Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

Qualitative Assessment of Lower Urinary Tract Dysfunction Study Prospective Observational Cohort Study Protocol

Project 1A

Manual of Operations

Version 4.0

Based on Protocol Version 7.0

Current Version: December 18, 2015

LURN Phenotyping Study Manual of Operations Table of Contents

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1. GENERAL

1.1. Overview

The study Manual of Operations (MOO) is supplied to each participating site to aid in the conduct of the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) Phenotyping Study Protocol. The role of the MOO is to facilitate consistency in protocol implementation and data collection across participants and study sites.

A MOO is a handbook that details a study's conduct and operations. It transforms the study protocol into a guideline that describes a study's organization, operational data definitions, recruitment, screening, enrollment, interviewing, follow-up procedures, and data collection methods.

The MOO is a dynamic document that will be updated throughout the conduct of the study to reflect any protocol or consent amendments as well as the refinement of any forms, surveys, or study procedures. Each page of the MOO will contain the version number and date. As pages are revised, an updated version number and associated date will replace the original page(s) in the MOO. All previous versions should be archived.

The MOO will include all of the relevant sections that apply to the specific study.

Please refer to **Appendix A** to view the LURN Phenotyping Protocol. This portion of the MOO outlines details regarding Project 1A: Prospective Observational Cohort Study that are not in the protocol. The current version of the MOO and protocol documents are available on a website maintained by the Data Coordinating Center (DCC) at https://nih-lurn.org/.

1.2. Sponsor

The LURN project is a cooperative research network sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health (NIH). Ziya Kirkali, MD, is the NIDDK Project Officer.

1.3. LURN Specific Terms and Definitions

1.3.1. LURN-Specific Terms

1. **LUTD (Lower Urinary Tract Dysfunction)** – Any disturbance or abnormality in the structure and/or function of the lower urinary tract. The International Incontinence Society (ICS) indicates that a dysfunction is accompanied by an observed sign. It encompasses all urinary symptoms, including storage, voiding, incontinence, and post-micturition symptoms. Symptoms of LUTD are highly prevalent and occur in both sexes to a similar extent, with 51% of men and 59% of women exhibiting storage symptoms; 26% of men and 20% of women exhibiting voiding symptoms; and 17% of men and 14% of women exhibiting post-micturition symptoms.
2. **LUTS (Lower Urinary Tract Symptoms)** – Subjective reports of an experience that may lead person to seek care from health care professionals. Lower urinary tract symptoms can also indicate pathologies other than lower urinary tract dysfunction.
3. **Non-Urologic Patient Factors** – Related to LUTS, these factors may:
    - Impact the evaluation, diagnosis, and/or treatment of patients with LUTS.
    - Be the primary or contributing and underlying cause of LUTS in some patients.

- Mediate the relationship between LUTS and bother or functional impact of LUTS.

4. **Phenotyping** – Characterizing by observable traits and/or defining physiology.
5. **Overactive Bladder (OAB) Subjects** – *ALL of the following criteria have to be fulfilled to be eligible:*
    a. 18 years of age or older.
    b. Able to speak, read, and understand English.
    c. Enrollment in the LURN Observational Cohort Study.
    d. Symptoms of urinary urgency, with or without urgency incontinence, usually with frequency and nocturia, consistent with the 2002 ICS definition of overactive bladder (OAB).
    e. Answered "sometimes", "often", or "always" 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?"). Subjects who answered "never" or "rarely" are not eligible since they are not deemed to have significant urgency symptom, which is the hallmark symptom of OAB. Subjects will be assigned into two subgroups using the following:
6. **OAB with Urgency Incontinence** – Answered "sometimes", "often", or "always" 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?")
7. **OAB without Urgency Incontinence** – 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?").

The approach outlined above allows us to operationalize the two OAB groups based on their self-reported urgency incontinence symptoms. Inclusion of patients who are "rarely" incontinent in the "OAB with urgency incontinence" group is supported by the literature. In population-based studies that used the LUTS Tool to investigate the prevalence of LUTS (e.g., the EpiLUTS study), participants had to report at least "sometimes" on the LUTS Tool to be considered to have the symptom(s).

8. **Urge** – The healthy spectrum of a desire to void (i.e., sensation to void).
9. **Urgency** – A sudden, compelling desire to pass urine, which is difficult to defer.

1.3.2. LURN Acronyms

AUA – American Urologic Association; a society that created the AUA symptom score questionnaire, which is a patient-reported measure of symptoms.

BEP – Benign Enlargement of the Prostate; more commonly called BPH.

BPH – Benign Prostatic Hyperplasia; an increase of the number of prostatic stromal and epithelial cells. Because the prostate surrounds the urethra, when the prostate grows larger, it can restrict the flow of urine. BPH may also be called BEP.

BTX – Botox; used as a treatment for OAB in patients with neurologic problems (like multiple sclerosis or spinal injury).

DO – Detrusor Overactivity; unexpected contraction of the bladder muscle during bladder-filling, one of the most common causes of OAB and associated with urge incontinence.

MDO – Myogenic Detrusor Overactivity; unexpected contraction of the bladder muscle, originating in the muscle cells, during bladder-filling.

MS – Multiple Sclerosis; a common cause of NDO.

NDO – Neurogenic Detrusor Overactivity; unexpected contraction of the bladder muscle, originating in the nerves involved in bladder activity during bladder-filling.

OAB – Overactive Bladder; characterized by urgency, but patients with OAB often also have frequency or urge incontinence (unintentional leakage of urine, combined with an urge to continue urination).

PSA – Prostate Specific Antigen; an antigen that can be measured using a blood draw. High values can indicate prostate cancer, BPH, or prostatitis.

PT – Physical Therapy; may be used to strengthen pelvic floor muscles for patients with incontinence.

PVR – Post Void Residual; the amount of urine left in the bladder after urination. A high PVR indicates urinary retention, which may be common in BPH, among patients on certain medications, and with nerve dysfunction. Chronically high PVR can increase the chance of developing UTIs.

SCI – Spinal Cord Injury; a common cause of NDO.

SNM – Sacral Neuromodulation; surgical implantation of an electrical stimulator that connects to the sacral nerve. Used as a treatment for a variety of diagnoses. Also known as Sacral Nerve Stimulation, InterStim (the device). Related to TENS.

SUI – Stress Urinary Incontinence; urine leakage during physical activity or during straining of abdomen (coughing, laughing, exercising).

TENS – Transcutaneous Electrical Nerve Stimulation; an electrical stimulator placed on the skin, a precursor to SNM.

TRUS – Trans-Rectal Ultrasound; used to perform prostate biopsies to distinguish between prostate cancer, BPH, or prostatitis in men who have high PSA values.

TUIP – Transurethral incision of the prostate; one or two small cuts in the prostate gland – can improve urine flow and correct other problems related to an enlarged prostate. http://en.wikipedia.org/wiki/Transurethral_incision_of_the_prostate

TURP – Transurethral Resection of Prostate; a surgical treatment for men with BPH or slow stream. http://en.wikipedia.org/wiki/TURP

UDS – Urodynamic Studies; procedures performed to measure the force of urine flow, post-void residual, detrusor overactivity, and leak point pressures. Also known as urodynamic testing, the patient experience during the procedure is detailed here: http://urology-partners.com/Forms/Urodynamic_Testing.pdf

UTI – Urinary Tract Infection

1.4. Study Organization and Responsibilities

LURN is comprised of six US clinical sites and a DCC. The Steering Committee is the governing body, consisting of the NIDDK Project Officer and the Principal Investigators (PIs) from each of the clinical sites and the DCC.

LURN was established by the NIDDK to advance our understanding of LUTD[1] in women and men. LUTD is a term intended to be comprehensive and to challenge current paradigms about how symptomatic pelvic disorders are defined as 'diseases.' LUTS[2] are likely caused and exacerbated by a variety of factors and thus do not represent the manifestation of a single disease. Clinical management of LUTD, including treatment outcomes, remains suboptimal since the biological and psychosocial factors that initiate, exacerbate, and modify this group of symptoms remain largely unknown. As an initial effort to better characterize the biological and psychosocial factors that initiate, exacerbate, and modify LUTS, the LURN investigators will establish a prospective observational cohort study of men and women with LUTS presenting for the first time to LURN physicians.

This LURN protocol falls under the category of an observational study defined as a biomedical or behavioral research study of human subjects.

The NIH further defines an observational study as one which is "designed to assess risk factors for disease development or progression, assess natural history of risk factors or disease, identify variations based on geographic or personal characteristics (such as race/ethnicity or sex), track temporal trends, or describe patterns of clinical care and treatment in absence of specific study-mandated interventions."

Over the course of several years, LURN will conduct clinical studies to "phenotype" LUTS. In the biological sciences, phenotype typically refers to the observable characteristics of a person—physical, behavioral, biochemical—as determined by genetic and environmental influences. The "phenotyping" effort in LURN seeks a description of the observable characteristics of the patient with LUTS and an explanation for why those characteristics are observed in some people and not others.

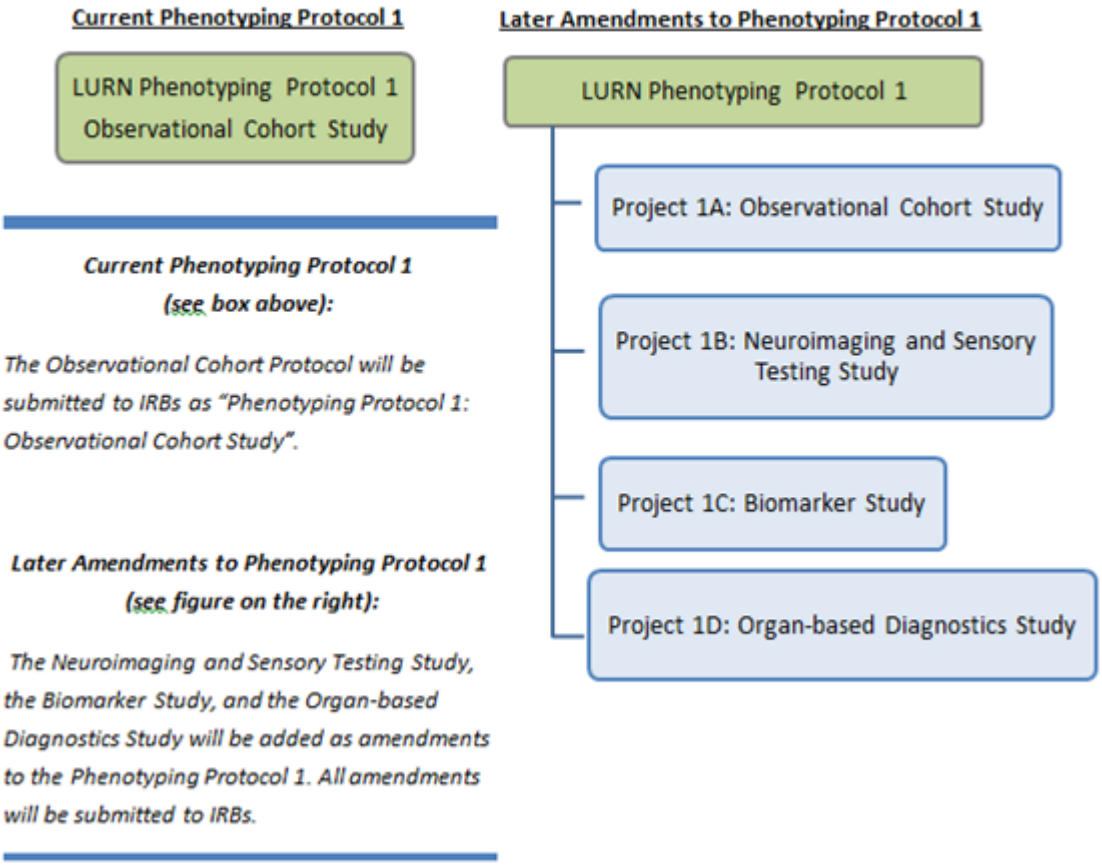
LURN is pursuing phenotyping research using distinct, but related, projects. The Phenotyping Protocol is the overarching effort and will be divided into four projects. Project 1a will be a large-scale accrual of LUTS patients into a registry. Standardized clinical data, comprised of information typically gathered at a new patient clinic encounter, will populate the registry. Using these data, subgroups of patients will be identified for further, more focused and in-depth studies of the different levels of factors affecting LUTS. Smaller projects will be developed to address hypothesis-driven research, and patient recruitment will be from groups who demonstrate a particular phenotypic profile based on the clinical data.

Examples of these are Project 1b: Neuroimaging and Sensory Testing; Project 1c: Biomarker Discovery; and Project 1d: Genitourinary Organ Physiology.

[1] Lower urinary tract dysfunction is any disturbance or abnormality of function of the lower urinary tract. The ICS indicates that a dysfunction is accompanied by an observed sign.

