulation lead, staying within the programmed capabilities of the medical device. The total duration of these structured stimulation tests will last for up to fifteen minutes. This time duration is within the normal variance of the surgical procedure itself, and will not significantly affect the surgical duration or affect the care of the patient. The total impact on the surgical procedure, including placement of catheters and electromyogram sensors and stimulation testing, will not last longer than 30 minutes.

2.5 Visit 3: Computed Tomography *(Aim 3)*

As part of their normal clinical care, patients undergo a stage-2 surgery procedure to implant the pulse generator of the implantable neurostimulator. Patients undergo the stage-2 procedure if they have responded positively to the stage-1 procedure, as determined by Dr. Gupta. Most patients undergoing the stage-1 procedure proceed to the stage-2 surgery, 2-3 weeks after the stage-1 implant. If a study participant does not respond to the stage-1 implanted stimulation lead and they are not having a stage-2 surgery, then they will be removed from the study.

On the same day that participants receive the implanted stimulator in the stage-2 outpatient surgery they will undergo a computed tomography (CT) scan of the pelvis as part of the research study. Again, prior to the CT scan, pre-menopausal women will undergo a urine pregnancy test to detect pregnancy. This test will be similar to visit 1, a research staff member (e.g. study investigator/coordinator/research staff) will administer the test and obtain the results. This test will be covered by the research study. This CT scan will be performed during the same clinical visit as for the stage-2 procedure. If allowed by scheduling and patient preference, the CT scan will be prior to the stage-2 implant, to allow the patient to leave the hospital once they are ready after the implant. Otherwise, the CT scan will be after the stage-2 implant when the patient is ready. This CT scan will be of the pelvis, to determine the final location of the

implanted stimulation electrode, with respect to landmarks like the participant's ischial spine. This CT scan is not part of the patient's normal clinical care for the Interstim implantation, but is the same procedure as used during other patients' care.

2.6 Patient-specific computational model (involves no direct patient interaction) *(Aim 3)*

As part of the research study, the pudendal nerve for each patient will be identified and segmented from the MRN images with Materialise Mimics Innovation Suite (Figure 2). We will co-register the three-dimensional surfaces from MRN, DTI, and CT images to create a patient-specific computational model, as has been done for other types of implant table neurostimulators [30], [52]. A software program (Comsol Multiphysics) will be used to estimate voltage fields generated by the neurostimulator electrode stimulation. These estimates will be validated using stage-1 recordings. The computational model will be used to predict electrode stimulation parameters for recruiting different parts of the pudendal nerve using the NEURON computational software. Computational modeling of implanted stimulator activation of nerves has been done previously by our research team [53].The computational model produced with the Mimics Innovation Suite will not be used to diagnose or be used as a diagnostic procedure. These software programs will be used to determine our ability to model the nerve and electrode.

2.7 Visit 4: Stimulation during cystometrogram *(Aim 4)*

As part of their normal clinical care, patients visit the clinic about 4-5 weeks after their stage-2 surgery. After their clinic visit, patients will undergo an experimental cystometrogram (bladder filling) in a urodynamics suite as part of this research study. This test will occur at the University of Michigan main hospital or a local UMHS clinic, as determined by Dr. Gupta's clinical schedule, in a urology cystometry suite. Prior to the test, pre-menopausal women will undergo a urine pregnancy test to detect pregnancy. This test will be covered by the research study and clinical staff will obtain the results.

Patients will be situated for a normal cystometrogram, in a reclining position, as shown in Figure 3 Top (from [54]) or in an upright sitting position. It is standard clinical practice to offer patients an antibiotic right before a cystometrogram. The antibiotic pill will be provided by and administered by the clinical staff. Clinical staff will insert standard urodynamic catheters into the urethra, bladder, and bowel (or vagina), and standard urodynamic EMG surface electrodes around the external anal sphincter and maybe perineal region, similar to the stage-1 procedure. Standard EMG surface electrodes may also be placed on the abdomen and/or lower back to record abdominal muscle activity. The primary urethra catheters will be a standard clinical-use Covidien Manoscan manometry catheter, to provide high-resolution urethra pressure data [50], [51], and a standard urodynamics catheter for infusing fluid into the bladder (2 urethra catheters in total). If the manometry catheter is unavailable one or two standard urodynamics catheters may be used to measure urethra pressures. Warm saline will be used to fill the bladder (~30-50 mL/min) through the bladder catheter until the participant just perceives filling. This is a standard clinical step in cystometrogram, using a standard clinical urodynamics instrument. Normal cystometrograms continue infusion until voiding (Figure 3 Bottom, from [54]), however stopping at this not-full state will allow for the assessment of stimulation effects on the bladder. Stimulation paradigms identified by the patient-specific model will be applied through the implanted neurostimulator until stimulation-driven voiding occurs or the participant expresses a very strong desire to void. At that point, the patient will be allowed to void and/or residual saline will be removed from the bladder via the bladder catheter. Approximately half of patients normally do not void around the catheter during a cystometrogram. For any participant like this,

