Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

Phenotyping of Patients with Lower Urinary Tract Dysfunction: Organ-based Diagnostics Pilot Study Protocol

Manual of Operations
Version 4.0

Current Version: September 17, 2017

1. Preparation for Study Implementation

- Consent Forms
- Phone Screening Script (appendix 1)
- Phone Screening CRF (appendix 2)
- Paper copies of Case Report Forms (CRFs) to record patient-reported data during the urodynamic procedures and a paper copy of the study evaluation for the subject to complete after the testing.
    - LUTS Tool – 1 month version (appendix 3)
    - AUA-SI (appendix 4)
    - Pilot Screening CRF (appendix 5)
    - UDS CRF (appendix 6)
    - Post Procedural Survey (appendix 7)
    - Pilot General Deviations (appendix 8)
    - Adverse Events CRF (appendix 9)

- Purchase or confirm availability of other study materials:
    - Gloves
    - Urine dipsticks
    - Serum pregnancy tests
    - Hospital gowns
    - 50 cc of 1% lidocaine
    - 4 L room temperature and 2 L refrigerated (4-8 degrees C, 39-46 degrees F) normal saline
    - Uroflowmetry equipment
    - Bladder scanner
    - Urethral profilometry and cystometric equipment
        - Laborie Urodynamics Setup (Laborie Medical Technologies, Williston VT)
        - 7 Fr double-lumen catheter for bladder cystometry
        - 9Fr triple-lumen catheter for Urethral testing
        - 9 Fr balloon catheter for rectal placement

2. Screening & Enrollment Procedures

2.1 Study Group

Adult women (age 18 or older) who are asymptomatic and continent will be recruited.

Subjects interested in participating in the study will be screened via a phone script (appendix 1). If deemed eligible via the phone screening CRF (appendix 2), the study coordinator will schedule the study visit. At the study visit, subjects will be consented and inclusion and exclusion criteria will be reviewed. A urine dipstick, post-void residual and serum pregnancy test (if pertinent) will be obtained. The LUTS Tool (appendix 3) and AUA-SI (appendix 4) questionnaires will be given. The Study Coordinator will complete the Pilot Screening CRF (appendix 5).

2.1.1 Eligibility criteria

Inclusion criteria

1. English speaking
2. Women
3. Aged 18 or older
4. No lower urinary tract symptoms as defined by the LUTS tool:
   a) answered "1-3 times a day" or "4 to 7 times a day" on question 2 of the **LUTS Tool – 1 Month Version** ("During a typical day in the past month, how many times did you urinate during waking hours?"), and
   b) answered "none" or "1 time a night" on question 3 of the **LUTS Tool – 1 Month Version** ("During a typical night in the past month, how many times did you wake up because you needed to urinate?"), and
   c) answered "never" or "rarely" on question 6 of the **LUTS Tool – 1 Month Version** ("During the past month, how often have you had a sudden need to rush to urinate?"), and
   d) answered "never" or "rarely" on question 15 of the **LUTS Tool – 1 Month Version** ("During the past month, how often did you leak urine?"), and
   e) answered "never" or "rarely" on question 16b of the **LUTS Tool – 1 Month Version** ("How often in the past month have you… Leaked urine in connection with a sudden need to rush to urinate?"), and
      - They must have only minimal to mild LUTS (AUA-SI <7) as assessed by the **AUA Symptom Index** (AUA-SI).
      - Willing to abstain from caffeine for 6 hours, nicotine for 2 hours, over the counter analgesics (NSAIDS), and alcohol for 24 hours
      - Willing to avoid taking anticholinergic medications (e.g., diphenhydramine) for one week prior to the procedure
      - PVR <150cc

Exclusion criteria

1. Pregnancy or ≤ 6 weeks postpartum or if breastfeeding
2. Any condition making conduct of the extended urodynamic test sequence impractical or impossible, including but not limited to:

    - prior surgery to bladder, urethra, or vagina
    - prior rectal surgery
    - inability to stand for prolonged periods