[2] Lower urinary tract symptoms are defined by the International Continence Society as subjective reports of an experience that may lead person to seek care from health care professionals. Lower urinary tract symptoms can also indicate pathologies other than lower urinary tract dysfunction. Abrams: Neurology and Urodynamics 21:167 (2002). See Appendix K

Figure 1: LURN Phenotyping Protocol 1 Structure & Amendments



Please reference the Study Directory on the study website (https://nih-lurn.org/) for participating sites' contact information.

1.4.1. DCC

Arbor Research Collaborative for Health is the DCC for LURN. The DCC provides project management, logistical coordination, and statistical leadership for the development, implementation, and analysis of the LURN studies. In addition, the DCC will conduct training in protocol implementation, data management, monitoring, quality control, and development and maintenance of the MOO. The DCC also supports regulatory and technical functions (i.e., LURN data entry website). For a complete list of DCC personnel, their roles, and contact information, please refer to the Study Directory on the study website (https://nih-lurn.org/).

1.4.1.1. DCC Contact Information

- Robert M. Merion, MD, FACS, Principal Investigator – bob.merion@arborresearch.org
  Phone: 734-665-4108

- Peg Hill-Callahan, Clinical Process Manager – peg.hill-callahan@arborresearch.org
  Phone: 734-369-9674
- Timothy Buck, Clinical Monitor – timothy.buck@arborresearch.org
  Phone: 734-369-9958
- Melissa Fava, Project Manager – melissa.fava@arborresearch.org
  Phone: 734-369-9770
- All DCC – LURN-DCC@arborresearch.org
- Monitoring Staff – LURN-Monitors@arborresearch.org
- Fax – 734-665-2103

The DCC recommends that study personnel use the DCC group emails to ensure timely responses.

1.4.2. Clinical Sites and Principal Investigators

Duke University
Durham, NC
Co-Principal Investigators: Cindy L. Amundsen, MD; Kevin P. Weinfurt, PhD (Steering Committee Co-Chair)

University of Washington
Seattle, WA
Principal Investigator: Claire Yang, MD (Steering Committee Co-Chair)

Northwestern University
Chicago, IL
Co-Principal Investigator: David Cella, PhD

NorthShore University Health System (Northwestern Sub-site)
Glenview, IL
Co-Principal Investigator Brian T. Helfand, MD, PhD

University of Michigan
Ann Arbor, MI
Principal Investigator: Quentin Clemens, MD

Washington University
St. Louis, MO
Co-Principal Investigators: Gerald Andriole, MD; Henry Lai, MD

University of Iowa
Iowa City, IA
Co-Principal Investigators: Catherine S. Bradley, MD, MSCE; Karl J. Kreder, MD, MBA

The following site-identifying numbers are used in conjunction with biosample shipment.

Site	NIDDK Site Code
Duke University, Durham, NC	B01
Washington University, St. Louis, MO	B02
Northwestern University, Chicago, IL	B03
NorthShore (sub-site) of NWU, Glenview, IL	B04
University of Michigan, Ann Arbor, MI	B05
University of Washington, Seattle, WA	B06
University of Iowa, Iowa City, IA	B07

1.4.2.1. Roles and Responsibilities of Investigators and Study Sites

The roles and responsibilities of the investigators and study sites will include:

- Maintenance of a study binder;
- Participation in protocol finalization and preparation of study materials;
- Compliance with protocol, MOO, Institutional Review Board (IRB)/Ethics Research Committee (ERC), and federal and state regulations;
- Membership in a Steering Committee and other committees;
- Recruitment, screening, and enrollment of participants;
- Protections of participants' rights;
- Data collection and participant follow-up through study completion;
- Transfer of data to the DCC and resolution of queries;
- Retention of study specific records;
- Communication of questions, concerns, and/or observations to the DCC;
- Training and assignment of study staff to designated roles and responsibilities. This is recorded on the Site Delegation Log. (See **Appendix E.**)

1.4.3. External Expert Panel (EEP)

The EEP has been established by the NIDDK. The EEP is currently composed of clinical urologists, researchers, epidemiologists, psychometricians, government agency representatives, and biostatisticians. The EEP will provide scientific oversight and advice for the duration of the Network. The Panel reports to the NIDDK. The EEP will meet in person at least

once per year to provide a review of all study protocols prior to implementation for their likelihood to achieve the overall goals established by the NIDDK. Telephone conference calls of the EEP will be scheduled on an as-needed basis. The EEP will evaluate the study progress, review ancillary study proposals (if applicable) prior to implementation, and monitor the safety of study participants. Reference the EEP Responsibilities and Operating Procedures and the EEP Membership List (**Appendix B**) for additional information regarding the EEP.

1.4.4. LURN Website

Publicly-accessible information about the LURN project is available on the LURN website home page. Some portions of the website are password-controlled to limit access to study group members (Clinical Centers, DCC, NIDDK, and the EEP), protect the integrity, security, and confidentiality of sensitive project information and the information system, and allow auditing of appropriate use.

The website contains workgroup/subcommittee member lists, meeting agendas, materials, and minutes, slides and presentations, master documents (including final protocols and consent templates), a calendar of events, and a study directory.

1.4.4.1. Website URL and Access Instructions

The URL for the LURN website is https://nih-lurn.org/. Website management resides with the DCC. The DCC is responsible for login accounts, study directory updates, postings, and maintenance. Upon assigning a username and password, an automatic welcome email will be generated, informing the user that access has been granted to the restricted areas of the website. Users must change their system-assigned password within 72 hours of the welcome email receipt, or website access will be denied.

Usernames and passwords should not be shared. New personnel requiring access to the LURN website should request a unique username and password. For new account requests or trouble with usernames and passwords, please contact the DCC: LURN-DCC@arborresearch.org

2. IRB/ERC SUBMISSION AND REGULATORY DOCUMENTS

Essential documents are those documents that individually and collectively permit evaluation of the conduct of a study and quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and the monitor with standards of Good Clinical Practice (GCP) and with all applicable regulatory standards. Following is the minimum list of essential documents that has been developed.

2.1. Protocol Version Control, Finalization, and Approval Process

Protocol version control is extremely important to ensure that all participating sites and their respective IRBs receive identical documents. Before a protocol is considered final and versioned (e.g., Version 1.0), it must go through a formal review by the LURN Steering Committee. The protocol is then reviewed by the EEP and the NIDDK. Once finalized, the protocol document, consent templates, and any supplemental materials will be distributed to the sites by the DCC. Sites should submit only materials distributed by the DCC to their IRBs. Finalized protocols must NOT be edited, changed, or altered.

All amendments (written descriptions of any changes to or formal clarification of a protocol) must undergo a similar approval process. Sites should only submit protocols and amendments to IRBs as instructed by the DCC or NIDDK.

2.2. Consent Form Finalization and Approval Process

A protocol-specific consent document template will be provided to all LURN sites. Site-specific language should be inserted into the templates. Please refer to **Appendix C** to view the Consent Template.

Each site-specific informed consent (IC) form will be reviewed by the DCC for inclusion of all essential elements and compliance with federal regulations and NIDDK Repository language. The DCC and the NIDDK Repository staff will review the site's consents and return the reviewed/edited draft consents to the sites for correction and submission to the IRBs. Below is a set of instructions detailing the DCC and NIDDK Repository review/approval process of the site-specific consent form(s).

The first four steps below must be completed prior to submitting any consent documents to the IRB/ERC.

1) Forward the IC documents to the DCC for review (LURN-Monitors@arborresearch.org).
2) Once IC documents have been reviewed and changes made, the DCC will forward the draft IC documents to the NIDDK Repository reviewer for review of the particular NIDDK Repository language.
3) The NIDDK Repository reviewer will send comments to the DCC as to whether the consents have NIDDK approval or need changes made in the consent documents.
4) The DCC will send the reviewed consents back to the site for revision, with DCC and NIDDK changes noted. If revisions are extensive, the DCC will instruct the site to send the revised consent back to the DCC for re-review.
5) After final approval, the site will submit its site-specific consents, along with the other materials, to the IRB/ERC for review.
6) The IRB/ERC may require changes to the consent form(s). Please forward requested changes to the DCC for review prior to resubmission to the IRB/ERC.
7) The IRB/ERC approval will be in the form of a letter or memo. The notification should include the title of the protocol, version number, PI name, and the IRB/ERC members. The memo should state that approval has been granted to open or continue the study.
8) The site will send a copy of the IRB/ERC approval and copies of the IRB/ERC-approved consents to the DCC.
9) The DCC will then forward the site IRB/ERC approval and copies of the approved consents to the NIDDK Repository reviewer, who will generate an approval letter addressed to the PI of the site.
10) The NIDDK Repository reviewer will send the NIDDK approval letter to the site PI and a copy to the DCC.
11) The site will file the NIDDK approval letter in its regulatory file.

File the IRB/ERC-approved consent documents (memo, consent, and other documents) in the site Regulatory Binder. Scan all IRB/ERC-approved documents and send electronically to the DCC. Throughout the course of the study, the DCC will request these documents when there is an amendment to the LURN Protocol 1, and at the time of each site's IRB/ERC annual renewal.

The DCC will send its annual IRB/ERC Continuing Renewal approval to the NIDDK Repository reviewer until the study is closed. The NIDDK Repository does not require receipt of copies of the site's annual IRB/ERC Continuing Renewal approvals.

2.3. Essential Documents for the Conduct of an Observational Study

Required regulatory documents are to be kept on-file at the site. Please refer to Appendix D for a list of Regulatory Binder tabs.

If the site maintains master files for Curriculum Vitae (CVs), regulatory documents, etc., a note to file should be placed in the study-specific Regulatory Binder to reflect the location of the documents.

Remember, when the study is finished and ready for archiving, all documents in the master files must be copied to be study-specific. During the conduct of the study, the documents will be stored for the length of time designated by the sponsor (NIDDK).

The following documents must be maintained in the Regulatory Binder throughout the study (see **Appendix D**):

1) **Study Protocol**

- Maintain a copy of the original IRB/ERC-approved protocol for the study and any subsequent IRB/ERC-approved revisions/amendments to the protocol.
- Any changes to the protocol must be submitted to and approved by the IRB/ERC prior to implementation.
- Include full copies of all final versions, stored in reverse chronological order, with the current approved version first.
- IRB/ERC submission/approval of revisions/amendments should be filed under Section IRB/ERC Approvals in the Regulatory Binder.

2) **CV: Investigators and Sub-Investigators**

- To document qualifications and eligibility to conduct studies and/or provide medical supervision of subjects, ensure the CV is complete and contains the following information:
    - Current appointments/positions/citations, etc.
    - Start and end dates (or "to present") for all appointments and positions (no date gaps).
    - Signed and dated (on first page) by the investigator (or sub-investigator) and all study personnel to verify document is current.
- Updated CVs are to be filed bi-annually.
- CVs may be kept in a "Master File" during the conduct of the study, but all the CVs must be archived with the study at the end of the trial.

3) **Medical Licenses**

- Maintain copies of all licenses for licensed personnel (e.g., MDs, PhDs, Nurses, etc.) for the duration of the study.
- Licenses may be kept in a "Master File" during the conduct of the study, but all the licenses must be archived with the study at the end of the study.

4) **IRB/ERC Approval**

- Documentation of the provision of IRB/ERC review and approval of the protocol ensures that the study is conducted with the appropriate local regulatory oversight. IRB/ERC approval will be obtained prior to initiation of the study and maintained throughout the conduct of the study and data analysis phase. Sites should maintain current IRB/ERC approval until directed by the DCC to close the study.
- All IRB/ERC approval letters must be on-file. They include, but are not limited to, the protocol, consent(s), study advertisement(s), training and educational materials, participant letters, questionnaires, or any other documents receiving IRB/ERC approval or opinion. All of these documents must be forwarded to the DCC. **NOTE:** If contingent approval is granted, evidence of final approval must be present before the study can be implemented.
- All annual or periodic renewals.
- Approval letter for any protocol amendments and modifications. (The sponsor and the IRB/ERC must approve all protocol changes prior to implementation unless the change is intended to eliminate an apparent immediate hazard to subjects.)
- Any local or country-specific regulatory authorization relating to the protocol.
- All approval letters from the IRB/ERC should be addressed to the PI and should include the following information:
    - Protocol title, number, and version;
    - Actual date of IRB/ERC approval;
    - Specifically state approval of the protocol;
    - IRB/ERC chairperson's or designee's signature;
    - Renewal date or statement indicating when the approval must be renewed;
    - List of the documents approved;
    - List of all sites covered by the IRB/ERC approval.

5) **IRB/ERC-Approved IC Forms**

- Maintain copies of the original IRB/ERC approval and any subsequent IRB/ERC-approved revisions/amendments to IC or consent addenda. Additional consent documents (e.g., screening consents) should be obtained per site requirements.
- Ensure that a version number and date is included on all consent documents.
- Include IRB/ERC approval letter with the IC if the IRB/ERC does not stamp the document.