they will have the catheters removed and will empty their bladder on to a void scale or into a toilet. This sequence will be repeated up to three times.

At two or more time points within a cystometrogram, the urethral leak point pressure (ULPP) will be measured during Valsalva and/or forceful coughing. This will occur after infusing saline into the bladder to in intermediate volume(s) below the sensation of fullness and then pausing. Urethral leakage may not be observed; however, urethral pressures will be recorded and compared to pressures during pudendal nerve stimulation. If leakage is observed, an equal amount of saline may then be reinfused. Pudendal nerve stimulation will be turned on to a stimulation paradigm for maximum urethral sphincter activation at a comfortable level, for a maximum of a 60-second pulse train while the ULPP measurement is repeated using Valsalva and/or forceful coughing. The saline infusion will then be resumed until the participant perceives fullness and then will be stopped. Leak point pressure will again be assessed without and then with pudendal nerve stimulation as before. Each assessment of leak point pressure may be performed with stimulation on and then repeated with stimulation off, or with

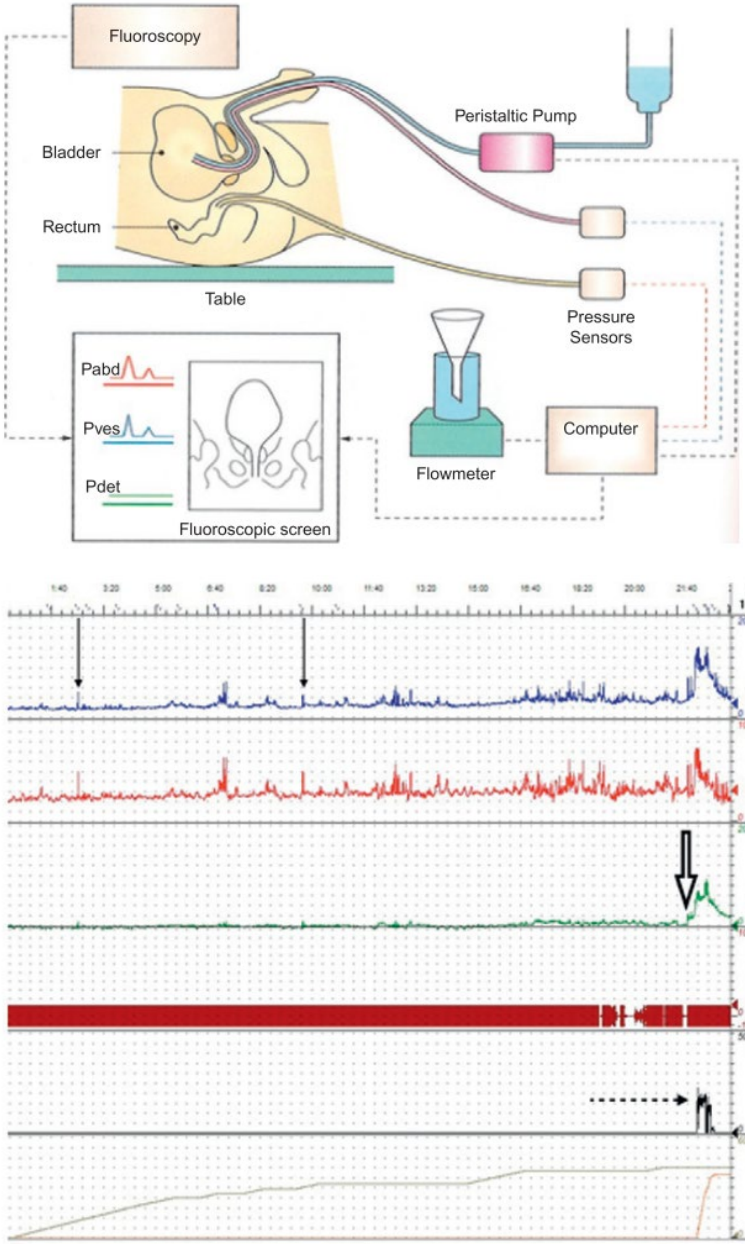

Figure 3. Top: Standard cystometrogram (CMG) setup, with a pump to infuse saline, bladder and rectal pressure catheters and sensors, and a flowmeter for voiding. From [45]. Our study will add one or more urethra catheters, abdominal, anal sphincter and/or perineal EMG, and will not use fluoroscopy. Bottom: Standard CMG outputs, with in-bladder pressure (Pves; blue), abdominal (rectal) pressure (Pabd; red), bladder muscle pressure (Pdet=Pbes-Pabd; green), EMG, urine flow (black), and volume (infused, voided). From [45].

stimulation off and then repeated with stimulation on. The ULPP testing may be repeated at the Investigator's discretion and participant's agreement. The ULPP measurements and stimulation-driven voiding experiments may be integrated in a fill sequence, such that both assessments may be completed at the same fullness sensation bladder volumes, using the respective stimulation parameters for each assessment.

