Patient Reported Outcomes for Bladder Management in Neurogenic Bladder and Spinal Cord Injury

Protocol Summary

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Background and Introduction

Nearly 80% of spinal cord injury (SCI) patients have urinary issues, like incontinence or increased frequency, which can have a significant burden on patients' physical health and quality of life (QoL). Inappropriate management can cause hospitalizations and serious complications like urinary tract infections (UTI) and kidney damage. The gold standard for bladder management is clean intermittent catheterizations (CIC), where patients or caregivers perform regular urethral catheterization to empty the bladder. However, this task may be difficult for patients to perform independently due to physical limitations or it's simply inconvenient. Alternatives include an indwelling catheter (IDC) that drains the bladder continuously or reconstructive surgery (to divert urine to an different location so patients can intermittently catheterize independently). However, each IDC and surgery has an increased risk of treatment specific clinical complications compared to CIC. Patients believe that both independence and ability to carry out daily activities are just as important as physical health in selecting the right bladder management strategy. The Research Team agrees that patient centered outcomes for CIC, IDC, or surgery in neurogenic bladder patients will identify methods with the lowest complication rate, best QoL, and highest patient satisfaction.

Understanding the impact on QoL, particularly on physical, mental, and social health, for these three bladder management methods and the impact of urinary-specific complications using patient reported outcomes is of particular interest for patients, caregivers, and clinicians. These factors are important for comprehensive QoL assessment among patients with neurogenic bladder and SCI as identified in previous studies and by our patient partners and stakeholders.

This is a longitudinal observational study for three different bladder management strategies for an estimated 1,500 neurogenic bladder and SCI patients. Patients will be identified and recruited at the (1) University of Utah, (2) University of Minnesota, and (3) University of Michigan (4) University of Western Ontario. To be eligible, a patient must have a spinal cord injury or neurogenic bladder with urinary issues and be using one of the three bladder management treatments (CIC, IDC or urinary reconstruction). We plan to use the Neuro-QoL developed for PROMIS, a computerized adaptive test questionnaire to assess overall QoL and the Neurogenic Bladder Symptom Score (NBSS) to capture the impact of urinary specific issues and complications on QoL. The primary and secondary aims of this study are to compare total Neuro-QoL score and total NBSS score, respectively, across the three common bladder treatments. We will also compare scores for the sub-domains of these surveys, which include physical, mental and social function for the Neuro-QoL, and Incontinence, Storage and Voiding Symptoms, Complications, and a QoL item for the NBSS. Additionally, we will determine whether complication rates for one of the three methods impact Neuro-QoL scores.

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Purpose and Objectives

Our overarching goal is to create a better understanding of patient reported outcomes for three bladder management strategies (clean intermittent catheterization (CIC), indwelling catheter (IDC), and urinary diversion surgery. We will accomplish this through the following specific aims:

1) Compare overall patient reported QoL using the Neuro-QoL and to compare subdomains of Neuro-QoL (physical, mental and social function) for three bladder management strategies: CIC, IDC, and urinary diversion.

2) Compare patient reported urinary specific bother and complications using the Neurogenic Bladder Symptom Score (NBSS) and to compare specific NBSS subdomains (Incontinence, Storage and Voiding Symptoms, Complications, and a QoL item) for three bladder management strategies: CIC, IDC, and urinary diversion.

3) To understand the relationship between complication rates and overall QoL (using the Neuro-QoL) for three bladder management strategies: CIC, IDC, and urinary diversion.

Study Population

Age of Participants: 18-100

Sample Size:
At Utah: 1,500 - 1,800
All Centers: 4,200 - 4,400

Inclusion Criteria:
Inclusion Criteria:

1. Participants with spinal cord injury.

2. Participants with neurogenic bladder.

3. Participants must be undergoing or starting at least one of the three bladder management treatments at the time of enrollment.

   a) Clean Intermittent Catheterization (CIC)

   b) Have an Indwelling Catheter (IDC)

   c) Have a Urinary Division/Bladder Augmentation

4. Age 18 or older.

5. Willingness and ability to comply with study procedures.

6. Able to provide informed consent and authorization that the participant has been informed of all pertinent aspects of the study prior to enrollment.

Exclusion Criteria:
Patients will be excluded that do not have neurogenic bladder, belong to a vulnerable population (pregnant, prisoners, mentally handicapped, etc..), or are less than 18 years of age.

Design

Survey/Questionnaire Research
Observational Research

Study Procedures

Recruitment/Participant Identification Process:

1. Participants will be recruited during clinical visits for the Division of Urology. Participants with neurogenic bladder and or spinal cord injury will be asked in clinic if they would like to participate in the study. They will be provided with information about the study. If they agree to participate a study coordinator will obtain consent and authorization and then enroll them in the study.

2. Participants will be referred from the Rehabilitation Clinic and Physical Medicine and other clinics where spinal cord injury patients are treated. In cases such as these, we will go to the respective clinic and consent the participant if possible while they are at their clinic visits.

3. We will have a study website: nbrg.org where participants can click on a link for further information about the study and also be able to take a brief survey which will determine eligibility and then also have the ability to remote consent if they desire.

4. We will also have a Facebook ad that will link to the study's website. The Facebook ad will be constructed by the University of Utah's Marketing Department.

4. Public events where spinal cord injury patients attend will also be a possible recruitment entity where we would provide information to interested participants.

Informed Consent:

Description of location(s) where consent will be obtained:

Urology Clinic Physical Medicine and Rehabilitation Clinic Other University of Utah Health Care Clinics that involved potential participants At the study website Over the phone At public events where spinal cord injury patients would be in attendance

Description of the consent process(es), including the timing of consent:

Patients will be asked if they would like to participate in the study. If they agree than they will be given a consent and allowed to fully review the consent. The consent will specify when they will be contacted and how they will be contacted during the course of the study. When patients feel they have had enough time to fully review the consent they will be enrolled in the study. This process will be the same for patients consenting over the phone, except that patients will be either emailed or mailed a copy of the consent prior to the review of the consent. For patients that are remote consenting, the consent will be on the study website.

Procedures:

This study is an observational/questionnaire study. Patients will be identified and recruited at the (1) University of Utah, (2) University of Minnesota, (3) University of Michigan and (4) University of Western Ontario, