STU00217126
EH22-021

PROTOCOL TITLE:

Enhanced Clinical Decisions for Management of
Benign Prostatic Hyperplasia Using Patient-Reported Outcomes

PRINCIPAL INVESTIGATORS:

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VERSION DATE:

02/14/2025

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	N/A
IND / IDE / HDE #	N/A
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	Patients: N = up to 350 Providers: N = 20 Sexual and Gender Minority (SGM) supplemental study, Patients: N = approximately 100
Funding Source	National Institutes of Health
Indicate the type of consent to be obtained	☒ Written ☒ E-consent via REDCap ☒ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☒ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES

Aim 1: Integrate routine clinical tests with PRO assessment to enhance screening, diagnosis, and management of patients with Benign Prostatic Hyperplasia (BPH). PROs provide a cost-effective assessment strategy that can improve patient care by allowing for frequent surveillance and intervention. Men with BPH suffer from a variety of comorbid conditions (e.g., sleep disturbance, depression). We will use longitudinal modeling to identify risk factors and comorbidities that predict increased LUTS. Specifically, we will use PROs, developed by us in the LURN, to assess LUTS, including symptoms not captured by AUA-SI. We hypothesize that health variables from the PROMIS-29 Profile (e.g., sleep disturbance, depression, pain), when combined statistically with routine objective clinical variables (e.g., uroflowmetry, prostate size, intravesical prostatic protrusion) will provide unique predictive power for LUTS severity over time. Understanding these risk factors will facilitate preventative counseling and "just-in-time" interventions to improve in-clinic and telemedicine evaluations and treatment.

Aim 2: To examine psychometric properties of the LURN SIs, including clinically meaningful differences in men with BPH receiving known effective treatment. Longitudinal data will enable us to calculate effect sizes of the SI-10 and SI-29 from baseline to follow-up in the context of usual care, including guideline-driven treatment of BPH. LURN SIs will be anchored to patients' ratings of global change (PGI-I). A multiple-baseline design will allow estimation of test-retest reliability, while multiple longitudinal assessments provide quantitative estimates of minimally important differences (MIDs). We hypothesize that the SI-10 and SI-29 will have adequate test-retest reliability and precision to detect change across a range of severity in BPH in response to treatment.

Aim 3: To create care-coordination recommendations to facilitate the matching of evidence-based treatments to patients with persistent symptoms using PROs. PROs provide a patient-centered way to assess problems that may persist after treatment has been initiated. Many men discontinue medical treatment, and surgical treatments can lead to transient but distressing symptoms, including pain, urgency, and/or incontinence. These symptoms are not adequately captured by the AUA-SI. In addition, some patients may have persistent LUTS despite appropriate therapy that may be related to other health variables, as outlined in Aim 1.

We will use qualitative interviews with patients and providers to inform the creation of a care-coordination checklist that can be implemented in the medical record for patients with BPH. During the course of medical and/or surgical treatment for BPH, patients may have symptoms including pain, urgency, and/or incontinence. These symptoms are not adequately captured by the dominant questionnaire in the field – the American Urological Association Symptom Index (AUA-SI). In addition, some patients may have persistent LUTS despite appropriate therapy that may be related to other health variables. We plan to interview patients about their most important needs in between clinic visits to that we can develop better ways to follow these symptoms in between clinic visits using telehealth. We hypothesize that patient and stakeholder input will suggest care-coordination recommendations that will increase quality of care, in turn resulting in enhanced management (e.g., better recovery after surgery), improved quality of life, and decreased symptom bother for patients with BPH.

Sexual and Gender Minority (SGM) Sub-Study

Aim 1: Determine psychometric properties of LURN SIs in SGM patients with BPH. We hypothesize that the LURN SIs will demonstrate similarly large associations (Pearson $r \geq 0.5$) with criterial measures, as well as sensitivity to known effective treatments (with-subject Cohen's $d \geq 0.5$) in SGM patients with BPH.

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BACKGROUND:

LUTS attributable to BPH is one of the most common disease states, affecting approximately 30% of Medicare beneficiaries and costing over $4 billion annually. In 2013, there were over 6.3 million office visits related to BPH for Medicare beneficiaries alone, and this number is expected to increase with the aging population. As the most common condition contributing to non-neurogenic LUTS in men, BPH is also the focus of frequently updated medical and surgical management guidelines that directly influence provider decision-making and patient care. Therefore, LUTS secondary to BPH represents an actionable, high-impact disease state and ideal target to build upon our work as part of LURN, wherein we created three novel questionnaires for use in patients with LUTS.

For decades, the AUA-SI questionnaire has been the PRO used in men with BPH, as recommended in the "Surgical Management" guidelines updated as recently as 2021. The AUA-SI, however, has several drawbacks that leave room for improvement. First, the AUA-SI omits UI and pain, which in the LURN cohort, was present in 51% and 17% of treatment-seeking men, respectively, despite exclusion of men with infection or urinary pain as a primary complaint. A significant proportion of men present with pain, and pain can be an important differential diagnostic marker (e.g., between BPH and chronic prostatitis). Second, it yields a single score for overall LUTS, which is laudable for simplicity, but may be insufficient when different symptoms are differentially impacted by treatment or have different relationships with biomarkers, diagnostic subgroups, etc. Third, the methodology used to develop the AUA-SI was specific to BPH, which is advantageous once the patient has been properly diagnosed, but patients presenting to the urology clinic may be suffering from other diagnoses, including kidney stones, infection, chronic prostatitis, pelvic floor dysfunction, stricture disease, and more. Thus, a questionnaire for the urology clinic should be general purpose and created with broad populations in mind.