3. Urinary retention or post-void residual > 150 mL
4. Neurological impairment of any type, regardless of whether impairment is known or suspected to affect bladder function such as Multiple sclerosis, myasthenia gravis, Parkinson's Disease, or stroke within the past 6 months
5. Lidocaine allergy or contraindication. Lidocaine is contraindicated in patients with:

    - hypovolemia, heart block or other conduction disturbances
    - hepatic impairment (may lead to increased plasma levels)
    - known drug sensitivity to amide-type local anesthetics
    - Lower urinary tract symptoms, as quantified by the LUTS Tool 1

6. Pelvic organ prolapse past the hymen, which would be determined at time of catheter placement during urodynamics.
7. Positive urine dip (>+1 nitrites, >1+ LE, or >1+ blood) and urinary symptoms at the time of consent
8. Diagnosis of Interstitial cystitis / Bladder Pain Syndrome

2.2 The Day(s) Prior to the Organ-based Diagnostic Pilot Study Visit

Call the participants one week before their visit to confirm the visit and remind them of the following:

- Avoid consuming products containing caffeine (6 hours), nicotine (2 hours) and alcohol (24 hrs.).
- Avoid over-the-counter analgesics (NSAIDs, acetaminophen), muscle relaxants, and anticholinergics such as nasal decongestants (pseudoephedrine, phenylephrine) for 24 hours before the testing.
- In terms of fluid volumes, participants should drink the amount of fluid they would normally drink, and should not be dehydrated prior to the imaging session.
- To facilitate voiding on the day of testing, remind the participant to refrain from urination immediately prior to checking-in on the day of testing.
- Participants should dress comfortably to the testing.

3. Study Day

At the study visit, subjects will be consented:

- A urine dipstick, post-void residual and serum pregnancy test (if pertinent) will be obtained. The LUTS Tool (appendix 3) and AUA-SI (appendix 4) will be given.
- The inclusion and exclusion criteria will be reviewed. The Study Coordinator will complete the Pilot Screening CRF (appendix 5).
- If they do not meet study criteria they will not participate in the study.
- Double check the product and medication restrictions: No over-the-counter analgesics (NSAIDs, acetaminophen) or muscle relaxants (24 hours), anticholinergics such as nasal decongestants (pseudoephedrine, phenylephrine) (1 week), caffeine (6 hours), alcohol (24 hours) or nicotine (2 hours). Record any protocol deviations on the General Deviations CRF (appendix 7).

3.1 General Deviations

Any deviations from the study procedures should be recorded in the General Deviations CRF (appendix 7).

3.2 Study Procedures

Record results of the study procedures in the UDS CRF (appendix 6).Tests below are numbered to match the UDS CRF.

3.2.1 1. Uroflowmetry

Have the participant change into a hospital gown and read the following script to the participant: ***"Now we'll start the urodynamic testing. Your participation will help us determine whether this amount of testing is feasible for use in a larger study to determine responses to different groups of patients that have urgency with or without incontinence. You will undergo a series of tests during this period. Most of these will require insertion of a catheter into your urethra bladder, and rectum. You may experience urgency or urge to urinate during the testing. Do you have any questions?"*** Read the following script to the participant: ***"We want to make sure that you have an empty bladder before we place the catheter, so please try to urinate into the Uroflowmeter. This tool allows us to determine the strength of your urinary stream while voiding. After you urinate, we will use the ultrasound machine to determine whether there is any urine left in your bladder. If you cannot urinate, please let us know."***

- Guide the participant to the Uroflowmeter
- Record the time of day when the participant is done voiding per the UDS CRF (appendix 6)
- Record the volume voided and flow rate on the UDS CRF

"We will now measure how much urine is remaining in your bladder using a small hand held ultrasound machine."

- Record the residual volume on the UDS CRF

3.2.2 Urethral Testing

Guide the participant to the Urodynamics set up.

Explain the urethral profilometry testing. Read the following script to the participant: ***"We will now perform urethral pressure testing. During this time, we will insert and withdraw the catheter in your urethra three times while you are relaxed. After these tests, you will be asked to contract you urethra as hard as you can while we record the pressure that you generate."***

Preparation

1. Subject is placed in the low lithotomy/supine position.
2. With the participant's bladder still empty, the catheters are zeroed while held in the air at the level of the urethra.
3. A polyurethane 7 Fr triple lumen catheter is placed in the urethra/bladder.
4. A 9 Fr balloon catheter with a balloon on one end and 2 luerlock connectors on the distal tubing is placed in the rectum and filled with 10cc saline The saline is insufflate in the rectal balloon, and either added or subtracted to equalize the Pabd with Pves pressure. Insert the tube/balloon while it is empty then push water in and connect the catheter to the pressure line going to the transducers. The second luerlock stays closed unless water is added or subtracted in order to equalize the Pabd pressure with the Pves pressures.
5. The bladder is filled to 150 cc with room temperature saline
6. Abdominal (Pabd), vesical (Pves), and urethral (Pur) pressures are recorded directly and detrusor (Pdet) and urethral closure (Puc) pressures calculated on the urodynamic instrument.

At 150 cc bladder volume, urethral pressure profiles are performed as follows:

2. Urethral Pressure Profile

1. Attach the urethral catheter to the profilometer, positioning it in line with the urethra so that the catheter is pulled straight and not deflected upwards and downwards.
2. Advance the urethral catheter proximally so that both transducers are in the bladder.
3. Confirm that the pressures in the urethral and bladder transducer are equal. Also, ensure appropriate subtraction of the urethral and rectum transducers by asking the participant to cough.

4. Begin infusing room temperature saline through the urethral lumen at a rate of 10 ml/min
5. Activate the pulling mechanism on the profilometer so that the catheter is withdrawn at a constant rate (1 mm/sec) until the urethral transducer appears below the external urethral meatus and reaches atmospheric pressure.
6. Stop the profilometer.
7. Confirm that the reading in air approximates 0 cm H2O.
8. Reverse the profilometer so that it advances the catheter until the urethral transducer is back in the bladder.
9. Repeat step (4 through 8) twice, for a total of three measurements. Record measurements on the UDS CRF (appendix 6).

3. Maximum Urethral Closure Pressure During Pelvic Muscle Contraction

1. Detach the catheter from the profilometer and advance the catheter until the urethral transducer is at the point of maximum urethral pressure.
2. Instruct patient on proper pelvic muscle contraction technique prior to obtaining data. ***"Contract your muscles like you were wanting to hold gas in an elevator".***
    a. Confirmation that patient is performing the right maneuver includes the following: upward inward motion of the perineal body, anus contracting and downward movement of the clitoris.
    b. Monitor intravesical pressure during this time to confirm that the patient is not increasing intra-abdominal pressure.
3. Once the patient is performing the maneuvers properly, begin infusing room temperature saline through the urethral catheter at a rate of 10 ml/min and readjust the catheter to assure the urethral transducer is still at the point of maximum urethral closure pressure.
4. Ask the patient to perform the strongest contraction that she possibly can. Record the maximum pressure.
5. During this time watch the external urinary meatus and the catheter to make sure that the catheter is not moving relative to the urethra.
6. Repeat 2 more times, for a total of 3 measurements. Record measurements on the UDS CRF (appendix 6).
7. **Ask the patient if she feels she has done her best contraction and if not, allow her to repeat.** Use only the data from the set of 3 measurements she feels are her best effort.
8. If the subject cannot produce a contraction of the pelvic muscles during this testing despite efforts to elicit a contraction and only contracts the gluteal muscles, coach her not to contract her gluteal muscles and tell her it's ok that nothing happens.

Perform calibration confirmation. Elevate the catheter tip 25 cm from the transducer. Record adequacy on the UDS CRF

3.2.3 Bladder Tests

These tests are specific to bladder sensory and motor function. All manometric studies will be done using the Laborie urodynamic instrument described in the previous section.