- IRB/ERC-approved consent documents should not be altered by the subject or study staff personnel during the consenting process. Check-offs, signatures, and dates are the only pieces of information that need to be written in on the consent. Crossing out sections or adding additional comments in the consent are not allowed according to federal regulations.
- Consent form documents must be stored in reverse chronological order with the current approved version first. Place the most currently approved consent form(s) in a plastic sleeve. **NOTE**: Any changes to the consent form must be submitted to and approved by the site's IRB/ERC prior to use.

6) **IRB/ERC Membership List**

- The IRB's composition is constituted in agreement with GCP.
- IRB/ERC information, including membership list, chairperson, and general assurance number, or a letter stating that the IRB/ERC is in compliance with GCP.
- IRB/ERC membership list must be current.
    - If your IRB/ERC does not release its membership list, a Department of Health and Human Services (DHHS) Multiple Assurance Number must be submitted on the IRB/ERC letterhead.
    - If the IRB/ERC does not allow access to the membership list, an anecdotal note must be written to reflect the standard operating procedure of the IRB/ERC, and the note must be filed in the Regulatory Binder.

7) **Roles and Responsibilities Log (Site Delegation Log)**

- On the Site Delegation Log, maintain a list of all study personnel who are involved in the primary conduct of the study at the site. Document responsibilities assigned to research team members and their dates of involvement in the project. This helps to ensure the appropriate delegation of study-related tasks and documents authenticity of the written signature of personnel involved in the conduct of the study.
- On the Site Delegation Log, include:
    - Initials;
    - Printed name;
    - Legal signature, including first and last name;
    - List of delegated responsibilities;
    - Start and end date for delegated responsibilities.
- Included as Appendix to Regulatory Binder and in MOO as **Appendix E**.

6) **Safety Reporting – Serious Adverse Event (SAE)**

- An SAE is any untoward study-related medical occurrence that occurs during the trial.
- Report all SAEs to the DCC within 24 hours using LURNLink. (Please see protocol for reporting SAEs.)

- Notify your IRB/ERC of all SAEs, as per their guidelines.
- Maintain copies of the SAE report forms.
- Maintain documentation of notification of all SAEs to the IRB/ERC.
- The World Health Organization (WHO) grading scale for SAEs is included as **Appendix G**.

7) **Local Laboratory Information**

- Name of local laboratory and date

8) **Local Laboratory Certifications**

- Current College of American Pathologists (CAP) Laboratory Certification for your institution
- Current Clinical Laboratory Improvement Amendment (CLIA) Program Certificate for your institution

9) **Certificates of Confidentiality**

- Certificates of Confidentiality are issued by the NIH and/or the Food and Drug Administration (FDA) to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project.
- Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- The lead institution must ensure that all participating institutions conform to the application assurances and inform participants appropriately about the Certificate, its protections, and the circumstances in which voluntary disclosures would be made. This information is built into the template consents for the study.
- The Certificates of Confidentiality can be downloaded and printed from the study website in the Master Documents area.
- Certificates of Confidentiality receive modification when changes are made in the study and must be approved/ signed off by the Certificate Coordinator at NIDDK.
- New Certificates of Confidentiality are generated by the Certificate Coordinator following review and approval of the modifications to the study.
- Print the Certificates and keep the copies in your Regulatory Binder.

10) **Certification for Shipment of Biosamples**

- Each site must have at least one person certified to ship biosamples, and the certification (HAZMAT) must be current.
- Names of the research staff members who are certified, and a copy of the certificate, should be maintained in your Regulatory Binder.

11) **Human Subject Participation Training Certification**

- All investigators, sub-investigators, and study personnel listed on the delegation of responsibilities log must complete research ethics training.
- Any course on the protection of human subjects provided by your institution will meet this requirement.
- Documentation must include:
    - course title
    - student's name,
    - dates of completion and expiration (if applicable)
    - A brief description of the course. If the site-specific course is one that does not expire, this should be outlined in the description provided
- Training and certification can also be obtained at the following website:
    - NIH: Protection of Human Research Subjects
      http://ohsr.od.nih.gov
- New study personnel must complete all of the required human subjects training, and their addition must be approved by the IRB prior to their contributing to the study.

12) **Safety Reporting – Serious Adverse Events (SAE)**

- An SAE is any untoward study-related medical occurrence that occurs during the trial.
- Report all SAEs to the DCC within 24 hours using *LURNLink* (Please see protocol for reporting SAEs).
- Notify your IRB/ERC of all SAEs, as per their guidelines.
- Maintain copies of the SAE report forms.
- Maintain documentation of notification of all SAEs to the IRB/ERC.

13) **Advertisements/Educational Materials**

- After IRB/ERC approval, maintain copies of all advertisements (e.g., fliers, radio announcements, newspaper/internet advertisements), and educational materials (e.g., slide shows) utilized for the study.
- All materials filed in this section and used in the study should be IRB/ERC-approved and clearly listed on IRB/ERC approval letters/notices.

14) **Investigator Signature Page**

- Documents investigator and sponsor agreement to the protocol and/or amendment(s).
- Site PIs are required to sign the investigator signature page.
- The site PI must sign a new signature page for any amendment.
- Submit a scanned copy to the DCC (LURN-DCC@arborresearch.org), and file the original in this section.

15) **Monitor Signature Logs**
16) **Major Sponsor, DCC, and IRB/ERC Correspondence**

- Maintain a copy of all correspondence (emails, letters, faxes, memoranda, and phone contacts) between the investigator or research staff, sponsor, and DCC relating to the **clinical** conduct of the study, especially correspondence pertaining to:
    - Site activation letter;
    - Protocol decisions (by phone or email);
    - Protocol deviations;
    - Protocol modifications;
    - EEP roster and letters from the Project Officer.
- Maintain a copy of all pertinent communications with the IRB/ERC relating to the study (e.g., Study Hold, Removal of Subject, Protocol Deviation, and Notice of Final Study Report).

CVs, medical licenses, IRB/ERC approvals, laboratory certifications/accreditations (if applicable) should be kept current. Current copies of required documents (IRB/ERC approvals) should be forwarded electronically to the DCC when available. The DCC will assist sites in monitoring annual IRB/ERC renewals.

3. SITE TRAINING AND ACTIVATION

3.1. Site Training

Site staff will receive study training prior to implementation of the study. Reference the LURN Site Training Slides in **Appendix F** for additional information. Training will include, but not be limited to, review of:

- Main protocol
- Informed consent process
- MOO
- Data collection electronic Case Report Forms (eCRFs)
- Schedule of events
- Variable definitions
- Study-specific procedures
- Collecting, processing, labeling, shipping, and tracking of biosamples
- Use of LURNLink
- Site initiations and monitoring plan

Please notify the DCC of new study team personnel so they can receive the appropriate training and website access.

4. STUDY MONITORING

Each PI will be responsible for overseeing the study at their institution, and the DCC will be responsible for monitoring the conduct of the study. Monitoring responsibility will extend to determination of accurate and effective conduct of the protocol, and to recommendations regarding closure of the study. The NIDDK has appointed an independent EEP that will review the protocol prior to any clinician or participant recruitment, and will continue to monitor the study's safety and progress through regular reports prepared by the DCC and periodic meetings.

Oversight of monitoring will be performed to ensure that: 1) monitoring activities are appropriate to the study; 2) monitoring is accomplished in a regular, timely, and effective manner; and 3) recommendations that result from study monitoirng are implemented in a timely fashion.

Accepted principles of data and safety monitoring will be observed throughout the conduct of the LURN Observational Cohort Protocol.

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accorandance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s). Monitoring will include a combination of annual site visits and remote monitoring. Monitoring helps to catch problems and noncompliance before the actions become repetitive. It can identify systemic issues which can be corrected before a study is jeopardized.

Remote monitoring will occur at the DCC, and site-specific information in the form of reports reflecting data completion, integrity, and quality will be produced. These reports will be generated at least monthly and will be shared with the sites and NIDDK.

Please see **Appendix H** for a detailed monitoring plan specific to this protocol.

4.1. Monitoring of Site-Specific Information

4.1.1. Screening Logs

- Screening logs are integrated into the Patient Census page of LURNLink.
- The DCC will review the screening logs weekly.
- The DCC will query the sites should any questions arise following review of the screening logs.
- The screening logs will be reviewed by the Observational Cohort Protocol Workgroup and the Project Executive Committee (PEC) on a regular basis.

4.1.2. Subject Questionnaires

- Subjects can either answer through the patient portal or complete them on paper for the coordinator to enter into the database.
- Subjects will be given a unique URL and log-in information to access a portal in LURNLink to answer protocol surveys.

5. OBTAINING & DOCUMENTING INFORMED CONSENT

5.1. Informed Consent Process

A signed IRB/ERC-approved IC document must be obtained from each subject. Written consent should only be obtained after the PI or investigator's delegate is confident that the subject or legal guardian understands the information presented to the subject.

An investigator or designee shall seek consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence.

5.1.1. Definition of Screening Statuses

1) *Consented (Eligible)*: The subject meets the eligibility criteria, agrees to participate to the study, and signs the approved study consent.
    - Consented to study, refused biospecimen collection
    - Consented to study, refused genetic sample collection
2) *Refused (Eligible, Declined Participation)*: The subject meets the eligibility criteria for the study but refuses to participate in the study.
3) *Not Approached (Eligible)*: The subject meets the eligibility criteria, and either:
    - Administrative issues at the site caused the subject to not be approached; or
    - This subject is still eligible and still can be approached for consent.
4) *Not Eligible*: The subject does not meet the eligibility criteria.
5) *Other*: When this option is used, a comment must be entered onto screening log.

5.1.2. Re-Consenting Subjects Due to Amendments to the Protocol

The PI at each site determines the need for re-consenting based on the protocol amendment and subject population. If the PI is uncertain, the site's IRB/ERC should be consulted.

5.1.3. Consenting Non-English Speaking Subjects

Subjects who cannot speak English are specifically excluded from the LURN Observational Cohort Protocol.

5.2. Documentation

Site personnel must document in the subject's medical record that the participant has signed the IC form, met enrollment criteria, and was enrolled into the LURN Protocol 1 study. Other pertinent details of the consent process, including summaries of telephone conversations with subjects, must also be carefully documented in the medical record. Refer to **Appendix I** for the form that documents the IC process. The signed IC document should be maintained in the following locations:

- The original form is placed in the subject's research file.
- A copy is placed in the participant's medical chart (if the participant is a patient at the clinic).
- Subject or legal guardian will receive a copy.

Master files of signed consents at the sites are not condoned. All the subject's study-related documents are to be maintained in the subject's research file.

5.3. Health Insurance Portability & Accountability Act (HIPAA) Authorization

The HIPAA authorization form may be a separate document from the IC, but the study participant must review and sign the HIPAA authorization and the consent form. The format of the HIPAA authorization is established by the site's local IRB/ERC. Investigators should review information provided in Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, NIH Publication 03-5388 at http://privacyruleandresearch.nih.gov.

5.4. Subject Identification Numbers

The subjects in the LURN Observational Protocol will have a unique subject identification number assigned automatically by the LURNLink application.

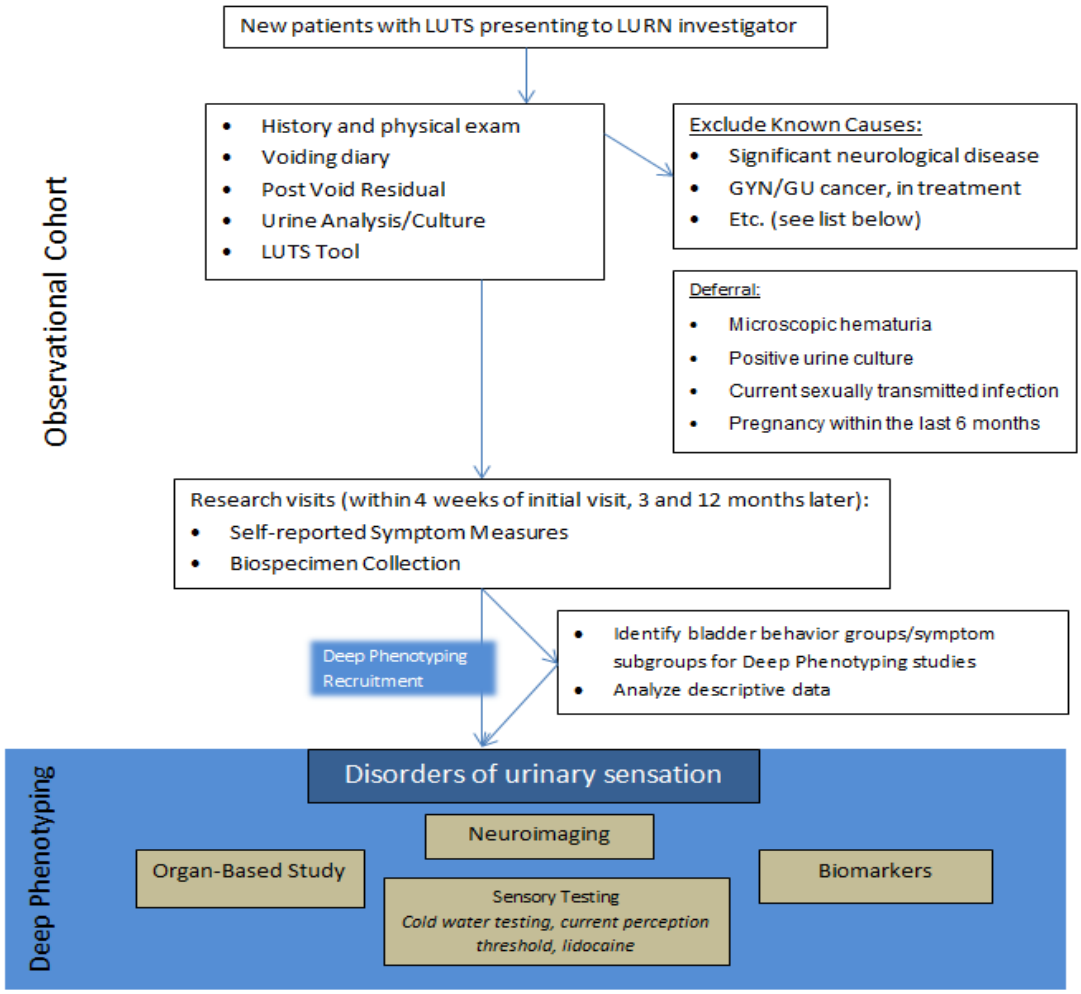
6. PROTOCOL & APPENDICES

Please refer to **Appendix A** for the LURN Phenotyping Protocol and associated appendices.

