
# Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

# Qualitative Assessment of Lower Urinary Tract Dysfunction Study Protocol 1

## Manual of Operations
## Version 5.0

## August 13, 2015

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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 LURN Protocol 1, Qualitative Assessment of Lower Urinary Tract Dysfunction Study. 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 Protocol 1. Details not outlined in the protocol are in this manual. 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. Study Organization and Responsibilities

The goal of the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) is to increase our understanding of lower urinary tract dysfunction (LUTD) by 1) improving the measurement of patient experiences of LUTD; 2) identifying and explaining the important subtypes of LUTD; and 3) disseminating data, research tools and biosamples to the research and clinical communities. This increased understanding of LUTD can inform strategies to prevent and/or manage disease and thus improve the lives of patients who suffer from the symptoms of LUTD.

The network plans to create a state-of-the-art resource for measuring patient-reported health for patients with lower urinary tract dysfunction (LUTD). In order to learn more about the dysfunctions of the lower urinary tract, the project will include a group of clinical centers and a DCC to study a number of causes and risk factors for LUTD in men and women.

The LURN Network 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.

This LURN Protocol 1 represents the first protocol of the LURN project. The study 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 gender), track temporal trends, or describe patterns of clinical care and treatment in absence of specific study-mandated interventions."

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

## 1.3.1. Data Coordinating Center (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/).

### 1.3.1.1. DCC Contact Information

- Robert M. Merion, MD, FACS, Principal Investigator – bob.merion@arborresearch.org, Phone: 734-665-4108
- Suzanne Kapica, Project Manager – Suzanne.kapica@arborresearch.org , Phone: 734-369-9864
- Peg Hill-Callahan, Clinical Study Process Manager – peg.hill-callahan@arborresearch.org, Phone: 734-369-9674
- Tim Buck, Study Monitor – jtimothy.buck@arborresearch.org , Phone: 734-369-9958
- 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 email to ensure timely responses.

## 1.3.2. Clinical Sites and Principal Investigators

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

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 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 survey communication.

| Centers | Site Numbers |
|---|---|
| Duke University | 01 |
| Northwestern University | 02 |
| University of Iowa | 03 |
| NorthShore University Health System | 07 |

### 1.3.2.1. Role 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, IRB, 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.

## 1.3.3. 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 EEP Membership List (**Appendix B**) for additional information regarding the EEP.

### 1.3.4. 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), calendar of events, and study directory.

### 1.3.5. 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 Rachel Marsden (rachel.marsden@arborresearch.org/734-369-9676) at the DCC.

# 2. IRB SUBMISSION AND REGULATORY DOCUMENTS

Essential documents are those documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and the monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory standards. The 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 Institutional Review Boards (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 (a written description of a change(s) 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

Protocol-specific consent document templates 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 Templates.

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 seven steps below must be completed prior to submitting any consent documents to the IRB.***

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 return the reviewed/edited draft IC documents to the site.
3) The site will make the required changes to the consent forms, and send the revised consents to the DCC for re-review.
4) The DCC will forward the draft IC documents to the NIDDK Repository reviewer for review of the particular NIDDK Repository language.
5) The NIDDK Repository reviewer will send their comments to the DCC as to whether the consents have NIDDK approval or need changes made in the consent documents.
6) The DCC will notify the site of the NIDDK reviewer response to the review of the consents. If further changes are requested by the NIDDK, the site makes the consent changes, and sends the consents to the DCC lead clinical monitor for review and approval.
7) If the NIDDK reviewer approves the consents, the DCC will send the notification to the site who will submit the consent documents to its respective IRB.
8) The IRB may require changes to the consent form(s). Please forward requested changes to the DCC lead clinical monitor for review prior to resubmission to the IRB.
9) The IRB 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 members. The memo should state that approval has been granted to open or continue the study.

10) The site will send a copy of the IRB approval and copies of the IRB approved consents to the DCC lead clinical monitor.
11) The DCC will then forward the site IRB 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.
12) The NIDDK Repository reviewer will send the NIDDK approval letter to the site PI and a copy at the DCC.
13) The site will file the NIDDK approval letter in their regulatory file.

File the IRB-approved consent documents (memo, consent, and other documents) in the site regulatory binder. Scan all IRB 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 annual renewal.

The DCC will send their annual IRB 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 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 Vitaes (CVs), regulatory documents, etc., then 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/Ethics Research Committee (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 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 Approvals in the Regulatory Binder.

2) **Curriculum Vitae (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 Approval**

- Documentation of the provision of IRB review and approval of the protocol ensures that the study is conducted with the appropriate local regulatory oversight. IRB approval will be obtained prior to the initiation of the study, and maintained throughout the conduct of the study and data analysis phase. Sites should maintain current IRB approval until directed by the DCC to close the study.
- All IRB 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 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 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 should be addressed to the PI and should include the following information:
  - Protocol title, number, and version;
  - Actual date of IRB approval;
  - Specifically state approval of the protocol;
  - IRB 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 approval.

5) **IRB Membership List**

- The IRBs 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 is in compliance with GCP.
- IRB membership list must be current.

- If your IRB does not release its membership list, a DHHS Multiple Assurance Number must be submitted on the IRB letterhead.
- If the IRB does not allow access to their membership list, then an anecdotal note must be written to reflect the standard operating procedure of the IRB and the note must be filed in the regulatory binder.

6) **Screening Logs**
   - Maintain electronic screening logs throughout the course of the study.
   - Screening logs contain information (including reason for failure to screen) regarding all potential participants approached for participation in the study and the outcome of that encounter. Please refer to Section 7 for further details about eligibility. Interview screening logs will also be utilized in the study and details on the logs can be found in Section 4.1.1.

7) **Roles and Responsibilities**
   - Contains the list of all study personnel who are involved in the primary conduct of the study at the site. It documents responsibilities assigned to research team members and their dates of involvement in the project. It 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.
   - Maintain a list of all study personnel on appropriate form and 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. Included in MOO as **Appendix E**.