Explain the rating of bladder urgency (show page demonstrating scales). Read the following script to the participant: ***"Several times during the urodynamics testing session we will ask you to rate your urgency to urinate. Urgency is different from normal bladder feelings. For urgency, we mean the sudden, compelling desire to pass urine which is difficult to defer, or a sudden feeling that you need to pass urine and if you don't you may have an accident. Please rate urgency from 0 (no urgency) to 10 (worst urgency imaginable)."***

4. Medium Fill-rate Cystometry

Cystometry is the measurement of intravesical pressures during bladder filling and during voiding, and the pressures are a reflection of organ compliance during filling, and motor strength during voiding. We will initially perform cystometry at a medium fill rate (50 mL/min), and collect concomitant sensory information during bladder filling. When the participant reports a full bladder, she will be allowed to void into a uroflowmeter.

Preparation

1. Subject remains in the lithotomy/supine position.
2. The UPP catheter will be removed.
3. The 7 Fr double-lumen bladder cystometry catheter is zeroed .
4. The bladder cystometry catheter is placed in the bladder and taped to thigh so catheter is not directly laying on thigh.
5. The 9 Fr balloon catheter remains in the rectum from UPP. If the catheter pulls out, replace it.
6. Abdominal (P_{abd}) and vesical (P_{ves}) pressures are recorded directly and detrusor (P_{det}) pressure calculated on the urodynamic instrument.
7. The patient is then moved to the sitting position.
8. A cough test is performed to ensure approximately equal pressure transmission to the bladder (P_{ves}) and rectal ($P_{abd)}$ catheters. Adjust catheter position if necessary.
9. The bladder is emptied through the bladder catheter.
10. The bladder will then be infused with room temperature normal saline: Fill the bladder at a rate of 50 mL per minute until the patient's maximum cystometric capacity is achieved.
11. During cystometry, the patient is queried on sensation.
12. Patient is asked to report other sensations per the UDS CRF.
13. Record measurements and responses on the UDS CRF (appendix 6).

The presence of DO will be recorded. DO is a urodynamic observation characterized by an involuntary rise in detrusor pressure (due to a contraction) during the filling phase, which may be spontaneous or provoked. There is no minimum pressure threshold to label detrusor overactivity. Symptoms such as urgency may or may not be present. Multiple DO events may occur during bladder filling or storage. The following information will be recorded for each DO episode:

- Number of DO episodes
- Volume at DO
- Change of Pdet (max) from baseline
- Sensation of urgency (yes/no)
- Sensation of pain or burning (yes/no)
- Leakage or incontinence (yes/no)

5. Stop test

We will utilize the voluntary stop test, as it will provide insights into both detrusor contractility AND another aspect of voluntary control of urethral function: the ability, or lack thereof, of the patient to exert voluntary control over striated sphincter function once a true voiding event has initiated.
For the voluntary stop test, the subject is asked to interrupt voiding by the examiner during mid-void. Bladder filling during Medium fill Cystometry will be stopped shortly after the subject reaches *strong desire to void*. The patient will then be given permission to void and shortly after initiation of the void, they will be asked to try to stop the void and hold until the measurement is taken, and then will be allowed to continue until they feel that they have emptied.

The Pdet and void stream flow rate will be recorded at the minimum flow that occurs during the stop test (in a normal person 0 cc/sec).

6. Rapid Fill-rate Cystometry

Rapid fill-rate cystometry is done to provoke a bladder contraction, as the rapid filling rate is more "irritating" to the bladder than at slower filling rates. The volume threshold for provocation will be determined, as this may be a significant difference between the cases and controls. This cystometric study will be performed at 100 mL/min, and concomitant sensory information will be documented during the filling phase.

1. The remaining fluid in the bladder will be drained completely via the bladder catheter (recorded above under PVR).
2. Bladder and rectal catheters will still be in place from the Medium fill cystometry.
3. The cough test will be repeated to ensure equal pressure transmission.
4. Begin filling with room temperature normal saline at 100 mL per minute.

5. Query patient of bladder sensations as described above and record first sensation of filling, first desire to void, normal desire to void, strong desire to void, urgency, and pain.
6. Record any episode of DO, include bladder volume at start, change in Pdet, presence of urgency, and leakage (incontinence).
7. Stop filling at the patient at the strong desire to void and ask the patient to void until they feel that they have emptied their bladder.