7. STUDY DESIGN

This study is a prospective observational study of new patients with LUTS presenting for clinical care to one of the LURN physicians. We will collect routine clinical and demographic patient information and validated, self-reported outcome measures, including information on LUTS, pelvic floor symptoms (sexual, bowel, prolapse), health-related quality of life, and psychosocial symptoms (anxiety, depression, stress, sleep disturbance) at presentation. Study participants will complete follow-up assessments 3 months and 12 months after their initial assessment to evaluate the trajectory of their symptoms in the context of the treatments they received. Biosample collection will be coordinated with these follow-up visits.

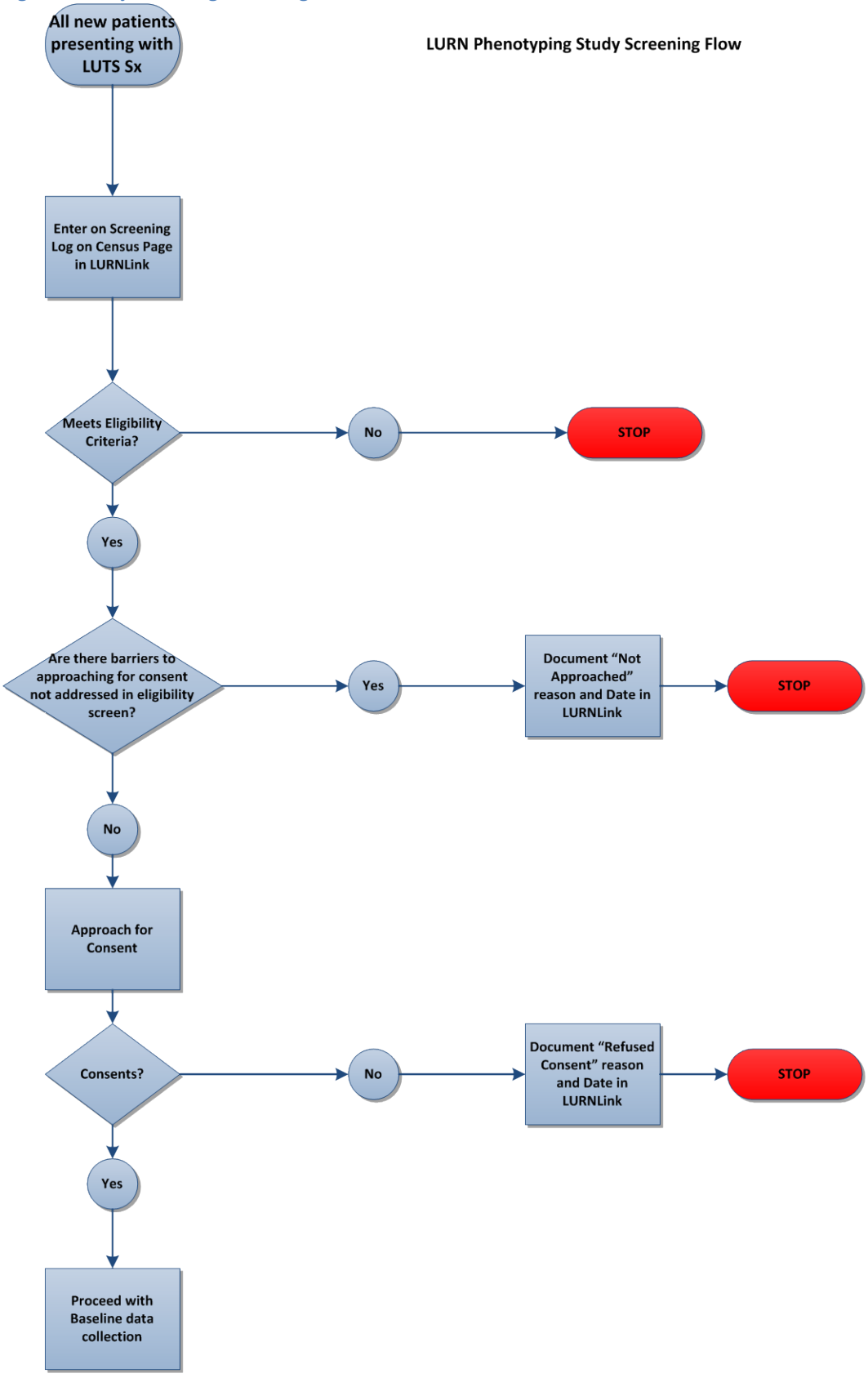
Figure 2: Study Schema



8. RECRUITMENT AND SCREENING

New patients with LUTS presenting to LURN clinical sites will be entered on the screening log (Census Page of LURNLink) and screened for participation based on the inclusion and exclusion criteria (below). We will collect reasons for exclusion of screened patients. Unless listed below, prior or ongoing treatments for LUTD will not preclude patients for participation (i.e., included patients do not necessarily have to be treatment-naïve). Eligible patients will be invited to participate in the study. We will collect reasons for non-consent of eligible patients. Consenting participants will complete the self-reported demographic and symptom measures and a 3-day urinary diary before starting any new treatment prescribed by LURN physicians. Standard clinical data will also be collected. All enrolled patients will be asked for permission to be re-contacted for future participation in other LURN studies.

Figure 2: Study Screening Flow Diagram



8.1. Eligibility – Inclusion Criteria

- Men and women presenting for new patient visits for evaluation or treatment of LUTS to one of the LURN physicians.
- Age ≥ 18 years.
- The presence of any of the symptoms reported in Table 1, based on responses to the LUTS Tool with a 1-month recall period and other screening questions. See the LUTS Tool Screening Algorithm (**Appendix L**).
- The ability to give IC and complete self-reported questionnaires electronically.
    - This inclusion criterion refers to the inability to respond to an electronic survey, NOT the preference to use paper. Someone who does not have access to the Internet is still eligible for the study and may choose to use a public computer or paper for survey responses.

Table 1: LUTS Appropriate for Study Inclusion

Symptom Cluster	Symptom
Storage	Daytime frequency
	Nocturia
	Urgency
	Incontinence/leakage (various types)
	Poor or absent sensation of bladder filling
Voiding	Slow/weak stream
	Splitting or spraying
	Intermittent stream/double voiding
	Hesitancy
	Straining
	Dribbling at the end of flow
	Paruresis (i.e., shy bladder, shy bladder syndrome)
	Poor or absent sensation of urethra during void
Post-Micturition	Feeling of incomplete emptying
	Post-micturition dribble (delayed)
Other or Poorly Characterized	Abnormal bladder or urethral sensations

8.2. Eligibility – Deferral Criteria

- Microscopic hematuria
    - Patient must undergo appropriate evaluation.
- Positive urine culture
    - Patient needs to be treated and have a subsequent negative culture before he or she is eligible. (Treatment, re-culture and reassessment should fall within the 4 week window from the initial visit)
- Current sexually transmitted infection
    - Patient needs to be treated and have a subsequent negative screen before s/he is eligible
    - Refers to acute non-chronic STIs such as gonorrhea, chlamydia, etc. Subjects with chronic STIs such as HSV or HPV are not deferred.
- Recent (within 6 months) pregnancy

8.3. Eligibility – Exclusion Criteria

- Gross hematuria
- Significant neurologic disease or injury, including but not limited to: cerebral vascular accident with residual defect, Alzheimer's dementia, Parkinson's disease, traumatic brain injury, spinal cord injury, complicated spinal surgery, multiple sclerosis
- Primary complaint is pelvic pain.
- Diagnosis of interstitial cystitis, chronic prostatitis, or chronic orchialgia
- Pelvic or endoscopic GU surgery within the preceding 6 months (not including diagnostic cystoscopy)
- Ongoing symptomatic urethral stricture
- History of lower urinary tract or pelvic malignancy
    - Includes prostate cancer
- Current chemotherapy or other cancer therapy
- Pelvic device or implant complication (e.g., sling or mesh complications)
- Current functioning neurostimulator
- Botox injection to the bladder or pelvic structures within the preceding 12 months
- In men, prostate biopsy in the previous 3 months
- In women, pregnancy
- History of cystitis caused by tuberculosis, radiation therapy, or Cytoxan/cyclophosphamide therapy
- Augmentation cystoplasty or cystectomy
- Presence of urinary tract fistula

- Current major psychiatric disorder or other psychiatric or medical issues that would interfere with study participation (e.g., dementia, psychosis, etc.)
- Inability to relay valid information, actively participate in the study, or provide IC (includes uncontrolled psychiatric disease)
- Difficulty reading or communicating in English
- Pregnancy occurring after enrollment is considered an endpoint

8.4. Screening

An electronic screening log will be utilized to monitor recruitment. The log will be part of the LURNLink data capture application.

- Screening log contains information (including reason for failure to screen) regarding all potential subjects approached for participation in the study and the outcome of that encounter.
- The screening log will contain the following details:
    - Date approached (MM/DD/YYYY);
    - Date of birth (DOB);
    - Sex (female or male);
    - Race (Choose from drop-down list.);
    - Ethnicity (Choose from drop-down list.);
    - Eligible (computed by your answers to the eligibility questions);
    - Education, employment, and marital status;
    - Consent status (if not enrolled, reason).

Once eligibility of the individual has been determined, **a unique Study ID will be assigned** by the LURNLink application.

8.5. Recruitment Plan

New patients with LUTS presenting to LURN clinical sites will be screened for participation based on the inclusion and exclusion criteria (below). We will collect reasons for exclusion of screened patients. Unless listed below, prior or ongoing treatments for LUTD will not preclude patients for participation (i.e., included patients do not necessarily have to be treatment-naïve). Individuals eligible for the Observational Cohort Study (based on the Eligibility Criteria) will be approached by a LURN investigator for release of their protected health information and contact information so that study staff may approach them to describe the study and obtain informed consent. See **Appendix J** for Recruitment Materials.

Overall recruitment will be monitored weekly.

8.6. Strategies for Approaching Participants

It is critical that site personnel put careful thought into how to maximize subject accrual and retention. Integration of research studies into existing clinical flow will enhance acceptance and cooperation with colleagues, as well as minimizing wasted time and frustration for the subject.