8) **Human Subjects Research 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. The course title, student's name, and dates of completion and expiration (if applicable) must be on the certificate. A brief description of the course must also be placed on file. 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.

9) **Safety Reporting – Serious Adverse Event (SAE)**
   - There will be no need for SAE reporting in this observational study.
   - Participants in the study will be told as part of the IC process that they may drop out of the study if they experience any discomfort.

10) **Major Sponsor, DCC, and IRB Correspondence**

- Maintain a copy of all correspondence (e-mails, 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 e-mail);
    - Protocol deviations;
    - Protocol modifications;
    - EEP roster and letters from the Project Officer.
- Maintain a copy of all pertinent communications with the IRB relating to the study (e.g., Study Hold, Removal of Subject, Protocol Deviation, and Notice of Final Study Report).

11) **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 (rachel.marsden@arborresearch.org) and file the original in this section.

12) **IRB-Approved IC Forms**

- Maintain copies of the original IRB approval and any subsequent IRB 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 approval letter with the IC if the IRB does not stamp the document.
- IRB 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 prior to use.

13) **Advertisements/Educational Materials**

- After IRB 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 approved and clearly listed on IRB approval letters/notices.

CVs, medical licenses, IRB approvals, laboratory certifications/accreditations (if applicable) should be kept current. Current copies of required documents (IRB approvals) should be forwarded electronically to the DCC when available. The DCC will assist sites in monitoring annual IRB 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;
- Study-specific procedures (Interviewing process, conducting WRAT reading subtest, etc);
- Use of LURN Website;
- Use of Box for sending secure audio files and completed questionnaires.

**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 trial 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 Protocol 1. Since the study is observational, and there are no research procedures that will produce SAEs, reporting will not be necessary as there are no anticipated SAEs during the conduct of the trial.

Monitoring is the act of overseeing the progress of a study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s). Monitoring will be conducted via 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. Screening logs will be monitored on a weekly basis by the DCC.

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.

## 4.1. Monitoring of Site Specific Information

### 4.1.1. Screening Logs (Clinician, Qualitative, and Cognitive)

- The completed screening logs should be emailed by the sites to the DCC (LURN-Monitors@arborresearch.org) every Friday of each week.
- Sites should include the date of the submission of the screening logs in the naming of the document in addition to the name of the site sending the logs.
- The DCC will review the screening logs and acknowledge receipt of the screening logs through an email to the sites.
- If no screening has taken place at the site, enter a note on the log to indicate no screening/interviewing for the week and send to the DCC.
- The DCC will query the sites should any questions arise following review of the screening logs.
- If the screening log must be revised, the site responsible for the log will revise the log and send back to the DCC with the new revision date in the naming of the screening log.
- Screening log information will be collated by the DCC and entered into separate spreadsheets for each of the interviews (clinician, qualitative, and cognitive).
- The screening logs will be reviewed by the Self-reported Measures Workgroup and the Project Executive Committee (PEC) on a weekly basis.
- Particular attention will be paid to recruitment issues and racial and ethnic diversity to ensure there is at least 25% of the interviews being conducted involve non-white race or Hispanic/Latino ethnicity.
- Refer to **Appendix G** for the screening log templates.

### 4.1.2. Interview Questionnaires (Clinician, Qualitative, and Cognitive)

**Clinician Questionnaires**

- The DCC will provide a fillable interview questionnaire for the clinician interviews (**Appendix H**).
- Clinicians will be asked to list and identify the most important and prevalent LUTD symptoms and concerns using open-ended queries
- An interviewee from Northwestern and NorthShore University Health System will conduct the clinician interviews and document the results on a clinician survey form (LURN Protocol 1 – Appendix A) while also recording the interview.
- Themes, symptoms and concerns provided by the clinicians (physicians, nurses or physician assistants) will be reviewed during the Self-reported Measures Workgroup teleconferences.
- The completed questionnaires should be sent through Box to the DCC every Friday. Refer to **Appendix I** for Box instructions.
- Audio recordings will be transcribed at the DCC.

**Qualitative Questionnaires**

- The DCC will provide a fillable interview questionnaire for the qualitative interviews (**Appendix H**).
- The LUTS Tool will be utilized in the qualitative interviews and the interviewee will be asked to rate how much each symptom bothers them on a sale of 0-10 with 0 being no bother and 10 being the highest possible bother.
- Two interviewers at Northwestern, University of Iowa, Duke University and NorthShore University Health System will conduct the qualitative interviews and document the results on a qualitative survey form (LURN Protocol 1 – Appendix B) while also recording the interview.
- Following each interview, audio recordings, scanned copies of interivew notes, and scanned copies of the LUTS Tool will be sent to the DCC through Box.
- Audio recordings will be transcribed at the DCC.

**Cognitive Questionnaires**

- Interviewers at Northwestern, University of Iowa, Duke University and NorthShore University Health System will conduct the cognitive interviews and document the results on a cognitive survey form (LURN Protocol 1 – Appendix C) while also recording the interview.
- Following each interview, audio recordings and scanned copies of interivew notes will be sent to the DCC though Box.
- Audio recordings will be transcribed at the DCC.

# 5. OBTAINING & DOCUMENTING INFORMED CONSENT

## 5.1. Informed Consent Process

A signed IRB-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 their 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.

The IRBs at Northwestern and NorthShore University Health System have indicated that clinicians will not need to sign an informed consent prior to their participation in the Clinician Survey (Project 1A) portion of Protocol 1.

### 5.1.1. Definition of Screening Statuses

1) *Agreed (Eligible)*: The subject meets the eligibility criteria, agrees to participate to the study, and signs the approved study consent.
2) *Refused (Eligible, declined participation)*: The subject meets the eligibility criteria for the study, but refusals to participate in the study.

3) *Not Approached (Eligible, Lost to Follow-up)*: The subject meets the eligibility criteria, contact is attempted and the subject cannot be found.
4) *Not Eligible*: The subject does not meet the eligibility criteria (if not eligible, please give reason).
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 the subject population. In the case of uncertainty on the part of the PI, the site's IRB should be consulted.