With an awareness of the need to create an updated outcome tool in urology, our group – as part of the LURN – contributed to the creation of new questionnaires in urology, using state-of-the-art methods for the development of PROs. Our methodology included a comprehensive literature review, expert input from LURN investigators, and qualitative interviews with primary care doctors, urologists, urogynecologists, nurses (in primary care and specialty clinics), and a diverse sample of people with LUTS recruited from community and clinical settings. What is needed now is research connecting these new LURN questionnaires to actionable phenomena in the clinic. Toward this end, we will incorporate PROs into the routine care of patients with LUTS secondary to BPH. Reports provided to the physician will combine PROs with routine clinical tests (e.g., urinalysis, prostate size). Integrated PROs will allow for routine symptom surveillance without the need for the patient to return to the clinic, enhancing telehealth-based approaches.

STUDY ENDPOINTS:

Aim 1: Longitudinal trajectories of LUTS in men treated for BPH. Serial symptom data will be collected over time using the LURN SI-29 (which includes the LURN SI-10 items) and the AUA-SI. Aim 1 will identify health variables from the PROMIS-29 Profile that predict trajectories of LUTS within the individual patient.

Aim 2: Test-retest reliability and minimally important differences in the LURN SI-29 subscales and the LURN SI-10. At the end of this study, we will have established the test-retest reliability of the LURN SI questionnaires and established minimally important differences in patients with BPH after known effective treatments.

Aim 3: A care-coordination checklist for monitoring of men treated for BPH. The goal of this project is to engage men with BPH and collect their open-ended input as to what symptoms, concerns, and challenges they face over the course of their treatment with BPH. In addition, 20 clinicians

will also be interviewed. The end product will be transcripts from up to 40 men with BPH and 20 clinicians, and an accompanying code book.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Not applicable

PROCEDURES INVOLVED:
Patients will be recruited from urology clinics at Endeavor Health, in which both Dr. Helfand and Dr. Glaser are practicing physicians, and Northwestern Memorial HealthCare (NMHC) NM Gay and Bisexual Men's Urology Program Clinic. Recruited patients with BPH will undergo standard of care treatment as determined by their urologist. In this study, the maximum sample size will be 350. We aim to recruit a sample size of at least 300 analyzable participants, so we set the maximum sample size to 350 to account for participants who enroll but do not provide usable data (e.g., participants who complete only a baseline assessment and provide no other data). To obtain a sample that is roughly representative of BPH patients, as well as to generalize to patients receiving different kinds of treatment, the sample will be stratified by whether they are to receive medical/non-surgical management (n = up to 225) or procedural/surgical management (n = up to125).

We created a battery of health measures to be specific to the management of BPH. The clinician will determine, on a case-by-case basis, the assessment schedule based on medical need, but sample schedules are presented in Tables 2.1 and 2.2 (medical management Table 2.1; surgical management Table 2.2). If a clinical follow-up visit is not required as part of standard of care as determined by the patient's personal physician (i.e., at Week 12 and Week 24 for medically managed patients), the follow-up visits can be completed remotely by phone, web, or app. Using PROs is already part of the management guidelines for BPH; the overarching hypothesis of this project is that a brief (i.e., clinically feasible) set of questions can aid in the management of BPH and can improve upon the existing method of the AUA-SI. We recognize that the proposed battery of measures is much longer than the one-page AUA-SI, but a longer battery of questionnaires is necessary for research purposes to clarify which measures would need to be dropped versus retained for use in the real-world clinic. In addition, scores from the one-page LURN SI-10 can be extracted from the longer 29-item questionnaire. Data analyses (see Section 1.4) will also include the LURN SI-10 score for maximum clinical relevance. Patients undergoing surgery will have more frequent queries in the immediate postoperative period (Table 2.2), as many men report bothersome symptoms of frequency, urgency, pain, and/or incontinence in this timeframe; thus, this period in particular is a target for better characterization and management of symptoms. We have had success with collecting data every 2 weeks as part of other research, supporting feasibility. Routinely collected objective clinical data, including urinalysis, prostate-specific antigen, uroflowmetry, post-void residual, prostate size, intravesical prostatic protrusion, and cystoscopic findings will also be collected and analyzed in combination with PROs.

For assessment of test-retest reliability, patients will receive the LURN SI-29 and AUA-SI questionnaires in two instances, 2 weeks apart. 60 patients will be needed for test-retest reliability; therefore, participants will be approached until 60 patients have completed 2 scorable questionnaires. Patients consented prior to their baseline clinic visit will complete the questionnaires 2 weeks (range 1-3 weeks) prior and then again at the visit, while patients who enroll at the baseline visit and have a scheduled diagnostic procedure at least 1 week but no longer than 3 weeks later (e.g., cystoscopy and/or prostate transrectal ultrasound), with no

treatments or interventions planned in the interim, will complete questionnaires at the baseline clinic visit and again 2 weeks (range 1-3 weeks) later. In this latter group of patients, we expect the lowest variation in symptoms over time due to minimal change in circumstances. In order to effectively assess test-retest reliability, we will target 2 weeks between questionnaire administration but will allow a 1-3-week time interval between questionnaires. The questionnaires will be delivered in Epic MyChart but could also be completed on paper or over the telephone; research coordinators will contact participants to remind them of these questionnaires in order to minimize missing data. Mode of administration will be recorded.