All stimulation parameters used will be within the normal hard-coded limits of the IPG. We will not be testing new paradigms that the IPG is not capable of performing. We may vary the combination of lead contacts that are active, the pulse width of applied stimulation (i.e. duration of each pulse), the frequency of applied pulses (i.e. cycles per second), and the amplitude (i.e. volts or milliamps) of the applied stimulation. If any stimulation paradigms are perceived as uncomfortable by the participant, they will be stopped and alternate paradigms will be attempted. Once testing is completed, the IPG will be returned to the clinically-determined stimulation settings for the patient.

2.8 Final surveys

Just before or after visit 4, patients will again complete the clinically-validated surveys on bladder health (IPSS/AUASI & M-ISI), sexual function (FSFI-6 for women, IEEF-5/SHIM for men), bowel function (CRAD-8), and pelvic pain (FGUPI for women, MGUPI for men). The AUASI and M-ISI surveys are already part of the normal clinical care for these patients at this time point and the F/MGUPI are sometimes also given already. The recruited patients who are in urinary retention with detrusor underactivity will take four surveys (IPSS/AUASI, M-ISI, SQOL-F/M, SF-12v2) at four timepoints in total (enrollment as described in section 2.1, and at approximately 2 weeks, 3 months, and 6 months after stage-1 implant). The 3-month time point for this group will align with the final survey set for all other patients, with this group only completing the IPSS/AUASI and M-ISI once at that point.

2.9 Patient timeline

Figure 4 gives a summary of the standard timeline for each study participant.

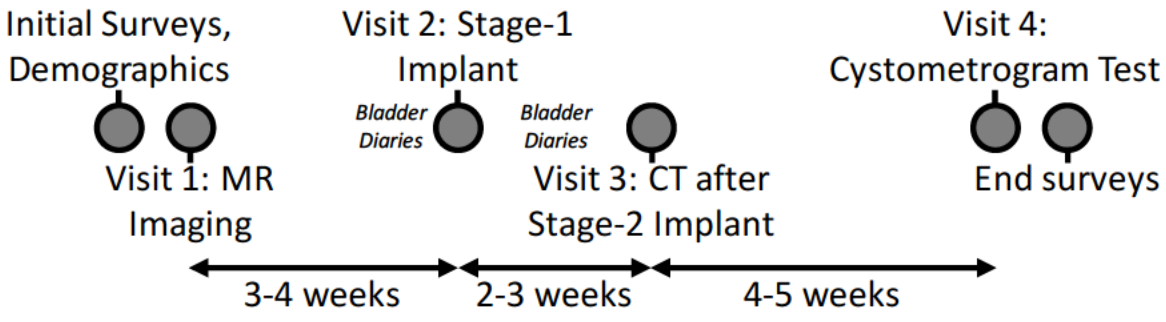

Figure 4. Per-participant study timeline. Intervals between each study event will vary based on scheduling flexibility. Some study participants will have additional surveys, as noted in section 2.8.

