Official Title: AMPLIFY: Amplifying Sensation in Underactive Bladder

Protocol#: Pro00106457 Version 1.17

NCT#: NCT04516434

Document Date: 04/10/2024

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

The overall objective of this study is to improve lower urinary tract symptoms (LUTS) in adult neurologically-intact women with underactive bladder through electrical stimulation of bladder sensory nerves or urethral sensory nerves. The first primary endpoints are that sensory nerve fiber stimulation to the bladder will decrease bothersome urinary symptoms during filling and emptying, stimulation to the urethra will decrease bothersome urinary symptoms during emptying, and that bladder stimulation will increase bladder sensation during filling and emptying, as determined by our lower urinary tract symptom questionnaire. The second primary endpoint is that sensory nerve fiber stimulation to the bladder or urethra will increase bladder emptying during pressure-flow studies in participants with poor baseline bladder function. In addition to these primary endpoints, we will also observe secondary endpoints that will be compared to paired baseline measurements. Secondary endpoints include (a) increased bladder or urethral current perception threshold relative to normative data, (b) decreased bladder volumes at cystometric endpoints with intravesical (bladder) electrical stimulation, and (c) increased detrusor contraction strength and contraction duration with intraurethral electrical stimulation.

Background & Significance

- Should support the scientific aims of the research

The storage and elimination of urine is regulated by neural circuits in the brain and spinal cord to coordinate function between the urinary bladder and the urethra (Fowler et al. 2008). During micturition (bladder emptying), the elimination of urine is facilitated by bladder muscle (detrusor) contraction and urethral and pelvic floor muscle relaxation. Urine flow through the urethra also activates sensory nerves to amplify bladder contractions and maintain efficient bladder emptying (Jung et al. 1999, Bump 2000). Incomplete emptying and urinary retention occur when these mechanisms are disrupted or poorly coordinated.

Incomplete emptying due to underactive bladder is a poorly understood health concern that symptomatically affects up to 40% of the population, with the highest prevalence of symptoms in older men and women (Jeong et al. 2012, Osman et al. 2014). Despite the high prevalence of symptoms, the diagnosis of an underactive bladder remains low due to the lack of consistent terminology and standardized diagnostic criteria. This results in defining underactive bladder by a symptom complex that may involve reduced motor drive (detrusor underactivity) during bladder emptying and/or reduced sensory drive during filling and emptying (Chapple et al. 2015). Symptoms experienced by persons with underactive bladder include nocturia, urinary frequency, urgency, incontinence, slow stream, hesitancy, straining, and sensation of incomplete emptying (Gammie et al. 2016, Uren et al. 2017). The most common symptoms are nocturia, slow stream, frequency, hesitancy, and the impact of these symptoms on quality of life is substantial for many patients (Gammie et al. 2016, Uren et al. 2017).

The management options for persons with underactive bladder include double-void, intermittent self-catheterization, or pharmacotherapy (Miyazato et al. 2013). However, these treatments are associated with poor quality of life and patients often fail to completely resolve the lower urinary tract symptoms (LUTS). There is a need to clarify the pathological mechanisms underlying underactive bladder to improve therapeutic outcomes. One approach to clarify reduced sensory drive is to evaluate the functional integrity of sensory nerves with quantitative sensory testing (Ukimura et al. 2004, Kenton et al. 2007). Current perception threshold (CPT) testing delivers electrical stimulation to activate nerve fibers that evoke sensory perception, and changes in bladder sensory pathways were demonstrated in persons with diabetic detrusor underactivity (Lee et al. 2009). These diagnostic tests, however, have not been applied to neurologically intact adult women with underactive bladder and may provide insight into pathological sensory dysfunction.

