Previously Implanted Pudendal Nerve Stimulation

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University of Michigan IRBMED

Protocol HUM00180124

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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.

Many animal studies have demonstrated bladder excitation in response to electrical stimulation of pudendal nerve fibers [4]–[7]. 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 [8], [9] or on distal pudendal branches originating from proximal or distal regions of the urethra [10], [11]. Penetrating electrodes within the pudendal nerve [12] or spinal roots [13] 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 [10]. 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 [14]. 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 [15] 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 [16]–[18]. 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 [19]. A recent modeling study suggested that it is possible to selectively activate different fascicles with a multi-contact cuff placed on the pudendal nerve [20]. While cadaver dissections suggested the surgical feasibility of cuff electrode placement to accomplish this selective stimulation [21], 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 [22], 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 [23]. 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. Stimulation with the Interstim IPG is at a continuous 15 Hz frequency, which differs from the frequencies tested extensively in preclinical studies.

Since 2005, a few clinicians worldwide have started placing the Interstim lead at the pudendal nerve [19], [24], [25]. This is often done in patients who failed traditional SNM or who have concurrent pelvic symptoms [26]. 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 [27], [28]. Patients at the University of Michigan health system who have previously received the Interstim at the pudendal nerve offer an opportunity to further study how stimulation of this nerve can drive bladder responses.

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 [29] and is prevalent in approximately 13% of women aged 19-44 years and 22% of women aged 45-64 years [30]. There are a number of therapies and treatments for SUI [31], including conservative measures and minimally invasive options with varying and limited efficacy [32]. Pudendal nerve stimulation may help maintain urethral closure during events that cause SUI, such as coughs, however it not been studied directly in patients.

Thus the goal of this study is to learn more about pudendal nerve stimulation with the patients who were previously implanted. These patients will undergo a standard clinical cystometrogram in which the bladder is filled to different volumes. Stimulation will be applied at different frequencies and during some periods when patients simulate SUI conditions. After the test session, the IPG parameters will be set to their normal clinical settings. We will collect surveys of patient pelvic organ function and have the participants complete a brief pelvic organ function

survey in the days before and after the study day. This study is not studying or establishing the efficacy of the Interstim system at the pudendal nerve.

1.2 Objective

The goal of this study is to examine the response of the bladder and urethra to different pudendal nerve stimulation frequencies, by studying previously-implanted patients.

1.3 Specific Aims

The aims of this study are to:

- **Specific Aim 1**: Determine the bladder's response to different pudendal nerve stimulation parameters in an acute setting.
- **Specific Aim 2**: Determine the change in urethral leak point pressure (ULPP) with pudendal nerve stimulation

1.4 Primary Outcomes

The primary outcome measure in this study is an evoked bladder contractions of at least 20 centimeters of water (cmH2O) in at least 50% of participants.

1.5 Secondary Outcomes

1) Selective stimulation of pudendal nerve branches for external urethral sphincter closure determined by comparing sensor recordings from distal pudendal nerve branches. 2) Measurement of effect of selective PNS on urethral leak point pressure (ULPP) using PNS configured for external urethral sphincter selectivity.

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 completed clinical study investigating skin-surface neuromodulation for female sexual dysfunction (HUM00101713). Dr. Bruns is PI with Dr. Gupta on a study to prospectively examine new patients receiving an Interstim IPG at the pudendal nerve (HUM00165005).

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. Dr. Gupta is the only clinician at the University of Michigan implanting Interstim IPGs at the pudendal nerve. Dr. Gupta is the clinical lead investigator on a study with Dr. Bruns to prospectively study new patients in whom she implants stimulators at the pudendal nerve (HUM00165005) and previously participated in HUM00101713.

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 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) [33], [34]
2 Bladder health: Michigan Incontinence Symptom Index (M-ISI) [35]
3 Sexual function: Female Sexual Function Index short form (FSFI-6) for women [36] and the International Index of Erectile Function (IEEF-5) also called Sexual Health Inventory for Men (SHIM) for men [37], [38]
4 Bowel function: Colorectal-Anal Distress Inventory 8 (CRAD-8) [39]
5 Pelvic pain: Female GenitoUrinary Pain Index (FGUPI) for women and Male GenitoUrinary Pain Index (MGUPI) for men [40].