3. Study Statistics and Data Analysis Plan

3.1 Sample size

The target population size (N=40) was selected based on Dr. Gupta's clinical practice and direct input from the funding agency (NIH SPARC). We seek to have 20 patients complete all parts of this study and yield data. Due to patient heterogeneity (e.g. prior surgical procedures that limit effects of neural stimulation; implanted hip replacements that obscure MRI data) and drop-outs among enrolled patients, we anticipate that approximately half of enrolled participants will complete all study steps and yield usable data. This study size is within the range of sample sizes used in prior pelvic floor / pudendal nerve anatomy mapping studies with cadavers (N=7 [23], 13 [55], 28 [56], 43 [57]). To our knowledge, no studies have performed pudendal mapping with MR imaging data. Additionally, this sample size is comparable to prior human subject studies stimulating the pudendal nerve or its branches (N=10 pudendal implant after sacral implant [58], N=12 cutaneous genital nerve [59], N=21 percutaneous genital nerve [60], N=30 pudendal versus sacral implant [26]).

3.2 Data Analysis plan

The primary outcome measures in this study, towards being able to model electrical stimulation of the pudendal nerve will be evoked bladder contractions of at least 20 centimeters of water (cmH2O) during the stage-4 test in at least 50% of participants. A second outcome measure will be identification of ULPP with and without stimulation. Results of the patient surveys (demographics, pelvic organ function surveys as defined above) and voiding diaries will be compared to our ability to selectively model and stimulate the pudendal nerve and cause bladder excitation and ULPP measures with stimulation to determine if there are any trends or relationships to participant characteristics.

3.2.1 Selectivity Index

For a given stimulation electrode location during the visit 2 stage-1 electrophysiology, a Selectivity Index (SI) will be calculated for each catheter or electromyogram sensor recording from distal pudendal nerve branches. This includes sensors in the proximal urethra (proximal perineal branch - PPB), distal urethra (distal perineal branch - DPB), and anal EMG (ischeal rectal nerve - IRN).

$$SI_{nerve\ X} = \frac{X}{PPB + DPB + IRN}$$

For the model-based or theoretical SI, PPB, DPB, and IRN represent the percentage of model axons activated within the proximal perineal, distal perineal, and inferior rectal nerves, respectively. For experimental SI, PPB and DPB are the maximal intraurethral pressures measured at proximal and distal sphincter locations. IRN is the maximum, normalized rectal nerve response. This SI will be used to determine whether any stimulation electrode combinations have selective recruitment of any individual pudendal nerve branches (SI > 0.67, for example). The SI calculation may be modified in some patients, as necessary, for factors such as the presence of a short urethra that only allows for a single intraurethral pressure measure (female urethras < male urethras) and/or the placement of EMG in the perineal floor between yields one or more additional sensors. During visit 4 experimental cystometrogram testing, experimental Selectivity Indexes will also be calculated as described above.

3.2.2 Bladder excitation

The primary metric of successful bladder excitation will be a target evoked bladder contraction of at least 20 cmH_2O during the visit 4 cystometrogram in at least 50% of participants. Additionally, any stimulation-driven or participant-driven voiding efficiency will be calculated as

[volume voided] / [volume voided + residual measured still in bladder].

3.2.3 Leak Point Pressure

The ULPP will be determined as the maximum urethra pressure during any Valsalva and forceful coughing events from the urethra catheter sensors. The ULPP during pudendal nerve stimulation will be compared to the ULPP without stimulation at each volume level tested.

4. Study Recruitment

Dr. Gupta will recruit patients in her clinical practice that fail conservative treatments for relevant bladder symptoms and are being considered for a pudendal nerve implant. Generally, these patients are very willing to help, as they have failed a series of prior conservative treatments and they know the pudendal implant is an off-label use. We will augment this recruitment by asking other U-M Urology clinicians to refer patients of theirs who may be candidates. Additionally, we will recruit patients from Dr. Gupta's practice and other Urology clinicians who have failed treatment with an implanted Interstim neurostimulator at the sacral nerve. Either Dr. Gupta will perform the subject recruitment or she will introduce the patient to the study coordinator, who will then discuss the study with the patient and perform recruitment. Patient information will not be shared outside of direct clinical conversations or inquiries by the study coordinator.