Table 2.1 Study questionnaires, medical/non-surgical intervention (Schedule of assessments: baseline, inter-visit follow-up, and clinic assessments)

	# Items	Week -2	Baseline (clinic)	Week 4	Week 8	Week 12 (clinic)	Week 16	Week 20	Week 24 (clinic)
LURN SI-29	28								
PROMIS-29 Profile	29								
AUA-SI	8								
Patient Global Impression of Improvement (PGI-I)	1								
National Cancer Institute Quick Food Scan	17								
3-Day Voiding Diary	9								
PROMIS-GI: Constipation	9								
PROMIS-GI: Diarrhea	6								
SHIM	5								
MSHQ-EjD	4								
STOP-BANG	8								
PRO Cognitive Function – Short Form 4a	4								
Patient Feedback Survey (optional)	6								

Note: Study time points (e.g., Week 4, Week 8) are approximate – Participants will be given a time window of ± 2 weeks. The minimum time between assessments will be approximately 4 weeks. Time windows may be adjusted based on COVID-19 protocols (e.g., if a clinic visit is converted to telehealth).

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Table 2.2 Study questionnaires, surgical/procedural intervention (Schedule of assessments: baseline, inter-visit follow-up, and clinic assessments)

	# Items	Baseline (clinic)	Preop **	Week 1	Week 2	Week 4 (clinic)	Week 6	Week 8	Week 12 (clinic)	Week 24 (clinic)
LURN SI-29	28									
PROMIS-29 Profile	29									
AUA-SI	8									
Patient Global Impression of Improvement (PGI-I)	1									
National Cancer Institute Quick Food Scan	17									
3-Day Voiding Diary	9									
PROMIS-GI: Constipation	9									
PROMIS-GI: Diarrhea	6									
SHIM	5									
MSHQ-EjD	4									
STOP-BANG	8									
PRO Cognitive Function – Short Form 4a	4									
Patient Feedback Survey (optional)	6									

Note: Study time points (e.g., Week 4, Week 8) are approximate – Participants will be given a time window of ± 2 weeks. The minimum time between assessments will be approximately 4 weeks. Time windows may be adjusted based on COVID-19 protocols (e.g., if a clinic visit is converted to telehealth). ** If surgery is not immediately scheduled, complete questionnaires every 4 weeks until surgery is scheduled.

To assess MIDs, we will administer the PGI-I as a measure of global change at each post-baseline time point. The PGI-I is a single-item questionnaire that asks respondents to rate their condition compared with prior to treatment on a 7-point scale from very much worse (1) to very much better (7). LURN SI-29 and SI-10 scores at 12 weeks post-baseline will be used to assess changes in scores since baseline.

In addition, participants will be offered the opportunity to complete a patient-response burden questionnaire (patient feedback survey) at the end of their study participation. This will provide a better understanding of how the participants perceived the PROs.

Uroflowmetry. Uroflowmetry is a test that measures the flow rate of urination while the patient is voiding. It also quantifies the voided volume. Uroflowmetry is usually captured during routine care with a urologist, but sometimes it is not deemed necessary or logistically challenging to obtain during routine clinical care (for example, the patient voids before being seen in clinic). In this study, if the patient does not receive a uroflowmetry test as part of routine care, we may include it as a research activity. In this case, the patient will receive instructions from the research coordinator on how to do the test. To ensure that the patient does not have an empty bladder for the test, the coordinator will ask the patient to drink some water from water bottles provided in the clinic space, while the study is being explained to them. If possible, the patient will be asked not to void until the uroflowmetry test. They will then do the test in a private restroom at the clinic. For uroflowmetry, the patient simply voids into a funnel which measures voided volume and urine flow rates. At the end of the test, a printed readout is produced, which will be stored in a locked filing cabinet. A bladder scan (handheld ultrasound) may then be performed to measure the post-void residual volume. The research coordinator will enter the necessary values from the printed report into REDCap. There are no risks associated with uroflowmetry, as it involves voiding of urine. The test takes less than 5 minutes to complete.
The data set from the LURN I study, funded by the NIDDK, will be used as a comparator dataset: it will be incorporated into the visualization graphs to offer a comparative baseline and will also be utilized to compare and contrast findings from our study data.

Crossover between treatment management arms: If a participant in the medical management arm decides to undergo surgery during their routine clinical care, they are allowed to switch to the surgical management arm. At that point, the participant's timeline is restarted based on the treatment type. Similarly, participants enrolled in the surgical management arm that do not complete surgery will be moved into the medical management arm if they are using medical treatment.

Minimizing missing data: Alternate data collection strategies. The primary mode of data collection will be patients completing surveys administered electronically via Epic MyChart. There may be some patients who are unable to complete their questionnaires electronically due to a low level of technological literacy or other information technology issues. In such cases, they will be offered the chance to complete the questionnaires via paper packets, which will be administered in the same order as the electronic questionnaires. We will use the 29-item version of the PROMIS Profile, version 2.1. If a patient in this study has difficulties with both electronic and paper questionnaires, a research coordinator will read the questionnaire to the participant, including response options, and record their responses for inclusion in the analyses.