The AUASI and M-ISI surveys were already part of the normal clinical care for these patients before they received the implant and the F/MGUPI are sometimes also given already. All surveys will be given to the participants during this study, even if participants have completed any of them previously. Participants will also complete a questionnaire on demographics. All of these surveys are loaded in section 29 of the IRB application. Surveys will be completed by phone, 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 Daily Diaries

From two days before until two days after the study visit (five total days), participants will complete a pelvic function diary (included as Daily Diary in section 44.1). Observations in these diaries will be added to the research data set for each participant.

2.3 Experimental Test Session

In the primary part of this study, participants will visit the clinic to undergo a cystometrogram (bladder filling) in a urodynamics suite. This test will occur at the University of Michigan main hospital or a local UMHS clinic, as determined by the clinical schedule, in a urology cystometry suite. Prior to the test, women capable of becoming pregnant will undergo a urine pregnancy test to detect pregnancy. 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 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 1 Top (from [41]), or in an upright sitting position. It is standard clinical practice to offer patients an antibiotic right before the 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 place standard urodynamic EMG surface electrodes by the external anal sphincter and perineal region, as done during the standard stage-1 implant surgery. The primary urethra catheters will be a standard clinical-use Covidien Manoscan manometry catheter, to provide high-resolution urethra pressure data [42], [43], 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 proximal and distal urethra pressures. At an empty bladder, thresholds to activate each of the distal catheter sensors will be determined for each electrode to generating a

standard strength-duration response curve [44] for each electrode. 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 a cystometrogram, using a standard clinical urodynamics instrument. Normal cystometrograms continue infusion until voiding (Figure 3 Bottom, from [41]), however stopping at a not-full state will allow for the assessment of stimulation effects on the bladder. Various stimulation paradigms will be applied via 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 time points within a cystometrogram, the urethral leak point pressure (ULPP) may be measured during Valsalva and/or forceful coughing. This will occur after infusing saline into the bladder to an 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 EUS 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 be again 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 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.

2.4 Survey Only Option

As part of the research procedure, potential study participants have the option of completing the surveys only. This optional study, HUM00169761 is a survey only study conducted by Dr. Gupta and colleagues.

During the initial recruitment phone call, participants will be informed of both studies and given the option to participant in one or both studies. In the event a participant is only interested in completing the surveys, the study coordinator or a clinical team member will consent the participant and administer the surveys. For participants interested in the experimental test session, the study coordinator will proceed with consenting and scheduling the study visit.

2.5 Patient Timeline

Figure 2 gives a summary of the timeline for each study participant.

3. Study Statistics and Data Analysis Plan

3.1 Sample Size

We plan to recruit at least 10 of Dr. Gupta's patients. This sample size is comparable to prior human subject studies stimulating the pudendal nerve or its branches (N=10 pudendal implant after sacral implant [45], N=12 cutaneous genital nerve [46], N=21 percutaneous genital nerve [47], N=30 pudendal versus sacral implant [25]). Dr. Gupta has implanted more than fifteen patients as part of her clinical duties at the University of Michigan. We will reach out to all of these patients but do not expect all to participate.

3.2 Data Analysis Plan

The primary outcome measures in this study will be evoked bladder contractions of at least 20 centimeters of water (cmH2O) during nerve stimulation in at least 50% of participants. The secondary 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 stimulate and cause bladder excitation and ULPP measures to determine if there are any trends or relationships to participant characteristics.