As has been reported previously, patients who fail the traditional sacral nerve Interstim implant often respond positively to pudendal nerve implants [26], [61]. Dr. Gupta will recruit sacral-nerve implanted patients who did not achieve clinical success to have a replacement implant at the pudendal nerve. Failed-sacral patients will be broadly recruited across clinicians within the Neurourology and Pelvic Reconstructive Surgery section at the University of Michigan Health System, which includes six Urologists who regularly see these types of patients and implant Interstim devices. Any patients not initially under Dr. Gupta's care who are interested in this study will be referred to her for subsequent care for receiving the IPG as well as any participation in this study. Additionally, we will also look for patients with urinary retention with detrusor underactivity and have failed bladder outlet surgery, S3 neuromodulation or a PTNS trial. These patients will be identified and referred to the study by Dr. Gupta and her clinic.

Aside from the first study visit – MR imaging – all other study participation parts will be linked to standard visits as part of clinical care. This plan will help retain subjects as they will not have excessive visits in addition to their normal clinical visits. Also, our study coordinator will maintain regular contact with each participant, reminding them of appointments. As we cannot fully control the timing of participants, due to the random nature of patients seeking assistance, we will have plans in place to stagger and/or delay surgeries for participants based on study progression as long as no significant impacts on clinical care are anticipated.

5. Study Population

We will recruit 40 participants for this study. We expect that 80% of participants will be women (N=32) and 20% men (N=8), as there is about a ~4:1 rate of Interstim implantation in women versus men [62]. Within that, we anticipate 32 Caucasian (26 women; 6 men) of which two women will be Hispanic, 2 African American (women), and 6 Asian American (4 women; 2 men). We will not decline any participants based on their group membership. Within the University of Michigan local Ann Arbor area, the demographics are 73% Caucasian, 14% Asian American,

8% African American, and 5% from other groups, which we rounded off to 15% Asian American, 5% African American, and 80% Caucasian. We will target to have at least eight patients as being clinically diagnosed with detrusor underactivity (DUA), which is one of the approved indications for Interstim use. Dr. Gupta has previously implanted DUA patients with Interstim at the pudendal nerve, and inclusion of a few of these patients within the study will allow us to test our ability to model and stimulate their pudendal nerve along with non-DUA patients.

5.1 Inclusion Criteria

- Clinically referred as having bladder problems that have not responded to conservative treatment. Normal clinical care includes referral to implant of Medtronic Interstim neurostimulator at the pudendal nerve. Fully eligible to receive an Interstim implant.
- Adult (18 or older), capable of providing own informed consent and communicating clearly with research team
- Capable of speaking, reading, and understanding English, as all study questionnaires are standardized assessments only available in English
- Capable of attending all experimental sessions (Visit 1: pre-stage-1 imaging, Visit 2: stage-1 surgery, Visit 3: CT after stage-2 surgery, Visit 3: cystometrogram test)

5.2 Exclusion Criteria

- Implanted materials that prohibit magnetic imaging.
- Any medical problems that prevent an individual from laying flat in an MRI or CT scanner, are are claustrophobic.
- Areflexive or atonic bladder.
- Pregnant or planning to become pregnant. If a woman of child-bearing potential wishes to participate in this study, they will be pre-screened with a test to detect pregnancy.
- Diagnosed neurogenic bladder, pudendal nerve damage, lower motor dysfunction, or other conditions that would affect the neural circuits involved in micturition.
- Unwilling to allow de-identified data to be stored for future use or shared with other researchers.

6. Study Sites

All research activities will be performed at University of Michigan Health System locations, also known as Michigan Medicine. All participants will be normal patients at Michigan Medicine. The MRI, and CT will be performed at the main hospital in Ann Arbor, or at another Michigan Medicine location with appropriate facilities. The stage-1 and stage-2 implant surgeries as well as the final visit testing will be performed at the main Ann Arbor Michigan Medicine hospital or another Michigan Medicine location, as scheduling permits. These sites are normal clinical sites for studies of this nature. Dr. Gupta has full clinical privileges at these locations, and sees patients across these locations. All members of the research team hold primary appoints within the University of Michigan Medical School. Data analysis and computational model development will occur at the research labs of Dr. Bruns and Dr. Lempka, which are in the University of Michigan North Campus Research Complex (NCRC), which is primarily filled with Michigan Medicine research institutes, research labs, and core facilities. NCRC is a short drive or bus ride from the main Michigan Medicine hospital and not far from other Michigan Medicine sites such as in Livonia. Drs. Bruns and Lempka regularly visit the main hospital for meetings with the study team and other clinical collaborators.