The proposed research will quantify sensory nerve sensitivity in the bladder and urethra in adult women with underactive bladder. We will then amplify sensory nerve activity via continuous electrical stimulation to improve LUTS associated with underactive bladder. Continuous direct electrical stimulation of the

bladder or urethra is investigational and not standard clinical practice. However, intravesical (bladder) electrical stimulation has been used in persons with detrusor underactivity (Gladh et al. 2003, Deng et al. 2017), overactive bladder (Yune et al. 2018), and neurogenic non-obstructive urinary retention (Lombardi et al. 2013). Intraurethral electrical stimulation has also been used in persons with spinal cord injury (Yoo et al. 2011), as well as in women with urgency urinary incontinence (Pro00084173). Achieving the proposed objectives will establish a prognostic marker for rationally guided electrical stimulation in women with underactive bladder. Understanding how these mechanisms contribute to impaired emptying in underactive bladder will enable the development of novel therapeutics to enhance quality of life.

There are no patents, conflicts of interest, or FDA submissions in the works related to this study.

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

We will only be evaluating adult women in this proposal. Men are excluded from this pilot study due to the high incidence of similar symptoms caused to a degree by prostatic hyperplasia and not necessarily an underactive bladder. Patients will be screened through Chart Review and on the phone to determine eligibility, and if found eligible, will be scheduled for an in-person study procedure visit at the Duke Urogynecology Office at Patterson Place, Durham, NC under the supervision of Dr. Cindy L. Amundsen, MD.

Design
Screening: Established patients with underactive bladder will be identified by MaestroCare chart review. New patients with underactive bladder will be identified by Duke urogynecologists who see patients at one of two urogynecologic offices (Navaho Clinic in Raleigh or Patterson Place in Durham). Providers or study staff may hand out a brochure describing the AMPLIFY study, and who to contact. Providers will notify study personnel by secure email or MyChart of potential patients who may met the study criteria and patient names will be transcribed into a database stored behind an enterprise-grade firewall in a shared folder on password protected Duke PIN stations. After the patients have undergone urodynamic testing (uroflowmetry, cystometry, pressure-flow) as part of their routine workup, study personnel will review urodynamic criteria to see if they meet inclusion and exclusion criteria. If they meet these criteria, patients will be contacted by study personnel via phone call to determine their interest in participating in the study. If the patient is interested, they will be screened by answering 5 questions from the Lower Urinary Tract Dysfunction Research Network Symptom Index-29 (LURN SI-29) (Cella et al. 2019) to determine bothersome urinary symptoms. After confirmation of inclusion and exclusion criteria, the participant will be scheduled for the in person study procedure.

Electronic informed consent: Electronic informed consent will be collected via REDCap survey on a clinic-provided portable device. Participants will be asked if they would prefer self-guided or coordinator-led electronic informed consent. Study personnel will be available for questions before, during, or after the consent. Study personnel will confirm if participants have unresolved questions or concerns. Signed electronic informed consent will be emailed by REDCap Auto-Archiver + e-Consent Framework. In the event participants are not comfortable with electronic data capture, paper informed consent will be made available.

Study procedure visit: Participants will be reminded by phone call or email 48 hours before the study visit to withdraw from medications affecting urination per our inclusion criteria. On the day of the visit, participants will sign and date the informed consent document and complete a compensation form, LURN SI-29 questionnaire survey, and demographics questionnaire survey. Pre-procedure vital signs, point of care urinalysis, and a pregnancy test will be obtained. Participants will be excluded with a positive pregnancy test or delayed until resolution of infection with a positive urinalysis (per exclusion criteria). If participants have negative urinalysis, negative pregnancy test, and meet inclusion/exclusion criteria they will undergo current perception threshold (CPT) testing in the bladder and urethra.

Participants will be assigned to the intervention arm based on CPT. CPT data will be analyzed immediately by percentage change against normative data to stratify investigational allocation to intravesical (bladder) electrical stimulation or intraurethral electrical stimulation (Kenton et al. 2007). The allocation will be as follows: 1) if percentage change of urethral CPT > percentage change of bladder CPT then participants will receive intraurethral electrical stimulation, 2) if percentage change of bladder CPT > percentage change of

urethral CPT then participants will receive intravesical electrical stimulation, or 3) if percentage change of urethral CPT = percentage change of bladder CPT then participants will receive intravesical stimulation when cystometry "first desire to void" > 275ml or intraurethral stimulation when pressure-flow detrusor pressure at maximum flow < 30 cmH2O and maximum flow < 10 ml/s. After the investigational session of stimulation, participants will undergo post-study urodynamic studies which will include cystometry and pressure-flow studies. At the completion of these procedures, participants will be given standard urogynecology post urodynamic study instructions. They will also be instructed to complete remotely a post-study condition LURN SI-29 questionnaire that will be emailed via RedCap 7 days after the study visit. At that time, they will be considered to have completed the study.

Devices: A single Gaeltec electrode catheter will be used to stimulate both the bladder (intravesical) or urethra (intraurethral). The Gaeltec catheter will be smaller in diameter than the Neurometer to facilitate easier voiding. The Neurotron devices are comprised of a CPT device to generate current and the automated paradigms, and a Neurometer catheter to deliver stimulation to the tissues. While the Neurotron devices are from the same manufacturer, the CPT device may be used with different electrode catheters. Neurotron devices and Gaeltec catheters are commercially available. Everyway Medical Instruments Ultra 9000 stimulation device will be used as a backup to the Neurotron CPT device during investigational sessions of intravesical and intraurethral stimulation (not CPT) if the Neurotron device cannot generate our selected stimulation parameters. The Ultra 9000 will be run on a 9V Battery, and will be used on TENS mode "normal" or EMS mode "constant" with an adjustable frequency, amplitude, and timer.

Specifics of each Procedure
Current perception threshold (CPT): All participants will undergo CPT testing. Participants will be instructed to empty their bladder prior to instrumentation. They will then be moved to a semi lithotomy position and a Neurotron catheter (12-French) with electrode will be inserted through the urethra into the bladder. Lidocaine will not be used for this catheter insertion because we want to preserve sensory reflexes. The catheter balloon will be inflated and positioned at the urethrovesical junction to stimulate the urethra 10-14 mm from the bladder neck. The catheter and electrode leads will be secured to the participant's leg with medical tape. The urethral electrode will then deliver sine wave stimulus pulses at 5, 250, and 2,000 Hz. For each frequency, the stimulation amplitude will be increased until first perception and then decreased until it is no longer perceptible. CPT will be established using an automated forced choice paradigm by the method of levels, where random triplicates of A/B/Rest stimuli will be presented. The A/B /Rest paradigm is defined as a true stimulus, a placebo stimulus, and a rest trial, where the participant must indicate verbally or by handheld monitor whether they can detect stimulation during the three sessions. Based on their response, the device adjusts stimulation output and randomizes testing order. The final CPT value determined by the device is defined as the average of the minimum amplitude of the stimulus consistently detected and the stimulus 40 μA lower that was consistently not detected. For bladder stimulation, the catheter balloon will be deflated and the catheter will be advanced into the bladder. We will perform CPT testing in the bladder using a forced choice paradigm as described above. Bladder pressure will be monitored from a lumen of the Neurotron catheter electrode but we are not retrograde filling so we do not expect overdistention within the 30 minutes of CPT testing. Testing order of the bladder and urethra will be randomized between patients. Participants will be instructed to inform the study staff of any unpleasant sensations they may experience and may elect to terminate stimulation and participation at any point.