### 5.1.3. Consenting Non-English Speaking Subjects

Subjects who cannot speak English are specifically excluded from the LURN Protocol 1.

## 5.2. Documentation

Site personnel must document in the subject's medical record that the participant has signed the informed consent, met enrollment criteria, and was enrolled into the LURN Protocol 1 study. If the participant is recruited from the community, then the above documentation should be included in a participant's research record created for this 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 C** 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 to be 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, and be reviewed and signed by the study participant in addition to reviewing and signing the consent form. The format of the HIPAA authorization is established by the site's local IRB. 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 Protocol 1 study will have a unique subject identification number. Physicians and healthcare providers who participate in the clinician interviews (Protocol 1A) will be assigned an ID number starting with the letters CL. Individuals who participate in the qualitative interviews (Protocol 1B) will be assigned an ID number starting with the letters QL, and individuals who participate in the cognitive interviews (Protocol 1D) will be assigned an ID number starting with the letters CG.

Every ID number will have four digits after the two letters. Participants recruited by Duke University staff will be assigned consecutive numbers 1000 through 1999. Participants recruited by Northwestern University staff will be assigned consecutive numbers 2000 through 2999. Participants recruited by the University of Iowa staff will be assigned consecutive numbers 3000 through 3999. Participants recruited by NorthShore University Health System will be assigned consecutive numbers 7000 through 7999.

# 6. PROTOCOL & APPENDICES

Please refer to **Appendix A** for the LURN Protocol 1 and associated appendices.

## 6.1. Study Design

### 6.1.1. Clinician Survey (Project 1A)

Primary Care Physicians (including Internal Medicine and Family Practice Specialties) will be interviewed about their clinical experience with LUTD patients to document the concerns of these patients.

Interviews will be conducted either in person or over the telephone.

Clinicians will be asked to list and identify the most important and prevalent LUTD symptoms and concerns using open-ended queries. Clinicians will also be asked to help generate patient-friendly language for symptoms. An interviewer from Northwestern University and NorthShore University Health System will conduct the clinician interviews and document the results on a clinician survey form (LURN Protocol - Appendix A). Themes, symptoms, and concerns provided by the clinicians (specialty clinicians, primary care physicians, physician assistants and nurses) will be reviewed during the Self-reported Measures Workgroup teleconferences. New items will be created for areas that are not covered by existing tools. Interviews will be audio-recorded and transcribed. Copies of recordings and transcriptions will be sent to the DCC via the secure online file-sharing system Box (see **Appendix I**). Clinicians will be compensated $125 for participation.

#### 6.1.1.1. Recruitment and Screening

The clinicians needed for this phase will be recruited from the professional networks of the LURN investigators and will reflect geographic diversity. Eligible clinicians must meet the criteria as outlined in Section 7.1.1.

# 7. ELIGIBILITY CRITERIA

## 7.1. Clinician Survey (Project 1A)

### 7.1.1. Eligibility Criteria – Clinician Survey

- 6 physicians with a urology-related specialty (e.g., urology, urogynecology)
  - 3 who treat mostly men;
  - 3 who treat mostly women.
- 5 Primary Care Physicians (including Internal Medicine and Family Practice Specialties)
- All participating physicians must meet the following criteria:
  - Board Certified;
  - Practice more than 5 years;
  - Evaluates more than 5 patients a week with LUTS (including men and/or women).
- 4 nurses or physicians assistants who work in urology clinics
  - 2 who work mostly with men;
  - 2 who work mostly with women.

### 7.1.2. Clinician Screening Log

- A screening log will be utilized to capture potential clinical staff (specialty physicians, primary care physicians, and health care providers) approached for the Clinician Survey (Protocol 1A) portion of the study at Northwestern University (NU), and NorthShore University Health System.
- Screening log contains information (including reason for failure to screen) regarding all potential clinical staff approached for participation in the study and the outcome of that encounter.
- Click on the appropriate answers found in the drop-down list in each of the columns when completing the screening log. The comment column allows for free text. This enables the DCC to filter/sort clinician information in the log for the collation of data for the weekly LURN Clinician Enrollment Report.
- The screening log will contain the following details:
  - Initials of person screened (First, Last);
  - Date approached (MM/DD/YYYY);
  - Subject type (physician, nurse, or physician assistants);
  - Specialty (mostly male, mostly female, or primary care);
  - Practicing at least five years? (yes or no) - FOR PHYSICIANS ONLY;
  - Board Certified? (yes or no) - FOR PHYSICIANS ONLY;
  - Evaluates at least five patients per week with LUTS? (yes or no) - FOR PHYSICIANS ONLY;
  - Works in a urology clinic? (yes or no) - FOR NURSES ONLY;
  - Age (in years, enter 998 if unanswered);
  - Gender (female or male);
  - Race (choose from drop-down list);
  - Ethnicity (choose from drop-down list);
  - Eligible (yes or no);
  - Consent status (If not enrolled, Reason);
  - Clinician, LURN subject ID number (CL####);

- Initials of study coordinator who screened the individual;
- Scheduled date of interview;
- Actual date of interview (fill in when interview has occurred);
- Study coordinator comments.

**Once eligibility of the individual has been determined, a unique Study ID can be assigned. The Study ID will be assigned by the institution recruiting the individual (refer to Section 5.4 and copy).**

- Enter Sample Screen Status Codes in the column under header "Screening Status."
  - There are screening log definitions which define the outcome of potential subjects for enrollment into the LURN Protocol 1 study. Definitions are as follows:
    1) *Agreed (Eligible)*: The clinician meets the eligibility criteria, agrees to participate to the study.
    2) *Refused (Eligible, declined participation)*: The clinician meets the eligibility criteria for the study, but refuses to participate in the study.
    3) *Not Approached (Eligible, Lost to Follow-up)*: The clinician meets the eligibility criteria, contact is attempted and the expert cannot be found.
    4) *Not Eligible*: The clinician does not meet the eligibility criteria (if not eligible, please give reason).
    5) *Other*: When this option is used, a comment must be entered onto screening log.
  - A number of columns in the screening log have drop-down choices under the column header which should be used when entering the data in the log.
- The DCC will provide separate electronic (Excel) files of the blank screening logs for the clinical interviewee (specialty clinicians, primary physicians, physician assistants, and nurses) to each site.
- Include the name of the site and the date of the log (submission date of the screening log to the DCC).
- The completed clinician screening log should be emailed to the DCC (LURN-Monitors@arborresearch.org) every Friday of each week to facilitate enrollment tracking across sites.
- It is imperative the DCC receives the clinician screening logs every Friday. Enrollment reports are generated from the data in the logs for the weekly LURN Protocol 1 Implementation conference call as well as the PEC calls and Steering Committee conference calls.
- The DCC will not accept faxed copies of the screening log. It must be transmitted electronically.