7. Informed Consent

Full, written consent will be obtained by Dr. Gupta while the patient is in clinic or by the study coordinator. In the instance consent is obtained by the study coordinator, the research team will adopt an optional electronic informed consent procedure using SignNow. This option will be our preferred method for obtaining consent. Once Dr. Gupta identifies an eligible participant, if consent is not obtained while the patient is in clinic, Dr. Gupta will notify the study coordinator who will reach out to the participant over the telephone to discuss the study and obtain consent with the patient over the phone using SignNow. The consent form will be read to the participant and time will be allowed for questions or if the patient would like to read/review the consent form on their own.

In the instance a potential participant does not have access to the internet or is not internet inclined, research staff will revert back to using the standard procedures for obtaining consent on paper during the MRI visit.

8. Waiver of Informed Consent

We are not seeking a waiver of informed consent.

9. Confidentiality of Data

Proper, standard procedures will be followed to protect participant identities. Patient information will be saved on a secure server and password protected. Experimental data will have coded references to each participant, and will be stored separately on a secure M-Box folder. The code key will be kept with the patient information. The study coordinator will have access to the patient information and code key. The study coordinator's office will have a locked door. Paper research records will be stored in a locked cabinet in the study coordinator's office. No patient-identifying information will be shared outside the research team.

10. Data Safety and Monitoring

10.1 Data Safety and Monitoring Plan

A full Data and Safety Monitoring Board will not be used for this study as it is a small study. Once data collection has begun, Drs. Bruns and Gupta will discuss project progression, participant safety, and overall data on a monthly basis via phone, email correspondence, or an in-person meeting. Additionally, a Medical Monitor within the Urology department will be identified to provide an outside council on any clinical issues that arise. Adverse Events (AEs) will be reported promptly to the IRB and to the Medical Monitor. If multiple patients experience adverse events related to research procedures, then the Medical Monitor will be consulted to discuss whether the study should be stopped or reassessed. If there is any evidence of a pattern of unanticipated AEs (regardless of causality), or Serious Adverse Events (SAEs), then the Medical Monitor will immediately review the data.

All research personnel involved in any way in this project will have completed training in the protection of human research participants per guidelines issued by the U.S. Department of Health and Human Services, Office for Human Research Protection. The protocol will undergo review and approval by the IRBMED and other necessary regulatory and oversight entities prior to implementation.

We will ask the subjects who consent to participate in the MRI procedures to sign a safety screening form (see attached MRI Safety Screening form) and heed safety guidelines regarding

appropriate clothing (removal of metal fasteners, jewelry, and any other metal objects that can be safely removed).

10.2 Severity

Drs. Gupta and Bruns will grade any Adverse Event signs and symptoms as mild, moderate, severe, or life threatening according to the following definitions in Table 1.

Table 1. Adverse events severity scale.

	Grade	Definition
0	None:	No adverse event
1	Mild:	Causing no limitation of usual activity with no treatment needed
2	Moderate:	Causing some limitations of usual activities and resolved with treatment
3	Severe:	Causing inability to carry out usual activities and requiring professional medical attention
4	Life Threatening:	Patient was at immediate risk of death from the event
5	Fatal:	Causing death

10.3 Serious Adverse Event

Serious Adverse Events (SAEs) will be identified as any adverse event (AE) that:

- Is fatal;
- Is life threatening, meaning the patient was, in the view of the investigator, at
- immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
- Causes a persistent or significant disability or incapacity;
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization if is longer than 24 hours or requires an intervention to treat emergent symptomatology (non-diagnostic);
- Is a congenital anomaly or birth defect;

Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed in this definition. We will report all SAEs to the IRBMED, including death, due to any cause which occurs during this study and until 30 days after the last participation in the study, whether or not expected and regardless of causality.

10.4 Termination of Subjects

10.4.1 Subject Decision

Subject participation is strictly voluntary and the research strictly knowledge driven; therefore, a subject may withdraw from further participation in the study without penalty or harm. Any reason(s) the subject may give for terminating his or her participation will be kept confidential.

We will store the study documents according to the procedures outlined in the Confidentiality of Data section of this protocol (Section 9). We will require no further information of the subject and the subject will be compensated for their completed study visits prior to termination.