Intravesical (bladder) electrical stimulation This procedure is specific to participants in the bladder stimulation arm. A sterile stimulation catheter (Gaeltec custom catheter, 7-French) will be placed in the bladder through the urethra and the electrode contacts will be positioned to be floating within the bladder. The electrode contacts will be surrounded by ~30 ml of saline infused through the catheter. Impedance measurements will be recorded to monitor electrode integrity. A single return electrode will also be placed on the abdominal skin above the pubic bone. Stimuli will be delivered as 0.2 ms charge-balanced biphasic rectangular current pulses applied between the catheter electrode and the return surface electrode. Stimulation frequency will be set at 20 Hz and amplitude will be adjusted individually to 80% of the maximum tolerable intensity (Jiang and Lindstrom 1999, Gladh et al. 2003). Participants will be instructed to inform the study staff of any unpleasant sensations they may experience and may elect to terminate stimulation at any point. Electrical stimulation will be applied to bladder sensory nerves for up to 60 minutes prior to the start of urodynamic studies (Gladh et al. 2003, Deng et al. 2017).

Intraurethral electrical stimulation This procedure is specific to participants in the urethral stimulation arm. A sterile stimulation catheter (Gaeltec custom catheter, 7-French) will be placed in the urethra and positioned with the electrode contact 10-14 mm from the bladder neck to stimulate the proximal urethral sensory nerves. The catheter and electrode leads will be secured to the participant's leg with medical tape. Impedance measurements will be recorded to monitor electrode integrity. A single return electrode will also be placed on the abdominal skin above the pubic bone. Stimuli will be delivered as 0.2 ms charge-balanced biphasic rectangular current pulses applied between the catheter electrode and the neutral surface electrode. Stimulation frequency will be 10 Hz (may switch 2 or 20 Hz in subsequent participants if unresponsive) and amplitude will be adjusted individually to 80% of the maximum tolerable intensity (Gustafson et al. 2004, Yoo et al. 2011). Electrical stimulation will be applied to urethral sensory nerves at "strong desire to void" during cystometry. The participant will then be given permission to void at

"maximum cystometric capacity" with continuous intraurethral stimulation. Participants will be instructed to inform the study staff of any unpleasant sensations they may experience and may elect to terminate stimulation and participation at any point.

Cystometry After bladder stimulation or during intraurethral stimulation, standard urodynamics will be performed to assess bladder sensation and storage. Residual urine volume in the bladder will be removed by catheterization prior to cystometry. A dual-chamber 8-French catheter will be passed through the urethra into the bladder for retrograde filling. A second 8-French catheter will be placed in the vagina to measure intra-abdominal pressure. A stimulation electrode catheter will only be inserted in the intraurethral stimulation arm per the above methods. EMG pads will then be placed at 3 and 9 o'clock on each side of the perineum in an area not obstructed by hair or skin folds. These pads each have adhesive, which allows them to adhere in place through the study. Both the urethral and vaginal catheters will be zeroed to atmospheric pressure. The bladder will then be filled with room-temperature sterile saline solution in a retrograde fashion using a pump. Bladder sensation and urgency will be assessed while filling. Bladder pressure will be continuously observed and recorded during the study for evidence of involuntary detrusor contractions. The following values will be recorded from this portion of the study: volume of first sensation during bladder filling, first desire to void, strong desire to void, maximum cystometric capacity, presence or absence of detrusor overactivity.

Pressure-flow study A standard pressure flow study will be performed to evaluate voiding function after stimulation. The transurethral and intra-vaginal catheters are left in place after cystometry and the participant will be asked to void around them, into a commode. Bladder and abdominal pressures will be recorded, as well as urine flow over time. Variables that will be recorded in this portion of the study include the following: voided volume, postvoid residual volume, pressure at maximum flow, flow time, abdominal pressure during voiding, interrupted versus continuous flow, and pelvic floor muscle activity during micturition (as determined by EMG activity).