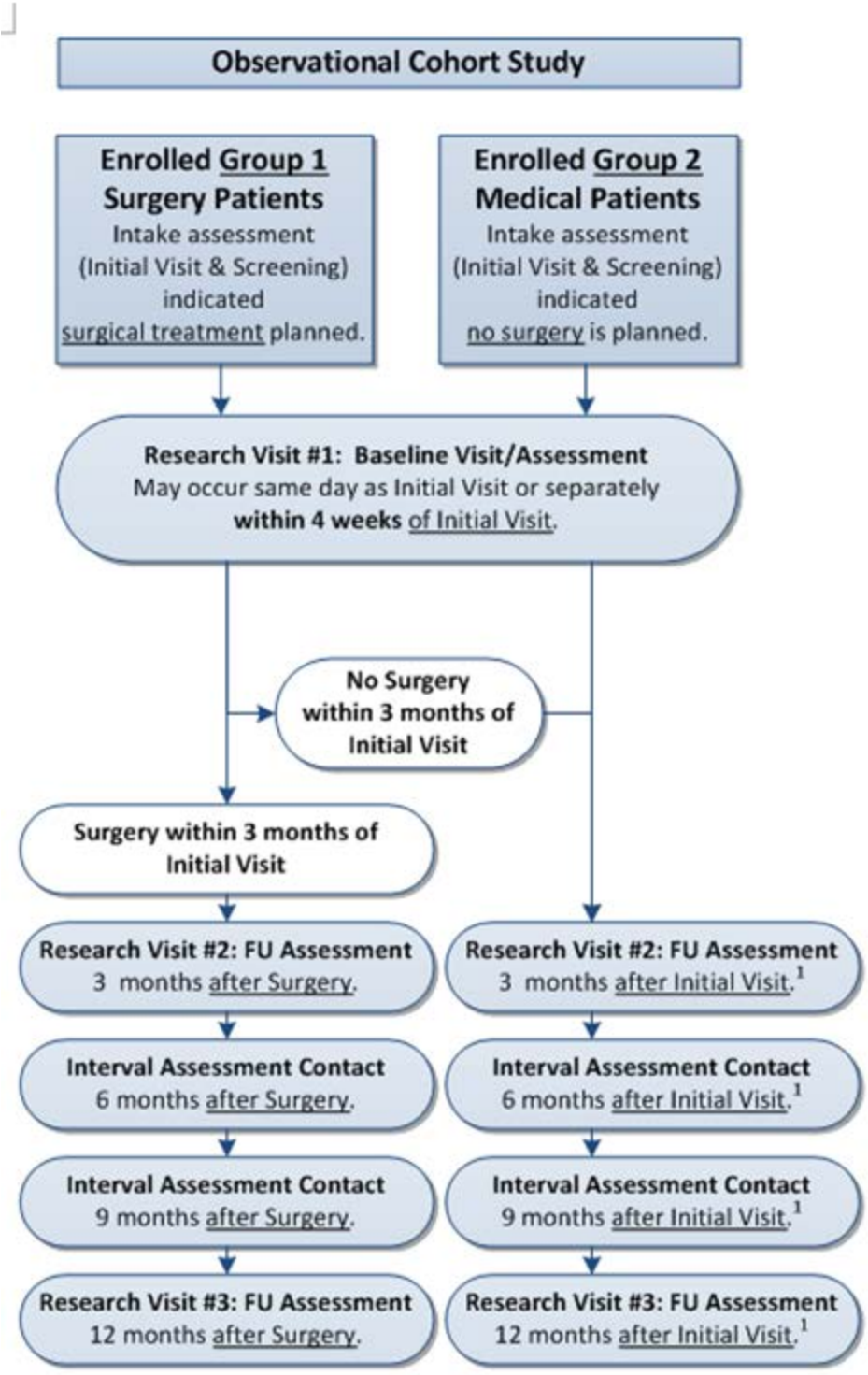
Prior to implementation, study staff should meet together to discuss implementation strategies, thinking about the following questions:

- How do you find out when patients will be seen in clinic? How will you know if the clinic appointment has been rescheduled?
- How will you know who is being considered for the study?
- What kind of communication do you need to establish with your clinical team? Will the study coordinator need to attend meetings of this group?
- What is the estimated interval of times the patient will be seen in your facility?
- If there is a short time period (or none), you will need to develop a plan to approach the subject prior to final acceptance. When is the optimal time?
- How long do you think you will need to explain the study and obtain informed consent from the potential subject? Where will you do that? In clinic or in the research area?

9. SCHEDULE OF VISITS AND PROCEDURES

	Initial Visit	Initial and/or Baseline Visit	3 Month Follow-up Visit	6 Month Assessment	9 Month Assessment	12 Month Follow-up Visit
Eligibility Assessment	X					
Demographics	X					
General Clinical Information	X					
Physical Exam Findings	X					
Clinical Testing (Urine Analysis)	X					
LUTS Tool (1 month recall period)	X					
LUTS Tool (1 week recall period)		X	X			X
3-Day Voiding Diary		X				
Self-Report Questionnaires		X	X			X
Biospecimen Collection (Blood, Urine, Saliva)		X	X			X
Perineal Swab Collection (Men)		X				
Vaginal Swabs Collection (women)		X				
Interval Treatments			X	X	X	X

Figure 3: Visit Schedule


Observational Cohort Study
Enrolled Group 1
Surgery Patients
Intake assessment
(Initial Visit & Screening)
indicated
surgical treatment planned.
Enrolled Group 2
Medical Patients
Intake assessment
(Initial Visit & Screening)
indicated
no surgery is planned.
Research Visit #1: Baseline Visit/Assessment
May occur same day as Initial Visit or separately
within 4 weeks of Initial Visit.
No Surgery
within 3 months of
Initial Visit
Surgery within 3 months of
Initial Visit
Research Visit #2: FU Assessment
3 months after Surgery.
Research Visit #2: FU Assessment
3 months after Initial Visit.[1]
Interval Assessment Contact
6 months after Surgery.
Interval Assessment Contact
6 months after Initial Visit.[1]
Interval Assessment Contact
9 months after Surgery.
Interval Assessment Contact
9 months after Initial Visit.[1]
Research Visit #3: FU Assessment
12 months after Surgery.
Research Visit #3: FU Assessment
12 months after Initial Visit.[1]

9.1. Initial/Baseline Visit

Patients will be screened for eligibility and approached for study participation during their initial visit to LURN physicians. As part of screening, patients will complete the LUTS Tool with a 1-month recall period (**Appendix A1** of Protocol) at the initial visit. For patients screened but not enrolled, we will collect reasons for exclusion and patient demographic information. Consenting participants will be asked to complete self-reported demographic and symptom measures and a 3-day urinary diary (within 4-weeks of the initial visit and before initiating treatment). The LUTS Tool with a 1-week recall period (**Appendix A2** of Protocol) will be administered to patients along with the self-reported questionnaires at baseline visit. If needed, a research coordinator will arrange a separate baseline visit to facilitate completion of the initial survey and biospecimen collection. At this baseline assessment, the intake questionnaire will be completed using an online module. Participants who are not comfortable using computers will be given the option to complete the questionnaires on paper. The LUTS Tool will be administered twice in 1 day (first with a 1-month recall period during screening and then with a 1-week recall period as part of the baseline questionnaires) if a participant's initial and baseline visits take place on the same day.

It is preferred that the biospecimen collection and response to the baseline questionnaires occur on the same day or as close as possible.

If the subject has initiated <u>new</u> treatment for LUTS prior to biospecimen collection, then we will keep the subject in the study for survey response and other clinical data, but we will not collect biospecimens other than DNA at the baseline visit. If these subjects consented to biospecimen collection, biospecimens will still be collected at the 3 month and 12 month follow-up visits.

9.2. Data Collected

9.2.1. Clinical Data Elements

<u>Demographics</u>

Demographic information will be collected for all participants, including date of birth, sex, race, ethnicity, level of education, employment, and marital status.

<u>History</u>

Patients will be queried regarding past medical and surgical history; diet and use of alcohol, tobacco, and caffeine; history of urinary, vaginal, or sexually-transmitted infections; pelvic, prostate, or urologic pain; obstetric history; and menopausal status and use of hormone therapy. We will collect family history with specific attention to identification of first-degree relatives who have been diagnosed and/or treated for LUTS. All current prescription and over-the-counter medications will be recorded. Metabolic syndrome will be determined by clinical history and patients' self-reported history or treatment of: elevated blood glucose, hypertension, elevated triglyceride, reduced HDL cholesterol.

<u>Comorbidities</u>

In addition to the health history abstracted above, we will calculate a ***Functional Comorbidity Index*** score for each participant to capture health status and competing risk of adverse health events. The Functional Comorbidity Index is an 18-item list of diagnoses that discriminates physical function and risk of mortality.

Physical Examination

Patients will undergo standardized physical examination, including assessment of height and weight; waist circumference; genitourinary (GU) evaluation (penis, scrotum, or vaginal exam, with quantification of pelvic organ prolapse using Pelvic Organ Prolapse Quantification [POPQ] system); pelvic floor muscles (including pelvic floor muscle contraction strength assessed using the ***Oxford Grading System***) and the rectum.

Tests

Dipstick Urine Analysis (UA)

Post-void Residual Urine Volume (PVR) – will be measured within 10 minutes of voiding by ultrasound or straight catheter (whichever is standard of care at the site).

Urine Culture (done at baseline, M3 and M12) – collecting positive/negative results, species, and colony counts. We will not collect information about culture sensitivity. A positive urine culture does not require that a subject be withdrawn from the study (Treatment, re-culture and reassessment should fall within the 4 week window from the initial visit).

Clinical Diagnosis & Treatment Plan

Clinicians will complete a standard form documenting the primary and secondary LUTD diagnoses and their recommended treatments.

9.2.2. LURN Modified Bladder Diary

Please refer to **Appendix N** to view the LURN Modified ICIQ Bladder Diary. The subject should be given the LURN Modified Bladder Diary to be completed at the Baseline/Initial visit. Verbally review the diary instructions with the subject, and make sure the following information is stressed:

1. Instruct participant that they *must* write "WOKE" and "BED" once per day.
2. Fluid (drinking) volumes and type are not always collected for clinicians, but this is a very important study item for LURN. Please instruct patients to carefully record the amounts and types of fluid they consume at any given time point.
3. Instruct participants to complete the diary for 3 consecutive days. (Note: We will ask you to enter data from all bladder diaries that are returned to you, including those that were conducted for less than 3 days or that were conducted on non-consecutive days. However, data from bladder diaries with less than 3 consecutive days will be less useful and may need to be excluded for some analyses. Therefore, we are asking all participants to complete the full 3 consecutive days.)
4. **Urine Output:** Participant enters the amount of urine passed in ounces (oz.) in the urine output column, day and night. Any measuring container will do. If the participant passed urine but couldn't measure it, a check goes in this column. Clarify to participants: This includes any urine evacuated during bowel movements.
5. **Stress Leakage**: The participant should write the word "stress" in the Leak column if they had a leak and the reason for leakage was any physical stress. This includes coughing, sneezing, lifting, jogging, running, walking briskly, or bending. It does not include leakage associated with standing up from a seated position.
6. **Urge Leakage**: The participant should write the word "urge" in the Leak column if they had a leak and the reason for leakage was any urgency. This includes standing up from

a chair, being on the way to the bathroom, or with triggers such as the presence of running water.

7. The instructions for the bladder diary are written at a high literacy level. Please give special attention to ensuring that the participants understand how to complete the diary.

9.2.3. SELF-REPORTED SYMPTOM MEASURES

Following is a list of Self-Reported Measures that the subjects will complete electronically at the Baseline, 3-month, and 12-month visits. The LURNLink application will generate a unique URL for each consented subject, at each time point that they can utilize to respond to the surveys. You will be sending the subjects their link via email. For a template email, please refer to **Appendix U**. For more information about the Patient Portal and URL, see **Appendix M**. In addition to the self-reported measures described below, there are also fields for the subject to report their race and ethnicity.

Lower Urinary Tract Symptoms

LUTS Tool – An instrument that assesses the severity and bother of 18 urinary symptoms. The LUTS Tool with a 1-week recall period will be administered to participants at the baseline, 3-month, and 12-month follow-up visits.

American Urological Association Symptom Score Index (AUA-SI) – A validated 9-item measure, which assesses urinary symptoms.

Urinary Diary – All patients will complete a 3-day urinary diary, including fluid intake, voided volumes, leakage episodes, and activity during leakage.

Pelvic Floor Symptoms

Bowel Symptoms

PROMIS Gastrointestinal Symptom Scales – Three validated instruments to assess constipation (9 items), diarrhea (5 items), and bowel incontinence (4 items).

Sexual Function

International Index of Erectile Function (IIEF, Men) – A 6-item measure that assesses erectile function in men.

Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-revised (PISQ-IR, women) – A validated measure of sexual function in women with pelvic organ prolapse, incontinence, and/or fecal incontinence.

Pelvic Floor

Pelvic Floor Distress Inventory – Short Form (PFDI-20, Women) – A 20-item validated measure with three subscales to assess pelvic floor symptoms in women, including urinary, prolapse, and colorectal.

Pain

Genitourinary Pain Index (GUPI) – A 9-item measure to assess GU pain in men and women.

Pediatric Disorders

Childhood Traumatic Events Scale – A 6-item measure assessing recollection of events associated with major upheaval, such as deaths.

Psychosocial Symptoms

PROMIS Depression and Anxiety Item Banks – Used to measure mood, affect, negative self-perceptions, negative social perceptions, fear, anxious feelings, hyperarousal, and somatic symptoms related to arousal.

Perceived Stress Scale (PSS) – Contains 10 items; assesses non-specific subjective stress.

PROMIS Sleep Short Form – A validated 8-item assessment of sleep patterns.

General Health-Related Quality of Life

International Physical Activity Questionnaire – Short Form (IPAQ-SF) – A 9-item assessment of four levels of activity.

PROMIS Physical Function Item Bank, Mobility Subdomain – Consists of 16 items that measure lower extremity function.