10.4.2 Investigator Decision

Study personnel (principal investigator, co-investigators, and study coordinator) will be authorized to release a subject from further study participation according to the following guidelines:

- The researcher believes that it is not in the subject's best interest to stay in the study.
- Subject becomes ineligible to participate.
- Subject's condition changes such that he or she needs treatment that is not allowed while taking part in the study.
- Subject does not follow instructions from the researchers.
- The study is suspended or canceled.

Upon termination of a subject, the investigators will ensure the subject is dismissed with any study documents to which he or she is entitled, as well as guidance for resuming medications safely. Subjects will be compensated for their completed study visits prior to termination. Investigators will require no further obligation or participation from a terminated subject.

11. Protection of human subjects

11.1 Potential benefits of this research

11.1.1 Potential benefits to society

Bladder dysfunction affects a large percentage of the population, well over 10%, leading to significant healthcare impacts. The knowledge gained here will provide key insights into function of a primary nerve in the bladder system, potentially leading to improvements in future technologies, and will also investigate the potential for directly controlling the bladder with pudendal stimulation. Direct pudendal stimulation for bladder voiding has been repeatedly studied in animal studies but only limited studies in humans. These patients provide an ideal opportunity to explore whether this preclinically validated approach has clinical merit, benefiting future candidates for this implant. Additionally, the use of magnetic resonance and ultrasound imaging technology to identify and map the nerve may help inform the healthcare treatment of future patients. These patients also provide an opportunity to assess whether pudendal nerve stimulation may offer the potential to treat stress urinary incontinence through improvements in urethral leak point pressure.

11.1.2 Potential benefits to participants

We do not expect patients to benefit directly from this study beyond the clinical care they will already receive. The use of MR imaging before the procedure and ultrasound and catheter sensors during the implant may help improve nerve targeting with the implant, thereby reducing surgery duration and improving outcomes, although we are not seeking to optimize the implant procedure and will not be testing the use of these standard clinical techniques against control surgeries without them.

11.2 Risks to Human subjects

Potential risks include release of identifying information, discomfort during imaging, physical harm from Magnetic Resonance Imaging if an individual has an implanted medical device that is

not accounted for, exposure to radiation during computed tomography scan, infection, and shock or burn due to electrical stimulation.

11.2.1 Potential Risks and Protection against risks

Participants will already be receiving the neurostimulator implant as part of their clinical care and thus all risks inherent to it are separate from what this study will add.

11.2.2 Identifying information

The primary risk of participation in this experimental study is the release of identifying information. The potential harm is release of research data leads to temporary embarrassment over the need of the patient to require treatment for bladder problems. The likelihood of this risk is Rare. Proper, standard procedures will be followed to protect participant identities. Patient information will be saved on a secure server and password protected. Experimental data will have coded references to each participant, and will be stored separately on a secure Box folder. The code key will be kept with the patient information. The study coordinator will have access to the patient information and code key.

11.2.3 Magnetic resonance imaging

The magnetic resonance imaging sequences (MRN, DTI) are not expected to add risks to patients. Some patients may not tolerate imaging scans, which could have a temporary psychosocial impact on a participant. The likelihood of this risk is Rare. As is standard in clinical MRI studies, these participants will be offered a dose of anxiolytic medication. If participants are unable to complete scans they will be removed from the study. If removed from the study, participants will still receive their normal clinical care for the implanted neurostimulator. MRI could cause significant physical harm if an individual has an implanted metal device that is not properly accounted for. The likelihood of this risk is Rare. All research subjects undergo a safety screening prior to imaging for contraindications to MRI such as metal foreign bodies and implanted devices (see section 44.1 for MRI safety screening form). Subjects will be changed into hospital attire and given ear plugs and or headphones for hearing protection during imaging using a Philips 3.0T Ingenia MR scanner. The 16 channel anterior coil and 12 channel posterior coil combination is used to image the pelvis. The imaging will last about one hour and will not require a contrast injection. These imaging techniques are diagnostic tools often used as part of standard clinical practice.