## 7.2. Qualitative Interviews with People Suffering from LUTD Symptoms (Project 1B)

Qualitative interviews will be conducted to ensure the completeness of the symptom framework of LUTD in existing self-report measures and identify new content areas that may be missing from these tools. Participants will be drawn from the clinical practices of

the Northwestern University, NorthShore University Health System, Duke University, and University of Iowa LURN investigators. All interviews will be conducted by staff at Northwestern University, NorthShore University Health system, Duke University, and University of Iowa. All interviews will be face-to-face at the sites. All participants will provide written informed consent and have an opportunity to ask questions about the study prior to agreeing to participate. A trained interviewer will use a qualitative interview guide (LURN Protocol 1 - Appendix B) to ask questions about LUTD as well as document responses. Interviews will also be audio-recorded and transcribed. Copies of recordings and transcriptions will be sent to the DCC via the secure online file-sharing system Box (see **Appendix I**). Each interview is expected to take no more than 90 minutes. The draft interview guide may be modified based on clinician input. After participation, participants will be compensated $40 using gift cards or site specific form of reimbursement (cash). The recruitment strategy and eligibility criteria are described below.

### 7.2.1. Recruitment Plan

Participants will be recruited from the clinics and local communities of LURN sites (see **Appendix J** for recruitment material templates). The following recruitment methods may be utilized:

- Flyers (e.g., in clinics, shopping centers, subways);
- Advertisements on websites;
- Directly through contact with research assistants in the clinics;
- Local health fairs.

As potential participants call in, they will speak with research assistants who will provide an explanation of the study, screen participants, and enroll subjects as they agree to be in the study.

As part of the screening interview, participants will be asked to spontaneously list their chief urologic complaints. Their open-ended reports will be compared to our symptom list in Table 1 of the LURN Protocol 1 (see **Appendix K**), to ensure that one or more symptoms are present listed.

Patients who are found to be ineligible for the study or who report symptoms for which minimum representation (see Sample section in the LURN Protocol) has been reached will be told that they do not meet the criteria for the study.

Overall recruitment and recruitment of sub-groups will be monitored weekly. Recruitment efforts will be adjusted as needed by the Self-reported Measures Workgroup if there are recruiting difficulties to certain subgroups or the minimum number of patients per symptom.

### 7.2.2. Eligibility Criteria – Qualitative Interviews

- 50% men, 50% women currently experiencing one or more LUTD symptoms based on screening.
- Within each gender, 50% of patients will be clinic referred, 50% will be drawn from the community by advertising.

- Participants from the community must not have sought care for their LUTD symptoms.
- Participants must be:
    - Currently experiencing any LUTD symptoms;
    - Willing and able to provide written informed consent and actively participate in the interview process;
    - ≥18 years of age at the time of consent;
    - Able to speak and read English.
- To ensure ethnic and racial diversity, at least 25% will be either non-White or Hispanic/Latino ethnicity.
- At least 16 participants (50% men and 50% women) will be identified as being likely to have abnormal bladder sensation, including a lack of sensation. These participants will include people with recent lower spinal cord injury, recent lower back surgery, women with a recent difficult vaginal child delivery, women with a recent radical hysterectomy, people with uncontrolled diabetes, as well as individuals age 65+.

To achieve these targets, recruitment will be halted in each of the following subsamples once the minimum targets, listed below, are reached. A total of 24 additional subjects may be recruited in any subgroups in which thematic saturation has not been reached with the original target sample size.

- 8 women with potentially abnormal bladder sensation;
- 8 men with potentially abnormal bladder sensation;
- 15 women referred from a clinic;
- 15 men referred from a clinic;
- 15 women recruited from the community;
- 15 men recruited from the community.

Members of the Self-reported Measures Workgroup will review the Qualitative Enrollment Reports on a weekly basis to review target participants recruited to date as outlined above.

### 7.2.3. Qualitative Screening Information

The study will utilize a “screening form” after contacting each potential participant for the LURN Protocol 1 study and adhere to the following directions:

1. Fill in contact name, contact information (phone number and/or email address), date of contact (initiated either by you or the potential participant), reason for unable to contact, and date(s)/times of calls.
2. Start with standard phone greeting, introduce self and confirm that you are talking to the person who expressed interest in the study.
3. Describe the study from the IRB-approved informed consent document.
4. Ask the potential participant if you can ask them a few questions to find out if they are eligible for the study. If they answer “No”, then thank them for their interest and terminate the call. The following statement should be used at any point during the call that the person is found to be ineligible: “Thank you for your answers in the study, however, based on your answers to my questions, you are not eligible to participate.”
5. If they answer “Yes,” then proceed in asking the participant the questions on the screening form.

6. If the participant is eligible, continue the screening process and inform the subject of the following:
   "Based on the answers that you just gave me, you are eligible to participate in this study. This study will consist of an interview lasting 60-90 minutes. You will receive $40 when you complete your participation in this study."
7. If the participant is not interested, thank them and terminate the call.
8. If the participant is interested, continue. "Great. Can we find time that will work for you for this study? I can send you some information about the study as well."
9. Confirm that the person's name, email address, phone number, and mailing address are on the screening form.
10. Ask the potential participant if they have any questions.
11. Answer any questions, and/or have a more senior person call the participant to follow-up.
12. Thank the potential participant for their time, tell them you look forward to talking with them in the future, and tell them to "have a nice day."