9.2.4. Biospecimen Collection

See Section 10 for collection and handling details.

9.3. Follow-up Visits – M3 and M12

Patients will be categorized into one of two groups as of their intake assessment: those for whom a surgical treatment is planned (i.e., surgical patients), and those for whom no surgery is planned (i.e., medical patients). We anticipate, based on a survey of LURN investigators, that surgical treatment will be planned for 10% of the study population. For medical patients, follow-up visits will occur 3 months and 12 months after the baseline visit. For surgical patients, follow-up visits will occur 3 months and 12 months after surgery. Postponement of follow-up visits based on surgical schedule will minimize the likelihood that a patient is asked to provide data and biosamples during the perioperative period. If a surgical patient's surgery has not occurred within 3 months of the initial visit, he or she will revert to the schedule of medical patients, with follow-up visits scheduled based on the date of the initial visit.

9.3.1. Definition of Surgery in Observational Cohort Protocol

"Surgery" entails any surgical procedure attempting to address urinary tract dysfunction, including:

- TURP
- Microwave therapy
- Laser treatment
- TUIP UroLift
- TUNA (transurethral needle ablation)
- Thermotherapy
- InterStim test procedure
- Placement of an InterStim implantable pulse generator (IPG) battery
- Removal of an InterStim IPG battery
- Burch colposuspension
- Placement of a sling
- Urethral bulking injections

- Urethrolysis
- Intradetrusor Botox injection
- Surgery for pelvic organ prolapse
- Posterior tibial nerve stimulation
- Other (specify)

Participation in follow-up visits will consist of repeat assessment with the LUTS Tool (1-week recall) as well as assessment of sexual function, bowel symptoms, depression, anxiety, and health-related quality of life. The research coordinator will review any interval treatments received, including non-traditional (e.g., herbal remedies) and non-medicinal (e.g., acupuncture) treatments for LUTD.

9.4. Follow-up Assessments – M6 and M9 (Remote Visits)

To ensure accuracy of patient report of interval treatments between the 3-month and 12-month assessments, the LURN site research coordinators will contact patients at 6 and 9 months to complete short assessments of interval treatments received.

9.5. Visit Windows

- Baseline visit: up to 4 weeks after the initial visit (the first time the patient is seen at the clinic)
    - Questionnaires and biospecimens must be collected within 2 weeks of each other. It is preferable that they be collected on the same day.
- 3-month follow-up visit: can occur 1 month to 4.5 months after the initial visit (or surgery)
- 6-month assessment: 4.5 months to 7.5 months after the initial visit (or surgery)
- 9-month assessment: 7.5 months to 10.5 months after the initial visit (or surgery)
- 12-month follow-up visit: 10.5 months to 15 months after the initial visit (or surgery)

10. BIOSPECIMEN COLLECTION

10.1. Biospecimen Collection for Biospecimen Repositories – Overview

The sample processing associated with this protocol requires advanced skills. Prior to study implementation, PIs should meet with study staff and discuss the following questions:

- How will the samples be collected? Who will draw those samples? Do most of your patients have clinical labs drawn before they come to their clinic visit or on the day of the visit? If the latter, how can you coordinate clinical and research blood draw?
- Who will process the samples from their raw state to their component states for storage? Who will pick up the samples? Where do you pick them up from? Who will centrifuge, aliquot, and label the samples? Who will notify you that there are samples to pick up? How will you ensure that the samples are processed within the recommended time interval?
- How will you ensure that the samples are handled and labeled properly?
- A checklist for biospecimen collection and processing can be found in Appendix T.
- If you are utilizing a research lab, have you met with them to discuss the study and the process for sample collection, processing, labeling, and storage? What about costs?
- Where will the samples be stored? Who has certification to ship biosamples?

- Information regarding biospecimen shipping is included in **Appendix O**.

10.1.1.

Biospecimen Collection Requirements

	REQUIRED SUPPLIES
Whole Blood – (DNA) Biorepository	**2 x 4.5 ml EDTA TUBES**
Serum – Biorepository	**2 x 10 ml blood for serum (serum separator tube)**
Plasma – Biorepository	**1 x 6 ml blood for plasma (lavender top), slower (300 g) centrifuge**
Urine – Biorepository	**2 x 90 ml urine cup**
Perineal Swab – Biorepository	**1 x Copan e-swab**
Vaginal Swab – Biorepository	**1 x Copan e-swab**
Saliva – Biorepository	**4 x salivettes**
Phlebotomy Requirements	**Gauge Butterfly needle and tubing**
Centrifugation	**Table top centrifuge**
Refrigerator/ Freezers	**Refrigerator, -20**^{o}C and **-80**^{o}C freezer

10.1.2. Biospecimen Collection Schedule

Sample Type	Enrollment	Month 3	Month 12
Whole Blood – (DNA)	**x**	**x** **If not collected at enrollment**	
Serum – Biorepository	**x**	**x**	**x**
Plasma (for Proteomics) – Biorepository	**x**		
Urine – Biorepository	**x**	**x**	**x**
Salivary Cuvette – Biorepository	**x**	**x**	**x**
Perineal/Vaginal Swab – Biorepository	**x**		

10.1.3. Biospecimen Collection Detail

Sample	Collected	Aliquot Volume	# Aliquots (labels)	Destination	Visits	Comment	Label Language
DNA (Whole Blood)	EDTA Tube x2	9ml	2	NIDDK Biorepository (Fisher BioServices)	baseline only (but can be collected at any visit)	Batch ship frozen monthly	EDTA-DNA
Serum	10ml serum separator x2	0.5ml in 2ml cryovials	10	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Serum
Plasma	Lavender Top - 6ml	0.5ml in 2ml cryovials	5	NIDDK Biorepository	baseline only	Batch ship frozen monthly	Plasma
Urine Assay Assure	15ml	N/A	1	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Urine Assay
Urine Centrifuged Pellets	30-50ml	1ml in 2ml cryovials	3	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Urine Pellet
Urine - Supernatant	30-50ml	5ml in 5ml cryovials	6	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Urine Supernatant
Vaginal Swab (WOMEN ONLY)	Colpan E-Swab	N/A	1	NIDDK Biorepository	baseline only	Batch ship frozen monthly	Vag Swab
Perineal (MEN ONLY)	Colpan E-Swab	N/A	1	NIDDK Biorepository	baseline only	Batch ship frozen monthly	Peri Swab
Saliva Collection - Morning	Salivette	N/A	2	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Day 1 and Day 2 AM Saliva
Saliva Collection - Evening	Salivette	N/A	2	NIDDK Biorepository	BL, 3M, 12M	Batch ship frozen monthly	Day 1 and Day 2 PM Saliva
TOTAL			33				
			24	(12-month visit)	24	(3-month visit)	

10.1.4. Biosample Materials Provision

Please note that catalog numbers and links are only given as examples. Sites may have contracts with other materials providers. The catalog numbers and links are provided here to give users an example of more detailed product specifications to assist with ordering supplies.

Biospecimen labels are to be requested through the use of the LURN Label Request Form. This is located on the study website under "Study Coordinators" → "Documents folder for Study

Coordinators". Complete the requested form and email to link listed below. All requests must be in by the 14th of each month so mid-month printing can occur.

Material	Cost	Order	Address
Biosample Labels	None to site	DCC	LURN-Admin@arborresearch.org
2.0ml Cryovials	None to site	NIDDK Biorepository	niddkrepository@thermofisher.com
0.5ml Cryovials	None to site	NIDDK Biorepository	niddkrepository@thermofisher.com
Copan E-Swabs	$368.02 (50 per pack, 10 packs per case)	480C	http://www.copanusa.com/media/brochures/Copan_ESwab_broch-web.pdf
Salivettes	$141.73/100	SAR-511534500	http://www.scimart.com/product/detail/salivette-synthetic-swab-for-cortisol-determination-100pack/
90ml Sterile Urine Collection Cups	$125/400	22-146-530	http://www.fishersci.com/ecomm/servlet/fsproductdetail_10652_661347__-1_0
Assay Assure 15ml	No cost to sites	DCC	LURN-Admin@arborresearch.org
C&S Urine Culture Vacutainer Tubes 4ml with Additive	$437.30/100	364951	http://catalog.bd.com/
10ml SST Phlebotomy Tube	86.65/100	367985	http://catalog.bd.com/
6ml EDTA Phlebotomy Tube	$36.31/100	368661	http://catalog.bd.com/

50ml Conical Centrifuge Tubes	$345.39/500	14-432-22	http://www.fishersci.com/ecomm/servlet/fsproductdetail_10652_661347__-1_0
Phosphate Buffered Saline (PBS) – 10%	$38.64/ea	70-011-044	http://tinyurl.com/oxwwhve
Esky USB Barcode Scanner	$24.55	Amazon.com	http://www.amazon.com/Automatic-Barcode-Scanning-Bar-code-Adjustable/dp/B00406YZGK/ref=sr_1_4?ie=UTF8&qid=1424716786&sr=8-4&keywords=symbol+scanner#
Shipping Materials to NIDDK Repository	None to site	NIDDK Repository	niddkrepository@thermofisher.com
Courier Costs to Repository	None to site	NIDDK Repository	niddkrepository@thermofisher.com

10.1.5. Biospecimen Collection Participant Restrictions

While it is preferred that biospecimens are collected on the same day as survey responses, they must be collected within 2 weeks of completion of questionnaires.

Patients should withhold initiating new medical therapies prior to the donation of baseline biospecimens. If they do not, then only DNA will be collected at the baseline visit. Biospecimens may still be collected from these patients at the 3- and 12-month follow-up visits.

Patients will be requested to abstain from caffeinated beverages (e.g., coffee, tea, energy-drinks, soda) for at least 6 hours prior to biospecimen donation. Participants will be asked to abstain from smoking and exercise for at least 3 hours prior to biospecimen donation, and to abstain from consuming probiotics for 24 hours prior to biospecimen donation. We will still accept the specimens if the subject has not adhered to our restrictions. However, it is critical to stress the importance of adherence to the subject, and to document non-adherence on the Biospecimen Collection eCRF. Please refer to **Appendix P** for Patient Instructions and Patient Worksheets for Biospecimen Collection.

Donation Type	Restriction	Time
All Biospecimens	Caffeinated Beverages	6 Hours
All Biospecimens	Tobacco Smoking	3 Hours
All Biospecimens	Exercise	3 Hours
All Biospecimens	Probiotics (Excluding Yogurt or Drinks)	24 Hours
Morning Salivary	Eat Breakfast, Drink Liquids, or Brush Teeth	Prior to Collection
Vaginal Swabs	Active Menstrual Bleeding	48 Hours
Vaginal Swabs	Douching, Feminine Sprays/Wipes	48 Hours
Vaginal Swabs	Spermicides, Vaginal Medications	7 Days
Perineal Swabs	Spermicides	7 Days
Perineal Swabs	Sexual Activity – Vaginal, Oral, Anal	48 Hours
Vaginal Swabs	Sexual Activity – Vaginal	48 Hours
Perineal Swabs	Perineal Medications, Antifungal Powder or Cream	48 Hours

10.2. Blood Collection

As a part of the LURN study, study participants will be contributing blood specimens. Blood will be drawn at a separate visit from the initial clinic visit, in coordination with urine and swab sample collection and dropping off salivary cuvettes. The instructions described below provide information for the Research Coordinator on how to obtain, process, and store blood specimens prior to shipment to the NIDDK Biorepository.

10.2.1. Collection Type

- Two 4.5ml EDTA Tubes (Purple/Lavender top)
- Two 10ml Serum Separator Tubes (e.g. tiger top)
- One 6ml Plasma Tube (EDTA Purple/Lavender top)

10.2.2. Blood Draw Order of Collection

Obtain blood samples in the following order:

1. Tiger Top (serum)
2. Lavender top (plasma)
3. EDTA tubes (whole blood)

10.2.3. Blood Collection, Processing, Storage, Packing, and Shipping

All specimen processing is to be done using standardized, universal blood collection procedures. The collection window for biospecimens is as follows:

- Biospecimens will be collected on Monday through Friday.
- Biospecimens should not be sent to the Biorepository over the weekend. Serum biospecimens will be collected during 3-month and 12-month follow-up research visits. Whole blood samples will not be collected at these follow-up visits.

The following is a brief description of these procedures.

Practice Standard Precautions: Use gloves, gowns, eye protection, other personal protective equipment and engineering controls to protect from blood splatter, blood leakage, and potential exposure to blood borne pathogens.

Handle all biologic samples and blood collection “sharps” (lancets, needles, luer adapters, and blood collection sets) according to standard guidelines and the policies and procedures of your facility.

Obtain appropriate medical attention in the event any exposure to biologic samples (for example, through a puncture injury) since they may transmit viral hepatitis, HIV (AIDS), or other infectious diseases. Discard all blood collection “sharps” in biohazard containers approved for their disposal.