Interviews. To maximize convenience for participants (patients and providers), interviews will be conducted via telephone or secure end-to-end encrypted virtual interview (e.g., Zoom) by a trained interviewer. Participants' email addresses and phone numbers will be shared with the interviewer. Providers will be recruited from across the United States through email invitations and consented verbally before the interview. These invitations will include detailed information about the study's purpose, procedures, and the voluntary nature of participation. A trained researcher will use a qualitative interview guide to ask questions regarding healthcare coordination gaps. Interviews will be audio-recorded and transcribed. Audio recordings of interviews will be transcribed using a HIPAA-compliant service, such as "TranscribeMe." These recordings will not contain any identifiable information, ensuring participant confidentiality. The recordings will be securely transferred to the transcription service through an encrypted platform.

Once the transcriptions are completed and securely returned, the transcription service will delete the audio recordings from their system. Transcriptions will be stored on a secure system (Box.com) accessible only to the research team, and all files will be reviewed to confirm the absence of any identifying details.

Interviews will be transcribed and imported into qualitative analysis software. The team will review a sample of five transcripts to create an initial codebook to capture themes mentioned by participants. Trained research assistants will then independently code one transcript, and then meet again to refine the initial codebook. Each transcript will be coded carefully by two trained team members applying codes. This process will be iterated throughout the analysis timeline to process new information and themes as they arise. Themes, concerns, and symptoms from the qualitative interviews will be used to determine prevalent topics for inclusion in a care-coordination checklist.

Each interview is expected to be less than 60 minutes. Participants will be interviewed at three time points: baseline, post-treatment, and follow-up. If we continue to observe new themes upon examining the qualitative data for 20 participants' interviews, then we will add interviews, two at a time until saturation is reached. We plan to interview no more than 40 patients.

For providers, each interview is expected to be less than 20 minutes. Providers will be interviewed once throughout the study period. We plan to interview up to 20 providers. Provider interviews will include topics such as care coordination for men with BPH and data visualization for symptom questionnaires. During these interviews, different data visualization formats will be shared with providers to solicit their feedback on the clarity, usability, and overall preference for each format. The aim is to identify which visualization methods best support clinical decision-making and enhance the interpretation of patient-reported symptom data in routine practice.

Sexual and gender minority (SGM) sub study:
In addition to the above, approximately n = 100 gay and bisexual patients with BPH seeking care at the Northwestern Medicine Gay and Bisexual Men's (NM-GBM) Urology Program clinic will be recruited in order to augment the representation of SGM patients. As the objective of this substudy is to evaluate the psychometric properties of the LURN SIs in an SGM population with BPH and ensure that the items reflect key concerns in this population, this sample will not receive the full battery of questionnaires listed above but will complete the simplified schedule noted in Table 2.3. These patients will be recruited through fliers distributed in-clinic that will include a link to verify eligibility and consent via REDCap. Immediately after consent, eligible participants will complete questionnaires via REDCap survey. If resources allow, questionnaires may be made available on paper. In addition, data will be extracted from the Northwestern Medicine Enterprise Data Warehouse (EDW) to obtain routinely collected objective clinical data, including urinalysis, prostate-specific antigen, uroflowmetry, post-void residual, prostate size, intravesical prostatic protrusion, cystoscopic findings, medication use and procedures received during the study period and linked to questionnaire responses using identifiers such as name, birthdate, and/or medical record number. If recruitment goals are unable to be met using this method, we will request an extract from the Northwestern EDW of patients seen at the NM-GBM in the last year that meet the study inclusion criteria for the purposes of remote recruitment. Email addresses will be obtained from the EDW for the purposes of recruitment, and eligibility and e-consent will be sent via REDCap. For eligible participants that e-consent, remote collection of the surveys listed in Table 2.3 will proceed as described above.

Table 2.3 Study questionnaires, SGM (Schedule of assessments: baseline, and post-treatment follow-up)			
	# Items	**Baseline (remote)**	**Week 12 (remote)**
Demographics / Medical & Family History	25	X	
Treatment Plan	4	X	
Treatment Received	4		X
LURN SI-29	28	X	X
AUA-SI	8	X	X
PGI-I	1		X
SHIM	5	X	X
MSHQ-EjD	4	X	X
Ejaculatory function importance survey	3	X	
Patient Feedback Survey (optional)	6		X

Statistical Analysis: See statistical analysis plan.

STUDY TIMELINES

For Aims 1 and 2, participant recruitment is expected to take 2 years, with each participant followed for 24 weeks. from the latter of baseline or treatment initiation. Participants that crossover into different arms will be followed for 24 weeks within their most recent arm.

The first phase of the study is expected to last 12 months.

PRIMARY STUDY: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria are:

1) Male sex
2) Age 50 years or older
3) Diagnosed by physician with BPH with planned medical or surgical treatment
4) Able and willing to complete questionnaires
5) Able and willing to provide informed consent
6) Ability to read, write, and speak in English
7) No plans to permanently move from study area in next 6 months

Note: Only English-speaking participants will be recruited at this time because the patient-reported outcome (PRO) system to be tested is currently only available in English.