For further assistance please see **Appendix G** (screening log templates).

### 7.2.4. Qualitative Screening Log

- Each site will maintain a separate participant screening log of those participants suffering from LUTD who will be approached for qualitative interviews (Project 1B).
- Screening log contains information (including reason for failure to screen) regarding all potential subject approached for participation in the study and the outcome of that encounter. Please refer to Section 7.2.2 for further details about eligibility.
- Click on the appropriate answers found in the drop-down list found under most of the columns when completing the screening log. The comment column allows for free text. This enables the DCC to filter/sort participant information in the log for the collation of data for the weekly LURN Qualitative Interview Enrollment Report.
- The screening log will contain the following details:
  - Initials of person screened (First, Last);
  - Date of contact #1(MM/DD/YYYY);
  - Unable to contact (yes or no);
  - Date of contact #2 (MM/DD/YYYY);
  - Unable to contact (yes or no);
  - Date of contact #3 (MM/DD/YYYY);
  - Unable to contact (yes or no);
  - Age (In years, enter 998 if unanswered);
  - Literate? (yes, no, or unknown/declined to answer);
  - Gender (female or male);
  - Race (choose from drop-down list);
  - Ethnicity (choose from drop-down list)
  - Uncontrolled Diabetes (yes, no, or unknown/declined to answer);
  - Recent events (surgery, delivery, etc.);
  - Primary symptom complaint (choose from drop-down list);
  - Secondary symptoms (choose from drop-down list);

- Indication of consent status (choose status from drop-down list);
- Reason not enrolled;
- LURN subject ID number (QL####);
- Subject type (clinic sample, community sample, or special sensory sample);
- Initials of study coordinator who screened the individual;
- Study coordinator comments.

- Under the header "Subject Type", a clinic sample is defined as "a participant seeking care in clinics." A community sample is defined as "a participant who has LUTD symptoms but has not sought care." A participant with special sensory is defined as "a participant who is likely to have abnormal bladder sensations or lack of sensation." These participants will include people with a recent lower spinal cord injury, recent lower back survey, women with a recent difficult child delivery, women with a recent radical hysterectomy, underactive bladder, people with uncontrolled diabetes, as well as older individuals (age 65+).
- We anticipate community participants would see a flyer and contact the clinic.
- The study coordinator will ask if they have ever had treatment in a clinic for LUTD.
- If the potential participant says yes, he or she should be considered to be an in-clinic participant, regardless of whether the clinic they had been to was a LURN clinic.
- Enter Sample Screen Status Codes in the column under header "Screening Status."
  - There are screening log definitions which define the outcome of potential subjects for enrollment into the LURN Protocol 1 study. Definitions are as follows:
    1) *Agreed (Eligible)*: The participant meets the eligibility criteria, agrees to participate to the study, and signs the approved IRB study consent.
    2) *Refused (Eligible, declined participation)*: The participant meets the eligibility criteria for the study, but refusals to participate in the study.
    3) *Not Approached (Eligible, Lost to Follow-up)*: The participant meets the eligibility criteria, contact is attempted and the subject cannot be found.
    4) *Not Eligible*: The participant does not meet the eligibility criteria (if not eligible, please give reason).
    5) *Other*: When this option is used, a comment must be entered onto screening log.
  - A number of columns in the screening log have drop-down lists which must be used when entering the data in the log.
- The completed logs should be emailed by the sites to the DCC (LURN-Monitors@arborresearch.org) every Friday of each week to facilitate enrollment tracking across sites.
- Include the name of the site and the date of the log (submission date of the screening log to the DCC).
- The DCC will not accept faxed copies of the participant screening log. It must be transmitted electronically. Included in the MOO as **Appendix G**.

- Once the site has identified participants who meet the eligibility criteria, and have completed the informed consent process, the study coordinator schedules an interview with the participant and enters the information on the "Qualitative Interview Log."
- The Qualitative Interview Log is submitted to the DCC every Friday following the same process as defined above.
- A template interview log is included in the MOO as **Appendix G**.

## 7.3. Item Writing (Project 1C)

Item writing will occur after completion of the open-ended, qualitative phase. Prior to writing new items, the investigators will create an item library (demarcated by measure name, item ID, item context, item stem, response options, and sub-domain thematic area) which will consist of all existing questionnaires and items for which LURN has been given permission to use, or items that are free of intellectual property concerns. These items will be derived from a variety of tools (e.g., the LUTS tool, the AUA-SI). This database will be in the form of an "item matrix," which can be used to keep track of items, changes to items, and the rationale for any changes to items. The team of people writing new items will consist of LURN investigators. All members of LURN will be invited to contribute, and the team will seek guidance from specific members as needed. During working group teleconferences, potential new items identified from clinician surveys and patient qualitative interviews will be presented for review

### 7.3.1. Recruitment and Screening

Since this phase involves the item writing for Project 1D, patients will not be recruited or enrolled.

### 7.3.2. Item Matrix

See Appendix M Domain Framework

### 7.3.3. Item Writing

The principle for rewriting items will be to preserve as much as possible of the original item, but to help the item fit within the broader administration framework, and to clarify items when needed. Reasons for items to be revised are clarity, precision, acceptability to respondents and adaptation to a standard data collection format.

Item Writing Standards include:

- Each question will be written in second person, past tense
- Questions will say "in the past seven days" instead of "in the past week"

## 7.4. Cognitive Interviews (Project 1D)

Cognitive interviews will occur after completion of the open-ended, qualitative phase, as well as after the new items from the pool are added. Cognitive interviews rely on intensive verbal probing of participants by a trained interviewer after the respondents complete each item on a paper-and-pencil version of the questionnaire of interest. Interviews will be audio-recorded and transcribed. Copies of recordings and transcriptions will be sent to the DCC via the secure online file-sharing system Box (see **Appendix I**). Participants will receive $40 for this study, using gift cards or site specific form of reimbursement.

### 7.4.1. Recruitment and Screening

For this phase, recruitment and screening for subjects with LUTS will be identical to the qualitative interview phase, with one modification. After obtaining informed consent, the research assistant will present items from the LURN item pool to the patients. We will also be recruiting a population of subjects who do not have LUTS symptoms (health controls).