The following procedures and considerations should be made when collecting blood specimens:

EDTA Tubes – DNA Sample: Collect two (2) 4.5 ml tubes for storage of genetic material. This sample will only be collected at enrollment. If, for some reason, it is not collect at enrollment, it can be collected at any in person visit utilizing the extra sample labels.

- Draw each tube to capacity
- Gently invert tubes 8-10 times
- Transfer the blood from each tube into two (2) 5 ml cryovials
- Place the proper labels on the cryovials

- Place the samples in a –80°C freezer as soon as possible but no more than 2 hours after collecting the samples

Always store the samples upright in the freezer storage boxes provided by Fisher BioServices until the samples are batch shipped to Fisher BioServices.

If for some reason the samples cannot be placed in a -80°C freezer within 2 hours of collection, the samples may be placed in a refrigerator (4°C) immediately after collection and then transferred to a –80°C freezer within 24 hours

Samples must be shipped using dry ice. Include stored genetic samples every time a batch of frozen serum or plasma is shipped to the repository

2) **Serum Aliquots – 10ml Serum Separator Tube:** Collect two (2) tubes for serum. This sample will be collected at all study time points.

- Draw tube to capacity.
- After collection, allow to coagulate at room temperature for 30 minutes.
- Centrifuge at 2,000 rpm using a standard table top centrifuge for 5 minutes.
- Using a transfer pipette, carefully aliquot approximately 0.5ml (500µl) of clear serum from the uppermost layer into ten 2ml cryovials.
- Attach one barcode label to each vial.
- Freeze at -80°C. (If serum is drawn at the clinic, it can be stored at -20°C for a maximum of 48 hours until more permanent storage at -80°C is available.)
- If processing cannot be performed immediately, samples should be placed into a refrigerator for up to 2 hours until processing can be performed.

3) Plasma Aliquots (for Proteomics): Collect 6ml EDTA (lavender top) tube. This sample will be collected only at enrollment.

- Draw to capacity.
- After collection, gently mix by inversion 8-10 times.
- Immediately centrifuge at 300 G using a standard table top centrifuge for 10 minutes at room temperature.
- Using a transfer pipette, carefully aliquot approximately 500 µl (0.5ml) of plasma into five (5) 2ml cryovials.

- Attach one barcode label to each cryovial.
- Freeze at -80°C.
- If processing cannot be performed immediately, samples should be placed into a refrigerator for up to 2 hours until processing can be performed.

10.3. Saliva Collection

As a part of the LURN study, study participants will be contributing saliva as a biological specimen. Participants are asked to collect salivary specimens using home collection kits. A total of four separate salivary specimens will be obtained, two on each of 2 days. These will be refrigerated and then returned to the site for storage and batch shipment to the NIDDK Biorepository.

10.3.1. Saliva Collection Schedule

The collection window for saliva specimens is as follows:

- Saliva may be collected any day of the week.
- Saliva should be collected during baseline, and at 3-month and 12-month follow-up research visits.

10.3.2. Instructions for Saliva Collection

Provide these instructions to the participant: (See **Appendix P**.)

1. The first specimen is collected immediately upon waking. Collect this specimen BEFORE breakfast, coffee, and brushing your teeth.
2. The second specimen is collected between 9 PM and 12 midnight. If you are in bed before 9 PM, collect specimen at bedtime.
3. Both specimens should be collected once on one day, and again on a separate day.
    - Pop the plastic cap off of the plastic tube and remove the cotton swab.
    - Place cotton swab in your mouth for 1 to 2 minutes. You can gently chew on it to increase your flow of saliva.
    - When the cotton swab is soaked with saliva, place it back into its container and close the cap tightly.
    - Please write the date and time on the label. If you happen to miss a scheduled collection time, it is **important** that you write the **actual** time of collection on the label. Please label items with **AM and PM** for clarity.
    - Store the salivettes in the refrigerator.

- Place salivettes in the envelope provided by the clinic.
- When you are finished with the collection, drop off or mail the envelope to the clinic where you are being evaluated.

It may be convenient to hand out the salivettes and return envelope at the time of consenting. The patient can then drop off the salivettes on the day of blood/urine/swab biospecimen collection.

10.3.3. Instructions for Saliva Processing

- Attach one barcode label to each salivette, corresponding to the day and time collected (e.g., Day 1 – AM; Day 2 – PM, etc.).
- Record samples in LURNLink on label worksheet and on the Biosample CRF.
- Place in -20°C or -80°C freezer.
- Send to Biorepository on monthly basis.

10.4. Swab Collection

Study participants will be collecting swabs for the culture of the perineal (men) and vaginal (women) area.

10.4.1. Swab Collection Schedule

- Swabs will be collected at the baseline clinic visit only.
- The swabs must be collected prior to obtaining any urine specimens. (Betadine or sterilizing soaps used for urine catheterization and/or clean catch voids could affect results.)
- If the specimen is obtained the same day as a gynecological exam, both vaginal and urine specimens should be obtained prior to the vaginal exam. (Ideally,

subjects should refrain from placing anything in the vagina for 48 hours prior to having specimens taken.)

- For women who are menstruating, the visit must take place at least 48 hours after menstrual flow ends.
- During the 48 hours before specimen collection, the subject should try to avoid:
    - Vaginal sexual activity (for women), or vaginal, oral, and anal sexual activity (for men)
    - Douching
    - Feminine sprays
    - Genital wipes
- Patients should also avoid the following for at least 7 days before the specimens are obtained:
    - Use of spermicides such as those in condoms or those used with diaphragms, cervical caps, contraceptive sponges
    - Vaginal or vulvar antimicrobial agents (such as antifungal medication) or wipes

10.4.2. Instructions for Swab Collection (See Appendix P.)

10.4.2.1. Vaginal Swab Collection (Female Patients)

- Physicians or Study Coordinators may perform swab, or patients may self-swab, based on individual preference.
- Separate lips of the vagina.
- Use Copan swab (for more details about Copan swabs, see **Appendix S**); do not moisten the swab with anything prior to collecting the sample.
- Swab middle 1/3 or upper 1/3 of the vagina, and rotate around vagina 3-5 rotations. (If patient feels this is too uncomfortable, leave the swab in the vagina for 5-10 seconds to ensure specimen adequacy.)
- Label the Copan tube with provided labels.
- Place in freezer at -20^{0}C.

10.4.2.2. Perineal Specimen Procedure (Male Patients)

- Study coordinators or patients can obtain.
- Use Copan swab; do not moisten the swab with anything prior to collecting the sample.
- Swab the perineal body, while avoiding the anal opening.
- Rotate the swab 3-5 rotations to ensure specimen adequacy.
- Place the swab in the Copan tube and label with provided labels.
- Place in freezer at -20^{0}C.

10.5. Urine specimens

50-100 ml urine specimens will be collected in clinic during all visits. Encourage patients to drink water to maintain adequate hydration on the morning of specimen collection visits. Male participants will provide clean-catch midstream voided specimens. Female participants will either provide clean-catch midstream voided specimens, or straight catheterization will be used to collect the specimens, based on provider choice. If possible, straight catheterization is the preferred method of obtaining urine samples in women.

10.5.1. Urine Collection Schedule

- Urine specimens will be collected at all study visits. At the baseline visit, urine should be delayed until after vaginal/perineal swabs are collected.

10.5.2. Instructions for Urine Collection

- Collect the initial catheterized or voided specimen into sterile urine collection containers.
- For female patients undergoing clean catch void for specimen collection:
    - Instruct patient to cleanse vaginal and urethral opening with antiseptic wipes. Use the first wipe to cleanse right side of the vaginal opening, the second wipe to cleanse left side of the vaginal opening, and the third wipe to clean the central portion of vaginal opening and urethral opening.
    - Patient should begin voiding into the toilet. After a *small amount* of urine has been released, place the sterile collection container under the urethra to catch the remainder of the urine. Provide the patient with at least two collection containers so that they can collect their entire urine volume.
    - Mark that each specimen is a voided specimen.
- For female patients undergoing catheterization for entire specimen collection (note that catheterization should only be used if it is standard of care for urine specimen collection/post-void residual assessment at your site), or for male or female patients undergoing post-void residual assessment:
    - Separate lips of vagina and place antiseptic cleanser on the urethra. A *small* amount of sterile lubricant may be used on the urethra or catheter tip for comfort.
    - Place sterile catheter into participant's urethra and collect urine specimen into a sterile urine container. Mark each container that this is a catheterized specimen.
- For male patients undergoing clean-catch void for sample collection:
    - Instruct patient to cleanse urethral opening with antiseptic wipes.
    - Patient should begin voiding into the toilet. After a *small amount* of urine has been released, place the sterile collection container under the urethra to catch the remainder of the urine. Provide the patient with at least two collection containers so that they can collect their entire urine volume.
- Process urine specimens as soon as possible. If processing cannot be performed immediately, samples should be placed into a refrigerator (4°C) until processing can be performed. Processing must be performed on the same day as sample collection.

10.5.3. Instructions for Urine Processing

10.5.3.1. Main Urine Specimen

- Gently sway or invert the urine specimens to ensure uniform suspensions without shaking.
- Place at least 10 mL (up to 15 mL if available) of urine into Assay Assure container and label. Place in -80°C. freezer.
- Combine remaining urine into three 50 mL conical tubes.
- Centrifuge 50mL conical tubes at 2000g for 10 min at 4°C.
- Remove supernatant #1 and keep for aliquotting. (See below.)

- Wash cell pellet with 2ml of 10% Phosphate Buffered Saline. Add PBS (up to 15ml), and gently pipette up and down to re-suspend pellet. Centrifuge again at 2000g for 10 min.
- Remove supernatant #2 and discard.
- Re-suspend pellet in 500 µl PBS. Add 1ml of PBS for total volume of 1.5 ml. Aliquot into 2ml cryovial
- Repeat process for each of the 2 remaining conical tubes. You should have 3 pellets in three 2ml cryovials.
- Pellets may not be visible or may appear as crystals at the base of the tube
- Label cryovials with barcodes.
- Freeze cryovials at -80 °C.

10.5.3.2. Additional Urine, If Remaining

- Using supernatant #1 from above (urine after 1st spin), separate into 5 ml aliquots in 5ml cryovials (6).
- Label the cryovials with barcoded labels.
- Freeze cryovials at -80 °C.

11. Shipping

See LURNLink Users' Manual (**Appendix M**) for information on creating a shipping manifest. One copy of the manifest should be sent with each shipment. A second copy should be stored at your site for record-keeping purposes.

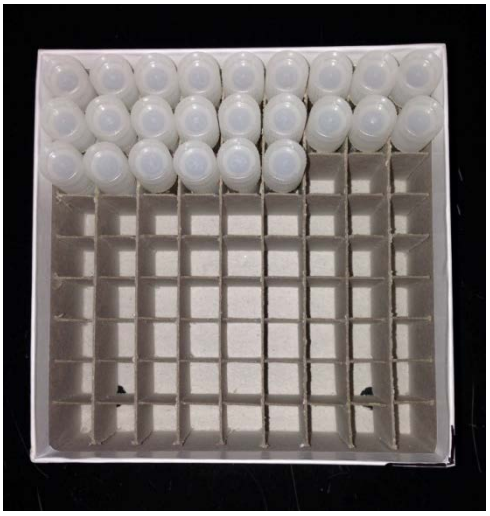
11.1. NIDDK Biorepository Shipments (All Bio specimens)

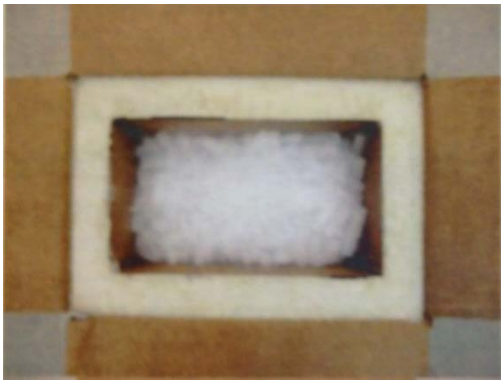
All frozen specimens (blood/urine/saliva/swabs) should be shipped on a monthly basis to the NIDDK biorepository using the provided airbill. **Specimens should be shipped on dry ice.**

The shipment address pre-populated on the FedEx air bill is as follows:

Heather Higgins Phone: 240-793-0353
NIDDK Biorepository
Fisher Bioservices
20301 Century Boulevard, Bldg. 6, Suite 400
Germantown, MD 20874

Assembling the LURNRepository Shipper:

1. Place up to 81 x 2 mL cryovials in each 2-inch high specimen box. Place the vials in the specimen box from left to right, top to bottom. Group vials by patient and visit. (If you need taller boxes and tuck-and-fold envelops contact the repository)	
2. Place each specimen box and an absorbent sheet (included) inside a plastic biohazard bag (part #STP711). Seal the bag.	
3. Place each plastic bag inside a white tuck-and-fold envelope (part #STP714). Place the box inside the long pocket of the envelope. This will be a snug fit.	