7. Cold Saline Fill Cystometry

Cold saline fill cystometry is another provocative test, and like the rapid-fill rate cystometry, will be used to determine the volume threshold for provoking a bladder contraction.

1. The remaining fluid in the bladder will be drained completely via the bladder catheter (PVR recorded above).
2. Bladder and rectal catheters will still be in place from the Rapid fill cystometry. The cough test will be repeated to ensure equal pressure transmission.
3. Begin filling at a rate of 50 ml/min with cold (refrigerated) normal saline (4-8°C).
4. Query patient of bladder sensations as described above and record first sensation of filling, first desire to void, normal desire to void, strong desire to void, urgency, and pain.
5. Record any episode of DO, include bladder volume at start, change in P_{det}, presence of urgency, and leakage (incontinence).
6. Stop filling at the patient's strong desire to void, ask the patient to void until they feel that they have emptied and drain the remaining fluid using the bladder catheter.
7. At the conclusion, assess *Perception of coldness in the bladder*:

8. Lidocaine Pre-Treatment Medium fill rate Cystometry

Anesthetization of the bladder urothelium with lidocaine will evaluate the effect of the sensory function of the bladder on generation of a contraction. The bladder will be anesthetized with 50 cc of liquid topical lidocaine 1% instilled into the bladder. This will be followed by **rapid fill-rate cystometry as described previously and then cold saline fill**

1. Fill the bladder with 50 cc of 1% lidocaine via the bladder/urethral catheter that is already in place and leave lidocaine in bladder for 15 minutes. Flush the catheter with 2cc of sterile water after lidocaine.
2. The bladder will be drained completely via the bladder catheter
3. Bladder and rectal catheters will still be in place from the Cold Saline fill cystometry. The cough test will be repeated to ensure equal pressure transmission.
4. Begin filling with room temperature normal saline at a rate of 50 mL per minute.
5. Query patient of bladder sensations as described above and record first sensation of filling, first desire to void, normal desire to void, strong desire to void, urgency, and pain.

6. Record any episode of DO, include bladder volume at start, change in P_{det}, presence of urgency, and leakage (incontinence). Record DO even if not symptomatic.
7. Stop filling when the **Lidocaine** *strong desire to void (above)* is reached, or when the **Normal Room Temperature Rapid Fill** *strong desire to void* plus 50% *(first fill)* is reached, whichever comes first, to avoid over-distending the bladder if there is significant impairment of sensation after lidocaine. Circle which one comes first. Between fills, aspirate back with syringe to confirm empty.
8. Void. If unable to void, drain the bladder using a straight catheter.

9. Lidocaine Pretreatment Rapid Fill-rate Cystometry

1. The remaining fluid in the bladder will be drained completely via the bladder catheter (recorded above under PVR).
2. Bladder and rectal catheters will still be in place from the Medium fill cystometry. The cough test will be repeated to ensure equal pressure transmission.
3. Begin filling with room temperature normal saline at 100 mL per minute
4. Query patient of bladder sensations as described above and record first sensation of filling, first desire to void, normal desire to void, strong desire to void, urgency, and pain.
5. Record any episode of DO, include bladder volume at start, change in P_{det}, presence of urgency, and leakage (incontinence).
6. Stop filling when the **Lidocaine** *strong desire to void (above)* is reached, or when the **Normal Room Temperature Rapid Fill** *strong desire to void* plus 50% *(first fill)* is reached, whichever comes first, to avoid over-distending the bladder if there is significant impairment of sensation after lidocaine. Circle which one comes first. Between fills, aspirate back with syringe to confirm empty.
7. Void. If unable to void, drain the bladder using a straight catheter.