- After administering the cognitive interview, the research assistant will administer the Wide Range Achievement Test (WRAT) Reading Subtest to the participant. See **Appendix L** for the WRAT Reading Subtest Guidelines, administration, and scoring information.
    - The interviews for the literacy assessment will need to be face-to-face, and not by phone as the WRAT cannot be administered by phone.
- Each item that is part of the cognitive interview will be reviewed by at least two individuals with low literacy, defined as a reading level less than ninth grade using the WRAT-4 Reading subtest.
- Every item will be reviewed by at least 1 White and 1 non-White participant.
- Each interview will include approximately 35 items.
- Participants will read and answer one item at a time, after which they will be asked to provide feedback on response categories, time frame, item interpretation, applicability, and overall impression of the items.
- Cognitive interview are expected to last less than one hour.
- Interviewers will summarize their findings from each interview.

#### 7.4.1.1. Eligibility Criteria – Cognitive Interviews Participants with LUTS

- 50% men, 50% women currently experiencing one or more LUTD symptoms based on screening.
- Within gender, 50% of patients will be clinic referred, 50% will be drawn from the community by advertising.
- Participants must be:
    - Currently experiencing any LUTD symptoms;

- Willing and able to provide informed consent and actively participate in the interview process;
- ≥18 years of age at the time of consent;
- Able to speak and read in English.

- To ensure ethnic and racial diversity, at least 25% of the sample will be non-White.
- Each item must be reviewed by at least two individuals with low literacy, defined as a reading level less than ninth grade using the WRAT- 4 Reading subtest.
- Participants who complete cognitive interviews cannot be the same individuals as those in the qualitative interview phase.

To achieve these targets, recruitment will be halted in each of the following subsamples once the minimum targets, listed below, are reached. Additional subjects may be recruited if the number of items to be reviewed is greater than 35, or if items are revised and in need of additional testing.

- 8 women referred from a clinic;
- 8 men referred from a clinic;
- 8 women recruited from the community;
- 8 men recruited from the community.

Members of the Self-reported Measures Workgroup will review the Cognitive Enrollment Reports on a weekly basis to review target participants recruited to date as outlined above.

#### 7.4.1.2. Eligibility Criteria – Cognitive Interviews Participants with LUTS

Participants without LUTS must be:

- willing and able to provide informed consent,
- ≥ 18 years of age,
- willing and able to consent and actively participate,
- able to speak and read English, and
- free of significant LUTS. Their responses on the LUTS Tool 1-month version administered during screening will include:
  - "1-3 times a day" or "4-7 times a day" on question 2 ("during a typical day in the past month, how many times did you urinate during waking hours?"),
  - "None" or "1 time a night" on question 3 ("during a typical night in the past month, how many times did you wake up because you needed to urinate?"), and
  - "Never" or "Rarely" for every other LUTS Tool item.

Half of the participants without LUTS will be male and half will be female. At least two women and two men without LUTS will be over age 60 and at least two women and two men will be under age 40.

In addition:

1. To ensure ethnic and racial diversity, at least 25% of participants with and without LUT will be non-White.

2. Among the participants with and without LUTS, each item must be reviewed by at least two individuals with low literacy, defined as a reading level less than ninth grade using the WRAT- 4 Reading subtest.
3. Participants who complete cognitive interviews cannot be the same individuals as those in the qualitative interview phase.

#### 7.4.1.3. Cognitive Interview Screening Log

1) The Data Coordinating Center will create for sites a template Cognitive Interview Screening Form available on the LURN study website through the check-out function. Each site will utilize this form when screening for potential participants for the cognitive Interview portion of the study (Project 1D).

2) The interviewer will follow the steps outlined in the screening form describing the study to the potential participant from the IRB approved informed consent document.

3) If the subject ***agrees*** to be asked questions about their LUTD, then proceed with the questions on the Cognitive Interview Screening Form. If the potential participant does ***not agree*** to be asked questions, thank them for their interest and terminate the call.

4) If the interviewer deems the potential participant to be eligible and the individual confirms they are interested in the study, continue to gather contact information from the individual and schedule and date and time for the Cognitive Interview.

5) If the interviewer deems the potential participant to be eligible but the individual is not interested in participating in the study, the interviewer will thank the individual and terminate the call.

6) Each site will maintain a separate participant screening log of those participants suffering from LUTD who will be approached for cognitive interviews (Project 1D). The screening log contains information (including reason for failure to screen) regarding all potential subjects approached for participation to the study and the outcome of the encounters.

7) The DCC will provide an electronic (Excel) file for the Cognitive Interview Screening Log. A number of columns will have drop-down boxes providing the choices for answers which you will click on and will be populated in the appropriate field for that participant.

8) If the participant is found to be eligible, the study coordinator will assign a unique participant identification number to the individual. Individuals participating in the cognitive interviews are assigned an ID # starting with the letters "CG". Every participant ID # will have four (4) digits after the first two letters (CG)

9) Participants recruited to the study will be assigned consecutive numbers by the site's study staff as follows:
    - Duke University - consecutive numbers 1000 – 1999 (e.g. participant ID # CG1000…)
    - Northwestern University – consecutive numbers 2000 – 2999 (e.g. participant ID# CG2000…)
    - University of Iowa – consecutive numbers 3000 – 3999 (e.g., participant ID # CG3000…)
    - NorthShore – consecutive numbers 7000 – 7999 (e.g., participant ID # CG7000…)

10) Sites must check-out their Cognitive Interview Screening Log from the study website each time they have information to enter. The log should be named as follows: e.g. Name of site, Cognitive Screening Log, MMDDYYYY. The date should be the date of submission to the DCC.

11) Add newly screened participants each week to the same Excel screening log. Your list of screened individuals will be cumulative in the log from week to week.