Uroflowmetry This standard procedure may be performed if participants are unable to void past the catheters in pressure flow studies. The dual chamber bladder catheter will be removed, and the participant will be instructed to void while sitting on a commode chair. A postvoid residual volume will be measured by straight catheterization. Variables that will be recorded include the following: voided volume, postvoid residual volume, flow rate, flow quality, and voided percentage. While this test sacrifices our secondary study objectives, we will still be able to fulfill our primary objectives of improved sensation and improved voiding function if the participant can void without catheters.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Inclusion Criteria:
- Females ages 18 and older
- Able to provide informed consent and agree to the study risks
- Willing to withdraw from medications affecting urination for the 48 hours prior to the procedure (e.g., alpha-adrenergic antagonists, cholinergic agonists, cholinesterase inhibitors)
- Has the below response to 2 of the 3 bulleted questions:

- Questions regarding self-reported poor sensation during bladder filling or emptying (one or more of the below)

  Question: In the past 7 days, where did you feel sensations when you felt you needed to urinate?
  Answer: "No" response for Bladder Area

  Question: In the past 7 days, how often did you have no sensation of urine flow while you were urinating?
  Answer: "Most of the time" or "Every time" response

  Question: In the past 7 days, how often did you feel that your bladder was not completely empty after urination?
  Answer: "Most of the time" or "Every time" response

- Questions regarding self-reported bothersome urinary symptoms (one or more of the below)

  Question: In the past 7 days, how satisfied were you with your bladder function?
  Answer: "Not at all satisfied" or "Somewhat satisfied" response

  Question: In the past 7 days, how bothered were you by urinary symptoms?

Answer: "Very bothered" or "Extremely bothered" response

- Standard uroflowmetry with a voiding efficiency (voided volume / voided volume + residual volume) of < 80%, voided volume + residual volume must be >150ml for measurement

Exclusion Criteria:
- Preexisting neurological impairment (e.g., spinal cord injury, multiple sclerosis, Guillain-Barre, cauda equina syndrome, cerebrovascular accident, Parkinson's disease, traumatic brain injury)
- Functional obstruction demonstrated by either elevated pelvic floor activity on EMG during standard pressure flow study or high tone pelvic floor on clinical exam)
- Pelvic organ prolapse beyond introitus
- Active urinary tract infection (candidate would be deferred until treated)
- Positive pregnancy test
- Less than 6 weeks postpartum
- Unevaluated hematuria
- Urethral stricture/stenosis
- Surgical obstruction i.e., urinary retention due to obstructive sling or other anti incontinence procedure
- Surgical procedures to increase bladder capacity (e.g., augmentation cystoplasty)
- Active sacral neuromodulation or ongoing posterior tibial nerve stimulation sessions
- Botulinum toxin injection in the past six months
- History of genitourinary or gastrointestinal cancer

Subject Identification Patient name and contact information will be recorded for eligibility screening. They will be considered enrolled once they complete the informed consent process and sign the consent form at their study procedure visit. Ineligible participants will be given a number SF001-100, whereas eligible participants will be given a number AMPLIFY01-20. An electronic enrollee log book will be kept by study personnel and will serve as the master list for enrolled participants. After being logged in the log book, the participant's name will no longer be used on case report forms; instead, their subject number will be used on case report forms. Each study participant will have a study folder. These will be managed by the research coordinator and kept under lock and key at the Duke Urogynecology Office.

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Subject Recruitment Participants will primarily be recruited from Duke Urogynecology offices (Navaho and Patterson Place). Advertisement brochures will be used provide contact information and a snapshot of the AMPLIFY study. MaestroCare and DEDUCE will also be used to identify established patients previously seen by providers that meet study eligibility criteria. We will contact patients via email, phone, or the MyChart portal to determine their interest in participating in the study. If they are interested, research personnel will perform a screening questionnaire and schedule a study procedure visit.

Subject Compensation There will be no direct cost to subjects participating in the study. They may incur costs for travel to the Urogynecology Clinic.