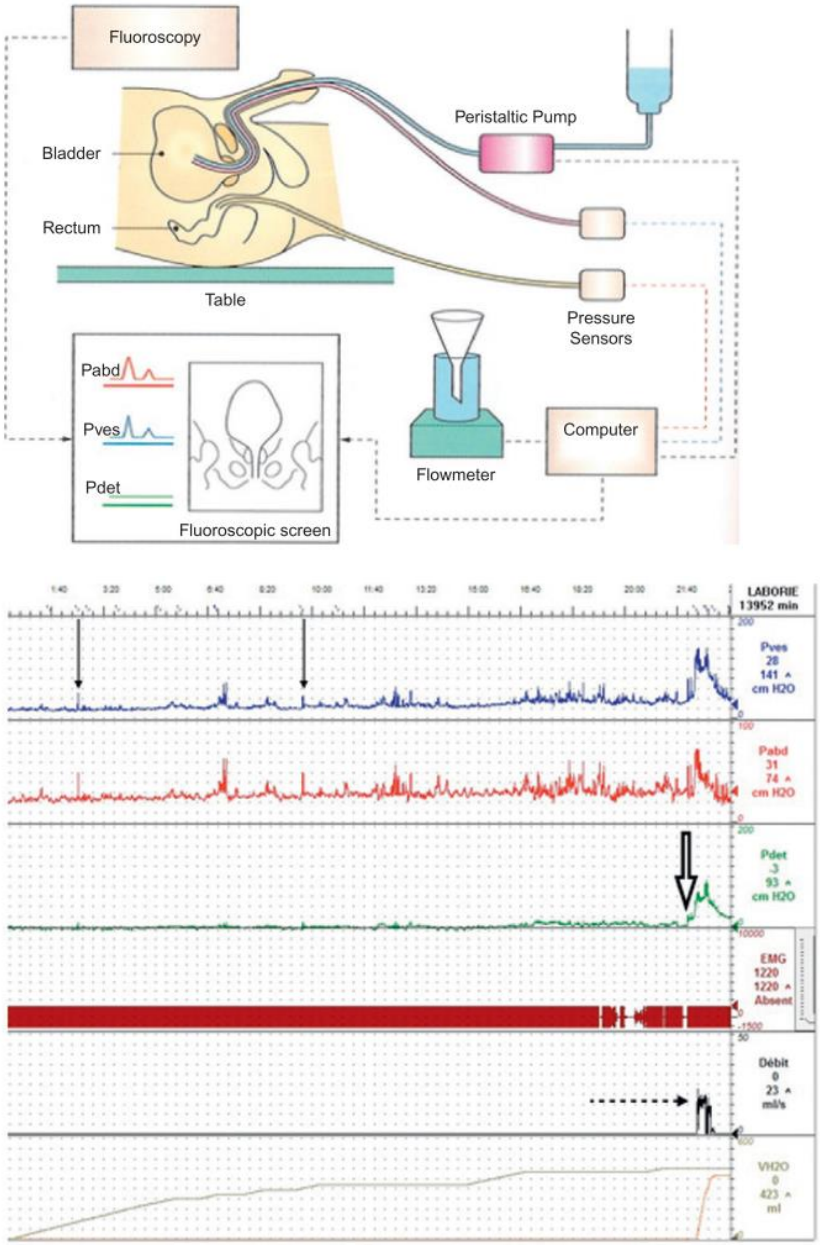

Figure 1. Top: Standard cystometrogram (CMG) setup, with a pump to infuse saline, bladder and rectal pressure catheters and sensors, and a flowmeter for voiding. From [37]. Our study will add one or more urethra catheters, anal sphincter and perineal EMG, and will not use fluoroscopy. Bottom: Standard 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 [37].

3.2.1 Bladder Excitation

The primary metric of successful bladder excitation will be a target evoked bladder contraction of at least 20 cmH_2O during the 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].