Exclusion criteria are:

1) Female sex or intersex
2) Younger than 50 years of age
3) Being a prisoner or detainee
4) Gross hematuria
5) Interstitial cystitis

6) Pelvic or endoscopic genitourinary surgery within the preceding 6 months (not including diagnostic cystoscopy)
7) History of cystitis caused by tuberculosis, radiation therapy, or Cytoxan/cyclophosphamide therapy
8) Ongoing symptomatic urethral stricture
9) Current chemotherapy or other cancer therapy
10) History of lower urinary tract or pelvic malignancy
11) Severe neurological of psychiatric disorder that would prevent study participation (e.g., bipolar disorder, psychotic disorder, Alzheimer's Disease)
12) Current moderate or severe substance use disorder

Deferral criteria are:
1) Microscopic hematuria without appropriate workup per AUA/SUFU Guidelines
2) Positive urine culture

SGM STUDY: INCLUSION AND EXCLUSION CRITERIA

Eligibility Criteria	
Inclusion Criteria	**Exclusion Criteria**
Age 50 years or older	Younger than 50 years of age
Diagnosed by physician with BPH	Being a prisoner or detainee
Able and willing to complete questionnaires	Gross hematuria
Able and willing to provide informed consent	Interstitial cystitis
Ability to read, write, and speak in English	Pelvic or endoscopic genitourinary surgery within the preceding 6 months (not including diagnostic cystoscopy)
No plans to move from study area during the project period	History of cystitis caused by tuberculosis, radiation therapy, or Cytoxan/cyclophosphamide therapy
	Ongoing symptomatic urethral stricture
	Current chemotherapy, cancer therapy or pelvic malignancy
	Severe medical comorbidity that would preclude participation (e.g., Alzheimer's disease)

VULNERABLE POPULATIONS

This research does not involve vulnerable populations such as neonates (of certain or uncertain viability), pregnant women, prisoners, children, or cognitively impaired adults.

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PARTICIPANT POPULATION(S)
N/A

RECRUITMENT METHODS
Patients—men with Benign Prostatic Hyperplasia (BPH) aged 50 years and older—will be recruited from Endeavor Health urology clinics as well as Swedish Hospital. This group has had much success in recruiting large samples of patients for research on LUTS. Both new and returning patients undergoing medical or surgical treatment for BPH will be eligible. Eligible patients will be identified in two ways: (1) A research coordinator will screen the electronic health record (EHR) for upcoming and past clinic appointments to identify patients who may be eligible. The coordinator will contact these patients by phone to describe the study and obtain informed consent remotely, which will be documented in Research Electronic Data Capture System (REDCap). Alternatively, (2) eligible patients who present for a clinic visit (either in-person or telehealth) will be referred to the coordinator to present the study, obtain informed consent (again either in-person or remotely), and document the consent and participant details in REDCap. During these interactions, research staff will explain the contents of the consent form focusing on the purpose of the study, study procedures, study duration, participants' rights and responsibilities, potential risks/benefits to participants, and how their protected health information will be used. Participants will be given the opportunity to ask questions about the study and will be provided with as much time needed to review and reach a voluntary decision on study participation.

For the 24-week duration of the study, participants will be contacted for study purposes by the research team via email, telephone, postal mail, secure end-to-end encryption, and Epic MyChart. The preferred method of communication for participants will be recorded.
For the SGM sub study. participants will be recruited from the Northwestern Medicine Gay and Bisexual Men's Urology Program at NMHC. Potential participants will be preliminarily screened by the study team and given a flier with a link to complete screening and electronic consent via a REDCap survey. In person screening and consent may be added as resources become available. Follow-up surveys approximately 12 weeks later will be administered via REDCap surveys sent by email. We will also submit our inclusion criteria to the EDW to obtain a list of patients seen at the NW-GBM clinic in the prior year for potential remote recruitment. These participants will be contacted via email addresses obtained from the EDW for remote eligibility screening and e-consent via REDCap.

CONSENT PROCESS
Consent will follow the "Biomedical Consent Document (HRP-592)" and will always be obtained before a subject participates in any component of the current protocol. For all participants, consent will be obtained using the HRP-592 consent form. The consent form will contain a detailed description of all study procedures, as well as any possible risks and/or benefits. The participant's email will be verified before initiating any email communications upon their approval. Participants will be given an opportunity to ask any questions and contact the research team.

Participants can be identified by PI/Co-PI referral, self-referral, or via chart review. The PI/Co-PI or study coordinator can provide a printed copy of the consent form to the patient in clinic if the patient seems to be eligible for the study. Research team members will call participants to confirm study eligibility criteria. If the participant is eligible, the research team member will answer any questions and send the consent form to the participant via REDCap, secure email, postal mail, or fax. The participant will be able to take the time to reflect on the study, discuss the study with their loved ones, and ask any additional questions that arise before providing consent. After the participant reviews the consent form in its entirety, has no further questions, and is interested in participating in the study, the consenting process will be completed by the research team. Participants may provide consent on the same day they are introduced to the study.

Participants will have the opportunity to sign the consent form in person in the clinic or via e-consent on REDCap. Screening, enrollment, and baseline can be completed on the same day or different days. The research team member will provide a printed signed copy of the consent form for patient records. If the patient signs an e-consent via REDCap, they will be able to download a copy of the signed consent at their convenience. If necessary, a copy of the signed consent form can also be mailed to the participant's home address. In the event that a consent form addendum is created, the participants will be given the opportunity to sign the addendum in clinic or via REDCap e-consent.