11.2.4 Computed tomography

As the computed tomography (CT) scan uses radiation, it has a higher risk than magnetic resonance imaging. Excess radiation exposure can increase the risk of cancer. The amount of added radiation for this study is like being exposed to as much as 2 to 4 years' worth of everyday exposure from the sun and other environmental radiation (3 mSv per year). The risk of cancer due to this added exposure is very small compared to the natural risk of cancer and still rare overall for participants due to the CT itself. As with MRI, CT scans are a common diagnostic tool as part of normal clinical care.

11.2.5 Clinical catheters

The standard urodynamic urethra and rectal catheters and manometry catheter added during the visit 2 stage-1 implant and the visit 4 cystometrogram testing have a risk of temporary infection (e.g. urinary tract infection), similar to any foreign object being placed in the body, even if temporarily. The likelihood of this Risk is Infrequent. Standard sterilization and handling techniques will be used to mitigate against the risk of urinary tract infections or other infections

due to placement of catheters during testing. It is also standard clinical practice for patients to be offered an antibiotic medication before the testing begins to mitigate against any risk of infection. Patients will be on standard post-operative medications for their neurostimulator implant, which provide relevant coverage for catheter infection risk as well.

11.2.6 Electrical stimulation

During the visit 2 and visit 4 testing of stimulation from the implanted stimulator, the electrical current may be tested over a range of amplitudes and pulse widths, providing a range of total charge delivered to the participant. Side effects related to higher currents, such as muscle contractions or discomfort, may occur, but are known to be reversible by either reducing the amplitude of the stimulation or stopping the stimulation entirely. Whenever using electricity to stimulate tissue, there is also the possibility of a shock hazard, including an electrical burn. However, only electrical stimulators approved by the United States Food and Drug Administration will be used in this study and all stimulation parameters will be within the limits of the stimulator. Therefore, the risk of tissue damage or electrical shock during the electrical stimulation is minimal.

11.2.7 Reasonableness of risks

The risks of study participation are minimal beyond risks that patients will already be undergoing as part of their normal clinical care prior to and including the implant of the neurostimulator. Release of personal information, risks of MR and CT imaging, and risks of infections due to catheter placement are all overlapping in scope and occurrence with activities that happen during normal clinical care of these patients. With these subject's participation, we anticipate greatly increasing the knowledge of a critical nerve's anatomy and ability of a 3rd line treatment (implantable neurostimulator) to interact with it. This study may lead to improved future treatments that will improve upon the treatment that patients like these are able to receive.

12. Research Costs

All research-specific costs will be covered by NIH award OT2OD028191 and [redacted], under direction of study investigators Tim Bruns and Priyanka Gupta. Study participants will not be billed for any research study procedures that are not part of their standard clinical care, including the visit 1 imaging, visit 2 additional clinical catheters, visit 3 CT imaging, and visit 4 cystometrogram. All normal clinical care procedures involved in the Interstim implantation at the pudendal nerve will be billed to the patient or their insurance provider following standard procedures.

13. Investigational Drug

There is no involvement of any investigational drug in this study.

14. Investigational Device

There is no involvement of any investigational device in this study.

15. Marketed Drugs/Device

The Medtronic Interstim implantable neurostimulator has no restrictions on its availability. It is commonly used at Michigan Medicine and worldwide for regulatory-approved implantation at a sacral nerve or at the off-label pudendal nerve location to be used in this study. We have discussed this project with the University of Michigan MICHR IND/IDE Investigator Assistance Program (MIAP), which provides comprehensive regulatory support to U-M investigators

involved in regulated clinical research. MIAP's assessment was that we are not testing the safety or efficacy of the device (Interstim) and do not have a control arm to our study. We are testing our ability to map the nerve. Thus the MIAP assessment was that there is not a requirement for an Investigational Device Exemption (IDE). The U-M IRB consults with MIAP when determining final IDE requirements. In the unlikely event that the IRB reverses this no-IDE assessment we will promptly work with MIAP to receive an IDE from the FDA.

16. Additional Requirements

16.1 Biosafety

This research does not involve the use of infectious agents, recombinant DNA, or gene transfer.

16.2 Point of care testing

This research does not involve laboratory testing of the patient.

16.3 Tissue procurement

This research does not involve use of redundant/residual biological specimens.

16.4 Clinical research unit

This research does not involve the use of the Michigan Clinical Research Unit (MCRU).

16.5 Nurse or student nurse research

No one participating in this research study is a nurse or student nurse.

16.6 Pregnant women and newborns

This research does not involve laboring women and/or newborns.

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