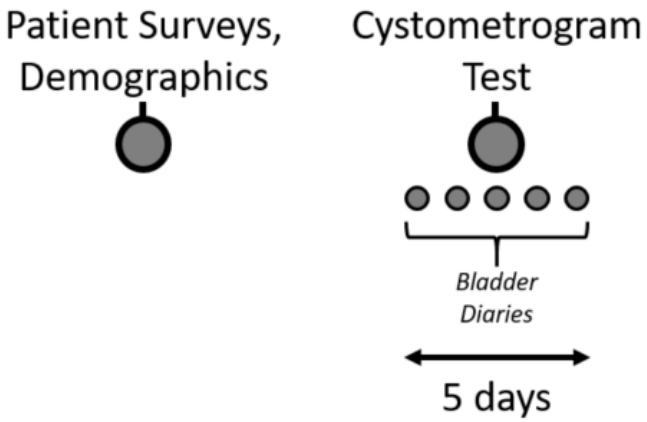

Figure 2. Per-participant study timeline. The interval between patient surveys and the test session is not fixed.

3.2.2 Strength-Duration Curves

For each electrode strength-duration curves will be created [44]. These data plots will show the minimum stimulation amplitudes that recruit each distal sensor location, for each tested stimulus pulsewidth. The response curves will be compared within and across participants for each distal sensor location, to see if there are trends, and will be fitted with standard strength-duration equations [48].

3.2.3 Selectivity Index

For a given stimulation electrode (among the four on an implanted stimulation lead), 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), perineal EMG (PEMG), and anal EMG (ischeal rectal nerve - IRN).

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

The PPB and DPB are the maximal intraurethral pressures measured at proximal and distal urethra catheter locations. PEMG is the maximum, normalized perineal EMG response. 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 in length) and/or an inability to place all EMG sensors. The SI for each electrode will be calculated to help us understand the relationship between the implanted electrodes and the pudendal nerve, and not as a measure of any sort of stimulation efficacy.

3.2.4 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

We will recruit patients from Dr. Gupta's clinical practice who have previously received a pudendal nerve implant. Generally, these patients are very willing to help, as they failed a series

of prior conservative treatments before receiving the pudendal nerve implant. Dr. Gupta or her clinical staff will identify patients from her clinical history chart review and will provide their contact information to the study coordinator. The study coordinator will send a letter to the patient and follow up with a phone call to recruit the patient. Patient information will not be shared outside of direct clinical conversations or inquiries by the study coordinator. The study coordinator will maintain regular contact with each participant, reminding them of the appointment to help retain subjects.

5. Study Population

We will recruit 10 participants for this study. If greater than 10 patients are willing to participate then we will recruit as many as are willing. We expect that 90% of participants will be women (N=9) and 10% men (N=1), based on the demographics of the patients in whom Dr. Gupta has performed this procedure. Within that, we anticipate 9 Caucasian (8 women; 1 men) of which none will be Hispanic and 1 African American (woman). We will not decline any participants based on their group membership.

5.1 Inclusion Criteria

- Previously received an implanted neurostimulator at the pudendal nerve.
- 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 the experimental session.

5.2 Exclusion Criteria

- Pregnant or planning to become pregnant during study. If a woman of child-bearing potential wishes to participate in this study, they will be pre-screened with a test to detect pregnancy.
- Currently has a urinary tract infection (UTI).
- Currently has or tested positive in the last 14 days for COVID-19, or is symptomatic for COVID-19.
- 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 study visit will be performed at the main Ann Arbor Michigan Medicine hospital or at a nearby satellite 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 will occur in the research lab of Dr. Bruns, which is 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 and Brighton.

7. Informed Consent

Full, written or electronic consent will be obtained by Dr. Gupta or the study coordinator. For

participants who are available in-clinic prior to the test session, a normal recruitment and consent by Dr. Gupta or the study coordinator will be performed. Typically, Dr. Gupta will introduce an eligible patient to the study coordinator who will then continue recruitment and discussion of the study, if necessary, and will then obtain informed consent. Otherwise, Dr. Gupta will perform the consent herself. Typically, the informed consent document will be sent to a participant prior to the test session for their review.

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, she will notify the study coordinator who will reach out to the participant over the telephone to discuss the study and either obtain consent or schedule a time to call the participant after they have had a time to review the consent form. In the instance a potential participant does not have access to the internet or is not inclined to use the internet, research staff will revert back to using the standard procedures for obtaining consent on paper during the first study visit.