Shortly after the participant is consented into the study, they will receive PROs for the baseline or pre-baseline visit. PROs will be collected in accordance to the study schedule set forth for surgical or medical management, or the SGM substudy.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

At Endeavor Health:
Participants will receive a sum of $60 in compensation for their time and effort by the completion of the study. They will be compensated after each completed study interaction as follows:

	Visit 1 (Baseline)	**Visit 4 (12 Weeks Post-Treatment)**	**Visit 7 (24 Weeks Post-Treatment)**	
Medical Management	$20	$20	$20	
	Visit 1 (Baseline)	**Visit 5 (4 Weeks Post-Procedure)**	**Visit 8 (12 Weeks Post-Procedure)**	**Visit 9 (24 Weeks Post-Procedure)**
Surgical Management	$15	$15	$15	$15

Participants will receive their payments in the form of gift cards at the end of each completed clinical visit. Participants who complete audio-recorded interviews will receive an additional $40 after each interview (at baseline, post-treatment, and follow-up) for a sum of $120 for three interviews. Providers will receive a compensation of $100.

At Northwestern Memorial HealthCare (NMHC) NM Gay and Bisexual Men's Urology Program Clinic:
Participants will receive a sum of $40 in compensation for their time and effort by the completion of the study. They will be compensated after each completed study interaction as follows:

	Visit 1 (Baseline)	Visit 4 (12 Weeks Post-Treatment)
Medical/Surgical Management	$20	$20

Participants will receive their payments in the form of gift cards at the end of each completed survey. -

WITHDRAWAL OF PARTICIPANTS
Participation in research is completely voluntary. Choosing not to be in this study or to stop being in this study will not result in any penalty or loss of benefit. Specifically, their choice not to be in this study will not negatively affect their right to any present or future medical treatment, or their present or future employment. Participants who wish to withdraw will be asked if the data collected from them can still be used for analyses; if so, the research team will retain their data, and if not, their data will be removed from the final data set used for analyses. At the time of withdrawal, study staff will thank participants for their participation, inform them that no further data will be collected, and no further contact will be made with them by research staff. The research team will update study records accordingly.

If the participant does not complete a scorable baseline LURN SI-29 questionnaire, the participant will be withdrawn from the study. Consented participants that do not complete the baseline assessments (see Tables 2.2 and 2.3) and withdraw prior to the first follow-up visit will not be counted towards recruitment targets.

RISKS TO PARTICIPANTS
Study-related risks are considered to be no greater than standard interview and questionnaire risks, including emotional distress when recalling stressful events. Our research team will make every effort to be supportive and can provide referrals to resources that may be helpful. There is a chance that a loss of confidentiality could occur, but all data will be de-identified and kept secure.

POTENTIAL BENEFITS TO PARTICIPANTS
The participants are not likely to have any direct benefit from being in this research study. However, possible benefits include: the opportunity to learn more about BPH, its treatment, and strategies for managing LUTS. In addition, the information collected in this study may help other men with BPH in the future.

DATA MANAGEMENT AND CONFIDENTIALITY
Data will be extracted from the EHR and de-identified. Study logistical data will be stored in REDCap, only accessible to authorized users. The PIs will train all staff on confidentiality and working with sensitive data.

Patient-facing study-specific activities include collection of patient-reported outcomes (PROs) and measurement of height, weight, and neck and waist circumferences that follow the schedule of assessments. The patients will undergo standard of care treatment as determined by their urologist – medical management or surgical management. Data routinely collected during clinical practice and part of EMR will be collected for this study.

The Endeavor Health, University of Chicago, and Northwestern REDCap database will be set up for this study and will be used for data collection. Northwestern University and University of Chicago will have access to this database for data review and data analysis throughout the study.

Clinical data and patient-reported outcomes (PROs) will be extracted from Epic via chart review, the Enterprise Data Warehouse (EDW) and Clinical Data Interoperability Services (e.g., REDCap-Epic integration). Data will be extracted via Epic chart review and patient-reported outcomes at baseline as well as at follow-up visits. These data include: date of tests/exams, date of birth, sex, gender, sexual orientation, race, ethnicity, education, marital status, family history of BPH or PCa, sexual activity, employment status, health insurance, prior BPH surgeries, BPH treatment plan, type and date of BPH surgery (surgical management), chief complaint as identified by the treating urologist, relevant current medications (i.e., alpha blockers, 5-ARIs, PDE5is, anticholinergics, B3 agonists, antidepressants, anxiolytics), comorbidities (i.e., DMI or DMII, depression, anxiety, hypertension, obstructive sleep apnea), substance use (i.e., caffeine, alcohol, tobacco), height, weight, neck and waist circumferences, laboratory tests (i.e., urinalysis, PSA, PHI, A1c, total cholesterol, HDL, LDL), urodynamics (i.e., uroflowmetry, UroCuff, PVR), prostate size, and intravesical prostatic protrusion.

CONFIDENTIALITY PROCEDURES

Original signed consent forms (completed via REDCap or on paper) will be kept separately from research data. They will be stored in REDCap or in subject files.

The Subject Identification Log that shall link the data collected during the study to source documents will be kept in a secure location with restricted access. Original copies of any paper documents generated during this study will be stored in locked file cabinets. Only study staff will have access to study materials and data. Collaboration Portal is secured by Endeavor Health HIT. Passwords must be used to access information, project specific access and access to designated Endeavor Health research users only.