Compensation is pro-rated as follows:

- $20 for completing informed consent
- $60 for completing any part of the procedure visit
- $60 for completing the entire procedure visit
- $60 for completing the final questionnaire

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Participants will be competent to give consent. The study personnel will determine competency.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

The potential benefits of the proposed study to research participants are as follows:
- Participants will experience standard procedural risks involved with invasive urodynamics and electrical stimulation. The potential acute benefit of decreased lower urinary tract symptoms (LUTS) and increased bladder emptying is reasonable relative to the risks of additional urodynamic testing that they may have otherwise undergone.

The potential risks for the study are as follows:
- The risk for breach of confidentiality of personally identifiable information. There is minimal risk given our Data and Safety Monitoring Plan but this risk will result in loss of confidentiality of study participation.
- Risk for breach of confidentiality with electronic informed consent. Participants will receive a signed copy of their consent via the email address they provide and this risk is disclosed in the informed consent form.
- Participants will be asked to withdraw medications (e.g., alpha-adrenergic antagonists, cholinergic agonists, cholinesterase inhibitors) that affect urination for 48 hours prior to study participation. This will create a risk of them being untreated for the medicated condition. We do not expect significant complications other than decreased quality of life from 48 hours of medication withdrawal. We will protect against the risk of significant adverse events during medication withdrawal by instructing participants to contact study personnel in the event of adverse effects.
- During invasive urodynamic testing, there is a risk of irritation and infection with catheterization. Participants may develop a urinary tract infection, hematuria, or pain and discomfort. We will minimize the risk of urethral irritation by lubricating the catheter with K-Y jelly and having the fewest de novo catheterizations possible Additionally, we will minimize the risk of infection by using sterile preparation techniques, as well as antiseptic cleaning of the working area.
- There is a risk of painful sensations from electrical stimulation to the bladder and urethra. Participants can elect to decrease or terminate stimulation at any point during the study. We will minimize the risk of activating nerve fibers carrying painful stimuli by individually adjusting current amplitude to 80% of their maximum tolerable intensity. Every subject will be titrated down from a stimulation parameter that they feel is uncomfortable. The stimulation amplitude will be guided by the values obtained from the Current Perception Threshold forced choice paradigm, where a baseline intensity alignment automatically increases amplitude until the participant reports detection. Participants will be informed of any sensations they may perceive as unpleasant and may elect to terminate stimulation at any point.
- Participating in this study while pregnant may expose the unborn child to unknown risks. There is no risk level because we have excluded pregnant women.

- There may be some unknown and unforeseeable risks related to the study. Participants will be informed of any significant new information learned during the study that might cause them to change their mind about participating in the study. Significant new findings developed during the research, which may relate to their willingness to participate will also be provided to them.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There will be no cost to the subject as a result of the participation.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Expected enrollment n = 20 neurologically-intact women with underactive bladder
Expected effect size (dz) = 0.67
Power (1 – β) = 0.8
Time to Target Accrual 2 years

To account for participants failing to meet our eligibility criteria, it is anticipated that a total of 100 adult women will be screened to achieve n=20 total study participants. We expect to screen all patients with ICD codes suggestive of underactive bladder because a DEDUCE query revealed that in 2019 Duke Urogynecology clinics saw 34 patients meeting our criteria and approximately 10 of those patients went on for urodynamic studies. It is our expectation that the lack of consistent terminology and diagnostic parameters for underactive bladder will result in a large patient population failing to meet our eligibility criteria. Our expected enrollment will enable detection of a 7.5% change in voided percentage after stimulation with power (1-beta) of 0.8.

Statistical Methods
Primary Aim 1: Use of intraurethral electrical stimulation or intravesical electrical stimulation to assess increase in voided percentage during pressure-flow studies
Hypothesis: Electrical stimulation will increase voided percentage, and this hypothesis will be evaluated with non-parametric tests.
Method: Data will be analyzed by Wilcoxon signed-rank test to determine the influence of intravesical and intraurethral stimulation on bladder emptying.