4. Crease the envelope near the middle, fold the envelope over and tuck the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. This will be a snug fit. 5. Push the box firmly into the short pocket of the envelope.	
6. Place a thin layer of ice in the bottom of the shipping box. Place up to six specimen boxes with cryovials on the dry ice.	
7. Fill the remaining space in the shipper with dry ice, leaving about 3 inches of space at the top of the foam insert.	

8. Place the foam insert on top of the dry ice in the opening. Set a copy of the shipment manifest on top of the foam insert. Close and tape the outer box.

9. Attach all shipping labels to the same side of the box.
- On the Class 9 dry ice label, enter the following: "1" next to "Number Pkgs" and the weight of the package in kilograms; weight of dry ice in kilograms; shipper's name and address; consignees' name and address.
- Affix the Class 9 label to the side of the box in the upper right corner.
- Affix your organization's "From" address label just to the right of the "Up" arrows.
- Affix the repository "To" address label just below the "From" address label.
- Affix the UN 3373 label below the dry ice label. Orient the label as a diamond.
- Affix a label with "Person Responsible" and the name and phone number of the person responsible for the shipment. Place the label below the repository "To" address label.
- Labels should not overlap each other or wrap around a corner of the box.

10. Complete the pre-printed FedEx air bill to ship specimens to the NIDDK Biosample Repository.
- Section 1, From: Enter the date of shipment, your name, phone number, and return address. Leave "Sender's FedEx Account Number" blank.
- Section 6, Special Handling: Check "Yes, Shipper's Declaration Not Required." Check the block next to "Dry Ice" and enter "1" and the weight of dry ice in kilograms.
- Section 7, Payment: Enter "1" under "Total Packages" and the total weight of the package in pounds.
- Follow the peel-and-stick instructions on the back of the air bill. Affix the air bill to the left of the UN3373 label.

11. If your organization does not have a daily scheduled FedEx pickup, call FedEx at 1-800-Go-FEDEX (1-800-463-3339). Give them the account number on the preprinted FedEx

air bill (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. **Please schedule shipments Monday through Wednesday to avoid weekend shipment delays. Ship all samples via FedEx Priority Overnight service. Do not ship samples on Thursday and Friday. The NIDDK Biospecimen Repository is closed on weekends.**
12. Send a shipment notiification to the repository at **bio-niddkrepository@thermofisher.com** on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number, and attach an electronic copy of the shipment log as an excel or CSV file.
13. Contact the repository by email at the above email address, or call Heather Higgins (240-686-4703) or Sandra Ke (240-686-4702) for questions regarding packaging and shipping.

12. DATA MANAGEMENT

The DCC has a comprehensive security plan for LURN Prospective Observational Cohort Protocol study data. The robust security plan was prepared with extensive consultation and has been approved by the Health Resources and Services Administration (HRSA). The security plan is based on the Privacy Act, the Computer Security Act, and OMB Circular A-130.

12.1. Gathering Data

- Data should derive from source documents. Source documents are original documents (the first place the information was recorded) that serve as the “raw data” for a study. Source documents include (but are not limited to) research clinic records, subject diaries, and recorded data from automated instruments.
- Data on race/ethnicity can be collected by asking the subject directly for the information. Write an anecdotal note regarding the conversation to use as a source document, and file in the subject’s research file.
- Keep in mind: **“If it is not written down, it did not happen.”**
- If you have questions about the meaning of a question or data element, you should contact the DCC monitors for the definition. The goal is to keep interpretation of data elements consistent so that data collected can be properly analyzed and interpreted.
- If you have questions about what a notation means on a chart, please contact your site PI for a definition and interpretation.
- All essential study documents must be retained by the investigator in a participant’s binder and generally include the following:
    - Source documents;
    - Signed consent forms;
    - Questionnaires completed by the participant.

12.2. Data Timeliness

- All screened patients, should be entered into the Census Page of LURNLink, which will function as the site's screening log. Sites will not be credited with recruitment, screening, or consent of individuals unless the data has been entered into LURNLink.
- The DCC will generate data for weekly enrollment reports, which will be made available for discussion on weekly calls with study investigators and coordinators.
- Information regarding whether a scheduled visit has occurred must be entered within 72 hours of the visit date.
- Information regarding whether samples were collected (yes/no; no detail) is required within 48 hours of the visit date.
- Information regarding sample collection details is required within 1 week of the visit date.
- CRF data (protocol and ad hoc) is required to be in the database within 3 weeks of the visit.
- Should the DCC generate queries to the sites, a specific time frame for resolution of the queries will be identified in the email with the attachment of the query spreadsheet.

12.3. Data Sources

- Subject Medical Records – laboratory results will be collected. Exam, lab, and procedure data will be collected.
- Subject Survey Response

13. PROTOCOL COMPLIANCE

Compliance in relation to studies is defined as adherence to all the study-related requirements, GCP requirements, and the applicable regulatory requirements.

Research studies are expensive endeavors, and every effort should be made to maximize adherence to the protocol and minimize noncompliance.

Please refer to the most recent version of the protocol to review eligibility criteria for each subject.

13.1. Protocol Deviations

A protocol deviation is defined as a variation from the protocol-directed conduct of a clinical trial. Any noncompliance with the study protocol, GCP, or protocol-specific MOO requirement is considered a protocol deviation. All protocol deviations should be reported to the DCC at LURN-Monitors@arborresearch.org.

Protocol deviations are submitted to the site's IRB/ERC as per their IRB/ERC regulatory guidelines.

13.1.1. Major Protocol Deviations

A major protocol deviation includes a deviation which impacts one of the following:

- The inclusion and/or exclusion criteria;
- The ability of the sponsor to evaluate the endpoints of the study;
- IC;
- IRB/ERC status (e.g., failure to keep IRB/ERC approval up to date).

13.1.2. Minor Protocol Deviations

A non-major protocol deviation (minor deviation) includes noncompliance with the study protocol, GCP, or protocol-specific MOO requirement that does not meet the definition for a major deviation.

Below is a list of some of the Protocol Deviations (Major and Minor) the DCC will be tracking:

- Subject enrolled, but does not meet eligibility criteria;
- Non-adherence to study design;
- Failure to obtain IC prior to initiation of study-related procedures;
- Falsifying research or medical records;
- Performing tests beyond professional scope;
- Working under an expired professional license/certificate;
- Breach of confidentiality;
- Improper or inadequate IC procedure;
- Other, specify.

Further information on protocol deviations can be found in the principals of International Conference on Harmonization Guidelines (ICH) 4.5, “Compliance with Protocol.”

Submit protocol deviation reports to your IRB/ERC per their reporting procedures. File responses to the deviation reports in the site’s Regulatory Binder under major correspondence.

13.1.3. Data and Safety Monitoring Activities

The roles and responsibilities of the entities monitoring participant safety and study quality are described in this section. All research studies supported by NIDDK must have a data and safety monitoring plan. The type of safety monitoring is determined by the size and/or nature of the study and is specified in the Notice of Grant Award.

- As indicated in RFA-DK-11-026 (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-11-026.html), an independent EEP has been established by the NIDDK. The EEP will provide scientific oversight and advice for the duration of the Network. The Panel reports to the NIDDK. The NIDDK may seek advice about the design of studies proposed by LURN investigators and their conduct from other stakeholders, if necessary.

  The major responsibilities of the EEP are to:

- Review all study protocols prior to implementation for their likelihood to achieve the overall goals established by the NIDDK;
- Evaluate study progress;
- Review ancillary study proposals (if applicable) prior to implementation;
- Monitor the safety of study participants.

Additional information on committee meetings, expertise of members, and general operating procedures can be found in **Appendix B**.

13.1.4. Study Termination and Completion

Study closeout activities are performed to confirm that the site investigator's obligations have been met and post-study obligations are understood. Examples of closeout activities include, but are not limited to the following:

- Verification that study procedures have been completed, data have been collected;
- Comparison of the investigator's correspondence and study files against the DCC's records for completeness;
- Assurance that all data queries have been completed;
- Assurance that correspondence and study files are accessible for external audits;
- Reminder to investigators of their ongoing responsibility to maintain study records and to report any relevant study information to the NIDDK;
- Assurance that the investigator will notify the IRB/ERC of the study's completion and store a copy of the notification;
- Preparation of a report summarizing the study's conduct;
- Participant notification of the study completion.

Subjects may be prematurely terminated from the study because of withdrawal of consent, failure to return (lost to follow-up), etc. Every attempt will be made to follow subjects who prematurely terminate from the study. Remember to provide documentation of the withdrawal or missed event and file in the subject's research file/binder.

13.2. SAE Reporting

Only report SAEs related to the protocol mandated procedures:

- Phlebotomy
- Perineal or vaginal swab collection
- Saliva collection
- Urine sample collection
- Survey response

If a medical problem occurs during a procedure that is both clinical and research-related, it is not considered a study SAE unless it can be solely tied to the research component of the

procedure (i.e., phlebotomy for clinical labs and biosamples during which patient faints and hits his head).

For an event to be considered as an SAE, one or all of the following must apply:

- Death
- Life-threatening
- Persistent or significant disability/incapacity
- Required in-patient hospitalization or prolonged hospitalization
- Congenital anomaly or birth defect
- Important medical events requiring medical or surgical intervention to prevent one of the outcomes listed above

The SAE reporting window for each subject begins with the first study procedure and ends 30 days after last study procedure.

SAEs must be reported to the DCC within 24 hours of the site's awareness of the occurrence. The site should complete the SAE report form in LURNLink within this time frame. Once you save the form, notification will immediately be sent to the DCC, EEP, and NIDDK personnel. Refer to the WHO grading scale (**Appendix G**) for assistance in determining events qualifying as SAEs.

13.3. Confidentiality Procedures

It is the responsibility of the study leadership to outline and enforce participant and study data confidentiality policies. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals, unless a release is approved by study leadership and NIDDK and is not in violation of applicable federal and state laws.

The following is a list of study participant confidentiality safeguards.

- **Data flow procedures:** Data identifying participants should not be transmitted from study sites to the DCC. Identifiers include, but are not limited to participant name, name code, hospital chart, record number, Social Security Number, address, or other contact information.
- **Electronic files:** Data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file.
- **Forms:** Forms or pages containing personal identifying information should be separated from other pages of the data forms.
- **Data listings:** Unique identifiers should not be included in any publishing data listing.
- **Data distribution:** Data listings that contain participant name, name code, or other identifiers should be stored and disposed of in an appropriate manner.
- **Data disposal:** Computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
- **Access:** Participant records should not be accessible to persons outside of the study without the express written consent of the participant.
- **Storage:** Study forms and related documents retained both during and after the study completion should be stored in a secure location. If computers are used to store and/or

analyze clinical data, the DCC or the investigator must address the following elements of computer security so that the data remains confidential:

- Compliance with Standards Regarding Data Security (HIPAA and 21 CRF Part 11).
- All servers, web servers, firewalls, etc. are configured and maintained according to industry best practice guidelines for back-up security, continuity of operations, and protection of Protected Health Information (PHI).
- There is a comprehensive security plan (at the sites and the DCC) in place for storage of electronic files, audiotapes, etc. containing all survey responses from the sites to the DCC.
- If study paper files are being stored, the minimal requirement is that investigator files are stored in lockable cabinets or in a lockable room. When not in use, or when unattended, the cabinets or room in which the files are located should be locked to assure confidentiality and security of information contained therein.
- Duplicate data types should be stored in a fire-proof safe or in an off-site storage facility.
- Study-related data should be stored in conditions that minimize the risk of damage or loss of information.

13.4. Retention and Study Documentation

The length of time all study files are to be maintained according to NIH policy requires that studies conducted under a grant retain participant forms for 3 years, while studies conducted under contract must retain participant forms for 7 years. Individual IRBs, institutions, states, and countries may have different requirements for record retention. Investigators should adhere to the most rigorous requirements and should retain forms and other study documents for the longest applicable period.

Following final analyses, the DCC will send study-related data to the NIDDK Data Repository, a research resource by the NIH. The Repository will store and distribute data from people with LUTD. After the LURN study ends, the participants in the study will not be able to withdraw their data because the Repository will not know which data is participant-specific. The participant data and all study-related data will stay in the Repository indefinitely.

Researchers who plan to use data from the study will be required to request and receive all of the necessary approvals or waivers from the NIDDK and study investigators before gaining access to the data. Data will only be released to scientists who are qualified and prepared to conduct a research study.

13.5. MOO Maintenance

The MOO is maintained and will be updated throughout the study by the Clinical Study Process Manager at the DCC as major changes in procedure occur during the course of the study. The updated version of the MOO will contain a new version number and change in date visible in the footer of each page of the document to facilitate any changes and/or additions. The MOO should be available in loose-leaf form to all site staff participating in the conduct of the study. The MOO will serve as a history of the project, documenting the time and nature of any changes in procedures and policies. The updated MOO will be distributed by the DCC to the sites.