All information collected during the course of this study will be kept confidential, except that sponsor's representatives, local IRB and FDA will have access to this information.

The sponsor's representatives and/or FDA will have access to relevant medical charts or hospital files for purposes of source data verification. A HIPAA waiver shall be obtained as part of the Informed Consent Form from the IRB giving access to the source data for this purpose.
No information which could identify a subject will be used in reports or publications.

Each participant will be assigned a unique study identification number. The link between participants' names, contact information, and study ID will be held in a separate, password protected electronic file that will be destroyed when the study has concluded.

For BPH patient participants, HIPAA authorization will be obtained during the consent process so

that we may collect relevant data about protected health information, such as their surgical history.

Qualitative interviews will be audio-recorded for transcription and subsequent analysis. Participants must consent to this recording prior to taking part in their interviews. Recordings will be stored securely until the end of the study, at which point they will be deleted.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Definition of an Adverse Event. An adverse event (AE) is any untoward medical occurrence or unfavorable and unintended sign in a research participant that occurs during or as a result of a research procedure. For this study, the list of study procedures has been reviewed, and specific procedures have been identified that are not standard of care and these will be considered research procedures. Since this study is primarily an observational study, and research procedures present minimal risk (survey response, EMR extraction), we anticipate few AEs. Complications that are a result of research procedures will be reported and tracked as AEs.

Assessment of Event Severity and Relationship to Treatment. The modified World Health Organization (WHO) grading system will be used for grading severity of AEs (Appendix AE). For AEs not covered by the modified WHO grading system, the following definitions will be used:

Mild:	awareness of sign, symptom, or event, but easily tolerated
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention
Severe:	incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention
Life-Threatening:	immediate risk of death

The investigator must also assess the relationship of any AE to the research procedure, based on available information, using the following guidelines:

Unlikely Related:	no temporal association, or the cause of the event has been identified; or the procedure cannot be implicated
Possibly Related:	temporal association, but other etiologies are likely to be the cause; however, involvement of the procedure cannot be excluded
Probably Related:	temporal association; other etiologies are possible, but unlikely

Definition of Serious Adverse Events. The term “serious adverse event” (SAE) is based on participant outcomes associated with events that could threaten a participant’s life or functioning. An event should be considered serious if it results in any of the following:

- Death
- Life-threatening AE (i.e., one that places the participant, in the view of the investigator, at immediate risk of death from the AE as it occurs)
- Persistent or significant disability/incapacity
- Required in-participant hospitalization, or prolonged hospitalization
- Congenital anomaly or birth defect

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, if based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The phrase “related to study” implies causality or attribution to the study procedures. For purposes of defining an SAE, if a causal relationship cannot be ruled out, then an AE should be considered ‘related to the study procedure(s)’. As noted above, it is very unlikely that any AEs will be attributable to this study.

Reporting Responsibility. All AEs must be recorded. The onset and end dates, severity and relationship to study procedure(s) will be recorded for each AE. Any action or outcome (e.g., hospitalization, additional therapy, etc.) will be recorded for each AE. Participants will be questioned and/or examined by the investigator or his/her designee for evidence of AEs.

All events that are serious and related (possibly or probably) must be reported to the IRB within 24 hours of the investigator being informed of the event. Required documentation related to the SAE must be submitted to the IRB no later than 10 working days of the date the investigator was first informed. Adverse events that are unexpected and related (or possibly related) to participation in the research, but are not serious, must be reported within 30 working days of the date the investigator first became aware of the event. All other adverse events (e.g., expected adverse events) will be reported to the IRB at the time of continuing review, and made available to the Safety Monitor for the quarterly meetings.

Data and Safety Monitoring Plan

The current project is an observational study involving human subjects. As such, we have identified a Safety Monitor who is not part of the study team.

Safety Monitor. Dr. Lisa Henn, PhD, will serve as the safety monitor. Dr. Henn is a biostatistician with extensive experience in observational clinical research, most recently in her role as a co-investigator at the data coordinating center for the Childhood Liver Disease Research Network (ChiLDReN). Dr. Henn also has expertise in survey instrument development and validation as well as structural modeling, which are relevant to this project. The Safety Monitor will receive an honorarium for her time.

DSMB Logistics. *Pre-study preparation.* Prior to study initiation, the Safety Monitor will independently prepare a safety and monitoring plan that requests data elements about the progress of the study (e.g., how many people screened, enrolled, withdrawn, completed). The study team led by the three Principal Investigators (PIs) will also prepare a written protocol for the study team’s procedures for handling clinical issues (e.g., contacting participants with elevated PROMIS Depression T Scores [i.e., T ≥ 70]). The study will not begin until the Safety Monitor is satisfied with the study team’s monitoring plan, and the study has received sIRB approval.

Meetings. Meetings will occur twice a year between the study team and the Safety Monitor via teleconference. Prior to each meeting, the Safety Monitor will review any adverse events associated with the study procedures, and any other relevant study data. After the Study Monitor has finalized their recommendations (in writing), the meeting will occur in order for the study team to receive the Safety Monitor’s recommendations and discuss any actions that need to be implemented. All reports and correspondence with the Safety Monitor will be reviewed by the study team and archived by the project manager.