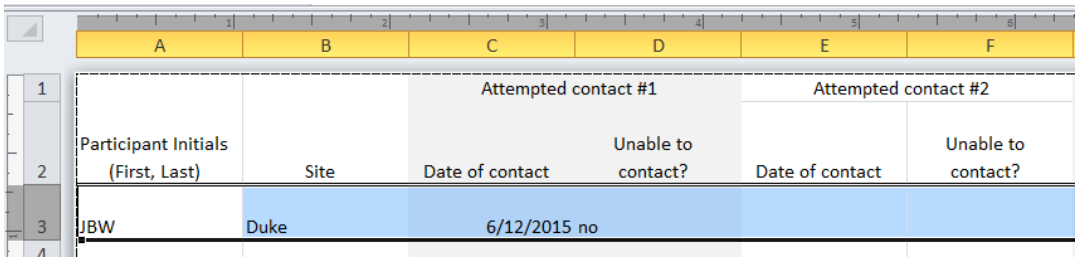
12) Save all logs at your site and check-in the Cognitive Interview Screening Log to the study website each time a new participant is screened or as often as possible.

13) Screening log contains information (including reason for failure to screen) regarding all potential subject approached for participation in the study and the outcome of that encounter. Please refer to Sections 7.4.1 and 7.4.2 for further details about eligibility.
    - Click on the appropriate answers found in the drop-down lists found under most of the columns when completing the screening log. The comment column allows for free text. This enables the DCC to filter/sort participant information in the log for the collation of data for the weekly LURN Cognitive Interview Enrollment Report.
    - The screening log will contain the following details:
        - Initials of person screened (First, Last);
        - Date of attempted contact #1(MM/DD/YYYY);
        - Unable to contact (yes or no);
        - Date of attempted contact #2 (MM/DD/YYYY);
        - Unable to contact (yes or no);
        - Date of attempted contact #3 (MM/DD/YYYY);
        - Unable to contact (yes or no);
        - Age (In years, enter 998 if unanswered);
        - Gender (female or male);

- Race (choose from drop-down list);
- Ethnicity (choose from drop-down list), If multi-racial or other, specify;
- Educational level;
- Primary symptom complaint (choose from drop-down list), If other primary symptom, specify;
- Secondary symptom #1 (choose from drop-down list);
- Secondary symptom #2 (choose from drop-down list);
- Secondary symptom #3 (choose from drop-down list);
- Other secondary symptoms, or specify “other”;
- Consent status (choose status from drop-down list);
- If not enrolled, Reason;
- LURN subject ID number (CG####);
- Subject type (clinic sample, community sample, special sensory sample);
- Initials of study coordinator who screened the individual;
- Study coordinator comments.

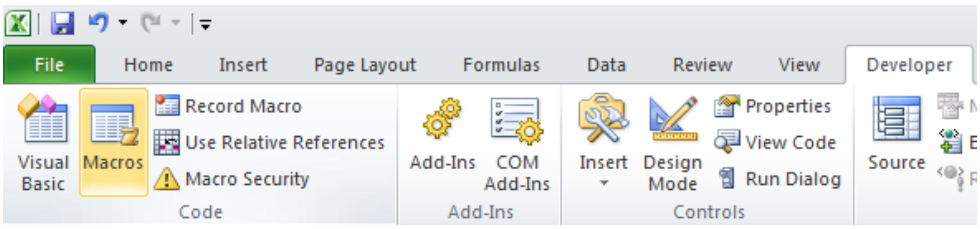
14) Once the site has identified participants who meet the eligibility criteria, and have completed the informed consent process, the study coordinator schedules an interview with the participant and enters the information on the “Cognitive Interview Log”. The Cognitive Interview log is submitted to the DCC via the study website check-in feature after the addition of each new participant following the same process as defined above.

15) After an interview has been scheduled with a participant, that participant’s questionnaire can be generated using the Cognitive Interview Screening Log spreadsheet. First, on the “Cognitive Screening Log” tab, select the row with this participant’s screening information as shown below (in this case, a questionnaire for participant “JBW” would be created):

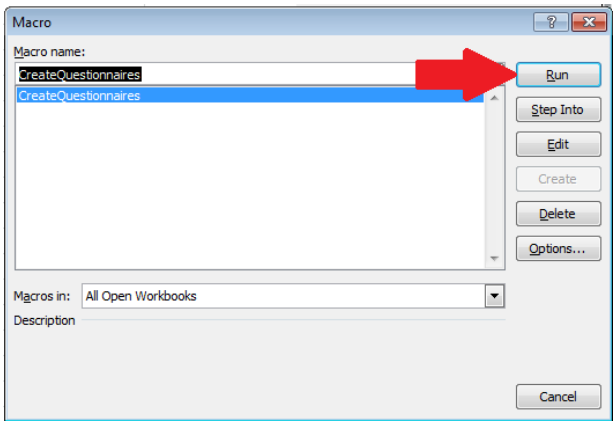


| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| 1 | | | Attempted contact #1 | | Attempted contact #2 | |
| 2 | Participant Initials (First, Last) | Site | Date of contact | Unable to contact? | Date of contact | Unable to contact? |
| 3 | JBW | Duke | 6/12/2015 | no | | |

16) Now, click on the “Developer” tab, and then click the “Macro” button:



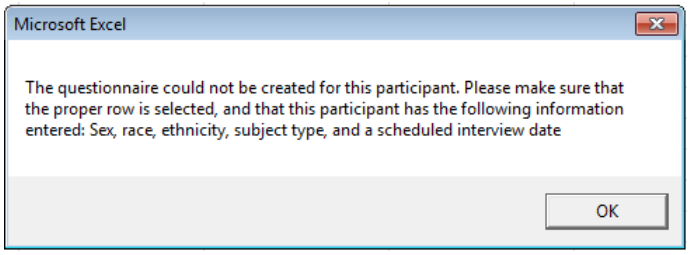

17) A window should now appear as below. Click on “CreateQuestionnaires” and then click “Run”:




18) The questionnaire sections to be given to this participant should now be populated in columns AS-BA. (Note: not all sections will be populated)

| AS | AT | AU | AV | AW | AX | AY | AZ | BA |
|---|---|---|---|---|---|---|---|---|
| 1st Section of Questionnaire | 2nd Section of Questionnaire | 3rd Section of Questionnaire | 4th Section of Questionnaire | 5th Section of Questionnaire | 6th Section of Questionnaire | 7th Section of Questionnaire | 8th Section of Questionnaire | 9th Section of Questionnaire |
| Frequency | Nighttime | Urgency | Flow | Incontinence | | | | |

19) If the questionnaire could not be created, then the following error message will appear:




Ensure that this participant has a sex, race, ethnicity, subject type, and a scheduled interview date entered into the spreadsheet. After making any appropriate changes, repeat steps #14-17.