10. Lidocaine pretreatment Cold Saline Fill Cystometry

1. The remaining fluid in the bladder will be drained completely via the bladder catheter (PVR recorded above).
2. Bladder and rectal catheters will still be in place from the Rapid fill cystometry. The cough test will be repeated to ensure equal pressure transmission.
3. Begin filling at a rate of 50 ml/min with cold (refrigerated) normal saline (4-8°C).
4. Query patient of bladder sensations as described above and record first sensation of filling, first desire to void, normal desire to void, strong desire to void, urgency, and pain.
5. Record any episode of DO, include bladder volume at start, change in P_{det}, presence of urgency, and leakage (incontinence).
6. Stop filling when the **Lidocaine** *strong desire to void (above)* is reached, or when the **Normal Room Temperature Rapid Fill** *strong desire to void* plus 50% *(first fill)* is reached, whichever

comes first, to avoid over-distending the bladder if there is significant impairment of sensation after lidocaine. Circle which one comes first. Between fills, aspirate back with syringe to confirm empty.

7. Void. If unable to void, drain the bladder using a straight catheter.
8. At the conclusion, assess *Perception of coldness in the bladder*:

These tests will be done in series as listed above. The total time for each testing session is estimated to be 3-4 hours.

3.3 Subject Evaluation

Subject fills out the Post test UDS written survey.

3.4 Data Collected

The primary data collected will be analyzed to assess the logistical and technical aspects of the study, including the times to complete each component of the study, and whether the clinician and study personnel are able to accurately record all study variables. The analysis will also examine whether clinically reasonable values are obtained for all measurements, whether from clinician or subject report or values downloaded from instruments. The data elements to be collected are listed in the "Measured Parameters" column in the table below.

	Tests	Measured Parameters
Questionnaires		LUTS Tool – 1 month version AUA-SI UDS survey
Uroflowmetry	**Uroflowmetry**	*Time to complete study (min)* Flow rate (ml/sec) Voided volume (ml) Maximum flow rate [Qmax] (ml/sec) Voiding duration (sec)Post void residual, ultrasound (ml)
Urethral Tests	**UPP (Urethral Pressure Profilometry)**	*Time to complete study (min)* *Participant tolerability* *Feasibility* Baseline data: • Abdominal pressure (P_{abd}) • Vesical pressure (P_{ves}) • Urethral pressure (P_{ur}) Calculated: • Detrusor pressure (P_{det}) • Urethral closure pressure (P_{uc})
		On trace of urethral pressure in cm H_2O proximal to distal (x 3) Identify location of peak pressure.

		Volitional (maximum urethral closure pressure during pelvic muscle contraction, at location of peak pressure) (cm H_2O) (x 3)
Bladder TestsBl	**Medium Fill Cystometrogram**	*Time to complete study (min)* *Participant tolerability* *Feasibility*
		First sensation of bladder filling (ml) First desire to void (ml) Cystometric capacity: strong desire to void(ml)
		Detrusor overactivity (# times), pressure in cm H_2O, volume in ml, does subject feel urgency at the time of DO (Y/N)
		Stop Test: Can stop (Y/N) Maximum P_{det} : pressure in cm H_2O at minimum void stream flow rate (trace over time; look for dip or drop to zero)
		Post-void residual (ml) (catheter drain)
		Sensations: pain, irritation, burning (Y/N)
	Rapid Fill Cystometrogram	*Time to complete study (min)* *Participant tolerability* *Feasibility*
		First sensation of bladder filling (ml) Strong desire to void (ml) Cystometric capacity: strong desire (ml)
		Detrusor overactivity (# times), pressure in cm H_2O, volume in ml, does subject feel urgency at the time of DO (Y/N)

		Sensations: pain, irritation, burning (Y/N)
	Cold Fill Cystometrogram	*Time to complete study (min)* *Participant tolerability* *Feasibility*
		First sensation of bladder filling (ml) Strong desire to void (ml) Cystometric capacity: strong desire (ml)
		Detrusor overactivity (# times), pressure in cm H_2O, volume in ml, does subject feel urgency at the time of DO (Y/N)
		Sensations: pain, irritation, burning (Y/N)
	Lidocaine Installation	*Time to complete study (min)* *Participant tolerability* *Feasibility*
		Lidocaine: Volume (ml), concentration (%) instilled, dwell time (minutes)

Other variables related to the technical aspects of the study (e.g., transition time between studies) will also be noted.