Study Team's Responsibilities. The multiple PIs will have the responsibility for continuous monitoring of the data and safety of participants in the study. The PIs also will discuss together any specific issues that arise in the course of the study regarding the data as well as the safety of participants. These will be furnished to the Safety Monitor as well as the IRB as needed. Any possible safety and/or ethical issues will be discussed at regular team meetings and the IRB will be consulted as necessary.

In accordance with IRB requirements, we will report both adverse events and all serious adverse events that occur during the course of the study to both the independent Safety Monitor and the Northwestern IRB. We will also follow the Northwestern IRB policies for expedited reporting of Adverse Events and Serious Adverse Events for Serious Adverse Events. We will comply with the required procedures by notifying the IRB by phone within 24 hours of becoming aware of the event and submitting the required documentation no later than 10 working days of the date the investigator first became aware of the event. Adverse events that are unexpected and related (or possibly related) to participation in the research, but are not serious, must be reported within 30 working days of the date the investigator first became aware of the event. All other adverse events (e.g., expected adverse events) will be reported to the IRB at the time of continuing review, and made available to the Safety Monitor for the quarterly meetings. Additionally, at the time of the annual continuing review, we will provide the Northwestern IRB with a summary of any unexpected and related adverse events as well as any other unanticipated problems that occurred since the last continuing review.

The study team will work with the Safety Monitor to provide relevant data needed for their independent oversight.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

To protect privacy, all information collected about the participant as part of this study will be stored without identifying information using unique identifiers. Data are transferred using secure, password protected electronic files which are stored on a password protected server which has electronic and data firewall safeguards in place to protect data being sent over an electronic interface. Hard copies of paper files are stored in a secure, locked file cabinet that is only accessible to study related personnel. Files containing identifying information obtained for purposes of tracking participants and monitoring of subject payments are kept in a locked file cabinet in a locked office separate from study-related data. Data will only be linked to identifying information through a study ID. Under no circumstances will individually identifiable data be released to anyone without the written consent of the subject. Results will be reported as group findings only. In the past we have found that all these procedures are effective at reducing risk for study participants.

COMPENSATION FOR RESEARCH-RELATED INJURY

N/A

ECONOMIC BURDEN TO PARTICIPANTS

As this is an observational study, all clinical activities are part of usual care and no additional costs will be incurred by participants. PRO monitoring will occur remotely and will not incur travel costs. Because interviews can be completed by phone, there is no cost of travel, parking, etc. The main cost to participants is their time, for which they will be compensated.

NON-ENGLISH-SPEAKING PARTICIPANTS

STU00217126
EH22-021

N/A

WAIVER OR ALTERATION OF CONSENT PROCESS
N/A

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
This study will involve the collection and use of Protected Personal Health Information (PHI), such as names, contact information, medical record number, and information included in the medical record, such as diagnosis and treatment information and test results. All information collected from participants in this study will be obtained exclusively for research purposes and accessed only by authorized study staff, in full compliance with IRB regulations. In addition, all sources of information will be coded using a participant number identifier ("participant ID"), which will preclude their being matched with identifying personal details.

As part of the informed consent process, every participant will be asked to provide HIPAA authorization. Participants' HIPAA authorization will attest to their understanding that the information they provide will be held as personal and confidential to the extent permitted by law. Access to study-related computer files will be permitted only by use of secure passwords. The list ("key") matching participant IDs to identifying information will be kept locked and secured.

In order to schedule and conduct qualitative interviews, Endeavor Health will share the participant's name, phone number, and email address via secure email with the University of Chicago research team. Participants' names, phone numbers, and email addresses will be stored in a separate REDCap.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE
Our team includes licensed physicians (Dr. Helfand, Dr. Glaser) and psychologists (Dr. Griffith), all with expertise in clinical care and research for people with urinary symptoms. Thus, we are exceptionally well qualified for this work. We have ample infrastructure (e.g., private rooms, telephones, computers) to conduct telephone interviews, as well as infrastructure to safeguard all data and carry out analyses. Dr. Smith is qualified to help lead this project as a multiple principal investigator (MPI) along with Dr. Griffith and Dr. Glaser. She is an experienced biostatistician who has worked on many observational studies, including the Lower Urinary Tract Dysfunction Research Network (LURN). The three principal investigators have been working together for years and bring complementary skill sets to the project.

MULTI-SITE OR COLLABORATIVE RESEARCH:
There are four sites: 1) Northwestern University, 2) NMHC, 3) Endeavor Health, and 4) University of Chicago (Prime awardee). We will use a Single IRB mechanism with Northwestern as the IRB-of-Record. The role of Endeavor Health is patient recruitment as well as data interpretation and study write-up.

The reliance pathway for this project involves Northwestern University IRB serving as the Reviewing Institution's IRB, agreeing to provide initial and continuing review. The University of

Chicago and Endeavor Health are the Relying Institutions. The Relying Institutions will ensure research activities comply with all IRB's determinations and monitor compliance with human research protection regulations and other relevant requirements.

We will fully comply with IRB guidelines:

No activities will occur at external sites until local IRB review is pursued or reliance agreements are fully executed. Any external site sign-offs or permissions will be acquired by external study teams in accordance with their local policies. IRB approval letters from external sites, documentation that IRB review at external sites is unnecessary, or fully executed reliance agreements will be provided when available with accompanying protocol updates. Non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.