Primary Aim 2: Use of LURN SI-29 questionnaire to assess whether electrical stimulation decreases urinary bothersome symptoms and increase bladder sensation during filling and emptying
Hypothesis: Intravesical (bladder) stimulation will decrease affirmatory responses to bothersome urinary symptoms and increase affirmatory responses to sensation during filling and emptying, whereas intraurethral stimulation will decrease affirmatory responses to bothersome symptoms during emptying.
Method: Data will be analyzed by the McNemar Exact Test or the Wilcoxon signed-rank test to determine the influence of intravesical or intraurethral stimulation on sensation.

Secondary Aim 1: Assess bladder or urethral current perception threshold (CPT) in women with underactive bladders
Hypothesis: Women with underactive bladder will have increased bladder CPT and increased urethral CPT (reduced sensory nerve activity) compared to normative data in asymptomatic women, and this hypothesis will be evaluated with the Dunn's multiple comparisons test.
Method: Data will be analyzed by the Kruskall-Wallis test to determine the CPT distribution between women with underactive bladder and asymptomatic women.

Secondary Aim 2: Use of intravesical electrical stimulation to assess volumes at cystometric endpoints
Hypothesis: Intravesical stimulation decrease cystometric volume endpoints, and this will be evaluated with the Bonferroni multiple comparisons correction.

Method: Data will be analyzed by repeated measures ANOVA to determine the influence of intravesical on perceptions of bladder filling.

Secondary Aim 3: Use of intraurethral electrical stimulation to assess contraction strength and contraction duration

Hypothesis: Intraurethral stimulation will increase detrusor contraction strength and contraction duration, and this will be evaluated with non-parametric tests.

Method: Data will be analyzed by Wilcoxon signed-rank test to determine the influence of intraurethral stimulation on detrusor function.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

The paper informed consent and case report forms will be placed in individual participant binders, which will be stored under lock and key in the Duke Urogynecology office. Electronic informed consent will be stored in the REDCap project's File Repository. The regulatory binder will be an electronic regulatory binder in the Forte eRegulatory Management System (eReg). The research study staff will have access to these documents. The staff processing the participant reimbursement will have contact with the reimbursement form, which requires the participant provide a SSN. These forms will be kept in an opaque envelope and handled only by the research coordinator. Electronic data will be stored behind an enterprise-grade firewall in a shared folder on the password protected Duke PIN stations. It will not be placed on personal laptops, phones, or thumb drives.

Participant privacy will be maintained through confidential phone screens and consultation behind closed doors in the Urogynecology Clinic. Participant information will be recorded in their subject binder and stored for six years per Duke protocol. Their electronic personal health information will be behind an enterprise-grade firewall and will not be shared with outside entities unless required by the sponsor.

Research study participants will be given contact information to Em Abbott, PhD and will be allowed access during working hours (9am-5pm) to answer questions related to study risks and procedures. To maintain patient safety oversight, Em Abbott, PhD will submit Adverse Event reports to an independent safety monitor after 5 participants have been evaluated with the intervention. The independent safety monitor is Dr. Nazema Siddiqui, M.D., a Duke Urogynecologist. We also have a Clinical Quality Management Plan where a Quality Management Reviewer will review all safety events during the review of the participant charts to ensure appropriate reporting according to DUHS IRB policy. If any Serious Adverse Events, Protocol Deviations/Violations, and/or Unanticipated Problem are observed during the review, these will be communicated to the study team promptly. The QM reviewers are Bonnie Thiele, Caroline Nagle, or Jessie Paradis. In addition to the Clinical Quality Management Plan, study staff will review participants' charts 30 days after the study visit to identify safety/adverse events and facilitate timely reporting. All protocol deviations and adverse events will be promptly reported to the Institutional Review Board in accordance with institution and Human Research Protection Program policies. All additional regulatory and monitoring requirements of the Investigational Device Exemptions will be carried out by the study team in accordance with 21 CFR 812.2(b)(1).