Additionally, during the consenting process the study coordinator will explain to all potential participants the option to participate in the experimental test session, complete the surveys only or both. Should a participant only want to complete the surveys, either the study coordinator or a clinical team member on HUM00169761 will consent the participant and send the surveys.

8. Waiver of Documentation of Informed Consent

We are seeking a waiver of documentation of informed consent. There are a set of surveys that get completed at the start of the study. There are also daily diaries for the participants to complete in the days prior to the session. It is likely that participants will not be in the clinic for normal healthcare prior to their visit for the test session. It would be simplest to send the participants the surveys and diary, along with the consent form for review, if they agree to take part in the research during the recruitment process with the study coordinator. This means, though, that participants may be completing surveys and diaries before formally signing the consent form. Then we will have participants sign the full consent at the start of the test session.

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.

Additionally, data from HUM00169761 will be keep separate from the data collected for this study. In other words, data will not be linked between studies. If a participant takes a survey that is part of both studies, then a duplicate will be placed in each record. The two data sets will be kept separate so that data for participants who are only in one study are not accidentally corrupted or included in the wrong study.

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 with minimal risks. Once data collection has begun, Drs. Bruns and Gupta will discuss project progression, participant safety, and overall data on a monthly basis via phone, video conference, email correspondence, or an in-person meeting. Adverse Events (AEs) will be reported promptly to the IRB.

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.

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 if they have completed the study visit 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 if they completed the 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. Similarly, 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 pressures.

11.1.2 Potential Benefits to Participants

Participants will not directly benefit from this study. The findings of the study will not be used to modify the healthcare of any patients. Through this study we will gain new knowledge about how the pudendal nerve controls the lower urinary tract. This knowledge may benefit future

recipients of neurostimulators for pelvic organ function.

11.2 Risks to Human Subjects

Potential risks include release of identifying information, infection, and shock or burn due to electrical stimulation.

11.2.1 Potential Risks and Protection Against Risks

Participants will already have received 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 or other pelvic 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 Clinical Catheters

The standard urodynamic urethra and rectal catheters and manometry catheter added during the 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. Additionally, research participants will be offered an antibiotic medication before the testing begins to mitigate against any risk of infection.

11.2.4 Electrical Stimulation

During the cystometrogram 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.

11.2.5 Reasonableness of risks

The risks of study participation are minimal beyond risks that patients have undergone as part of their normal clinical care prior to and including the implant of the neurostimulator. Release of personal information 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. While the participants may not normally undergo a cystometrogram test, it is a standard clinical tool that is commonly used to assess bladder problems. 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, such as the cystometrogram testing or pregnancy test, if required.

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 a related pudendal nerve project (HUM00165005) 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. In HUM00165005, new pudendal implant patients undergo the same cystometrogram test as here, as well as additional testing. MIAP's assessment was that study is not testing the safety or efficacy of the device (Interstim) and it also does not have a control arm. This is also true of this study, HUM00180124. In both studies we are testing our ability to stimulate and map the nerve. For HUM00165005 the MIAP assessment was that there is not a requirement for an Investigational Device Exemption (IDE), which is also our expectation for HUM00180124. 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.

A Manoscan ESO High-Resolution Manometry system will be used in this study. Covidien/Medtronic is the supplier. The manufacturer is Given Imaging, which is a company that was was purchased by Medtronic. The device provides high-resolution pressure measurements along the length of its catheter. It is a standard clinical diagnostic system for measuring esophageal pressure profiles and other measures in the gastrointestinal tract. The Michigan Medicine GI Lab has a Manoscan of its own for this purpose. In this study we will use a pediatric-sized Manoscan catheter to obtain high-resolution pressure data in the urethra and bladder of participants. The pediatric catheter is the same size as standard clinical-use urethra catheters. This manometry system will significantly improve our ability to map pudendal nerve control over the urethra in the participants. This system is purely being used for diagnostic purposes.

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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