20) Based on what is displayed in columns AS-BA, print out and combine each individual section that is shown to create the questionnaire. The individual

questionnaire sections are available on the website. Make sure that every questionnaire has the “Section 0 – Face Page” as the first page.

21) The interviewer at the site conducts the cognitive interview with the enrolled participant.

22) After the cognitive interview is completed, the research assistant will administer the Wide Range Achievement Test (WRAT) Reading Subtest to the participant. This test must be administered face-to-face. The WRAT score should be entered on the Screening Log in Column AP.

23) Following the literacy assessment, the cognitive interview recordings, and documents should be handled as follows:

- Responses from the cognitive interviews are audio-recorded at each site
- Following each interview, audio recordings, scanned copies of the interview notes will be sent to the DCC via a secure online file-sharing system called “BOX”
- Follow the “Box.com Instructions” in the document attached.
- Audio recordings will be transcribed at the DCC
- Site’s study personnel transferring the interview documents to the DCC will be provided a link to “BOX” prior to sending the materials to the DCC.

## 7.5. 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?
- When is the last time the patient was in your facility? What is the estimated interval?
- If there is a short time period (or none), then 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?

# 8. DATA MANAGEMENT

The DCC has a comprehensive security plan for LURN Protocol 1 study data. The robust security plan was prepared with extensive consultation, and has been approved by Health Resources and Services Administration (HRSA). The security plan is based on the Privacy Act, the Computer Security Act, and OMB Circular A-130.

## 8.1. 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 to file of 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, then you should 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;
    - Data Correction Forms (if applicable).

## 8.2. Data Timeliness

- Screening logs will be submitted to the DCC weekly (every Friday).
- The DCC will generate data for weekly enrollments reports, which will be made available for discussion on weekly calls with study investigators and coordinators.
- During the clinician interview, the interviewer will fill out the table of symptoms on issues described by the clinician and the importance of each symptom to patients.
- During the qualitative and cognitive interviews, audio-recorded interviews will be conducted of patients with symptoms of LUTD seeking care at one of the clinical centers and individuals with symptoms from communities near the clinical center.
- Following each interview (clinical, qualitative, and cognitive), audio recordings, and scanned copies of the interview form (with the interviewer notes) will be sent to the DCC.
- All audio-recordings will be transcribed at the DCC.
- Should the DCC generate queries to the sites, a specific timeframe for resolution of the queries will be identified in the email with the attachment of the query spreadsheet.

## 8.3. General Instructions for Completing Paper Forms

Forms created as fillable PDFs should not be printed and written on; they should only be completed and transmitted electronically.

When completing paper study forms, PRINT IN CAPITAL LETTERS using black ink. **NOTE:** participants must not be identified by name on any study document submitted with the forms if applicable.

**Header:** Complete the header information on every page, including pages for which no study data are recorded.

**Participant ID**: The participant ID must be recorded on EVERY page, including pages on which no study data are recorded.

**Time:** Use a 24-hour clock (e.g., 14:00 to indicate 2:00 PM) unless otherwise specified.

**Dates**: All dates must be verifiable by source documents. Historical dates are sometime not known (e.g., date of first symptom); therefore, conventions for missing days and/or months should be described (e.g., UNK or 998).

**Abbreviations**: Use of abbreviations not specifically noted in the instructions for completing the forms can be problematic and should be held to a minimum.

**Correcting errors**: If an error has been made on the study forms, place a single line through the erroneous entry and record the date and your initials. Indicate the correct response.

**Skipping items**: Do not skip any items. Some items may carry “Unknown” or “Not Applicable” response choices which should be selected when necessary.

**Incomplete data**: Data may not be available to complete the form for various reasons. Circle the item for which information is not available and indicate the reason near the appropriate field.

**Incomplete or illegible forms:** Incomplete forms that do not have adequate explanation compromise the integrity of the entire study. Errors, such as incomplete or illegible forms are problems that require time and energy to resolve.

**Do not leave forms incomplete or unused without explanation**.

# 9. 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.

## 9.1. 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 as per their IRB regulatory guidelines.

### 9.1.1. 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;
- Informed consent;
- IRB status (e.g., failure to keep IRB approval up to date).

### 9.1.2. Minor Protocol Deviations

A non-major protocol deviation (minor deviation) includes a deviation which 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 informed consent 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 informed consent 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."

Protocol deviation reports are to be submitted to your IRB per their reporting procedures. The response to the deviation reports are to be filed in the site's regulatory binder under major correspondence.

### 9.1.3. 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. NIDDK may also 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**.

### 9.1.4. 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 competed, 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 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.

## 9.2. SAE Reporting

There will be no need for SAE reporting in this observational study.

Participants in the study will be told as part of the informed consent process, they may drop out of the study if they experience any discomfort.

## 9.3. 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 such as 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.
    - **Box**, a file sharing system will be utilized as it adheres to the highest industry standards for security of data at every level of the Box experience.
    - The file sharing system will manage users, content folder permission, storage allocations and more in a centralized console at the DCC.

- Access permissions will be identified per group users, files and folders will be password protected, and the file sharing system will generate reports on file and user activity to get a complete audit trail.
- If study paper files are being stored, the minimal requirement is for investigator files are stored in lockable cabinets or in a lockable room. When not in use of 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.

## 9.4. 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.

## 9.5. MOO Maintenance

The MOO is maintained and will be updated throughout the study by the Lead Clinical Monitor 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 Lead Clinical Monitor at the DCC to the sites.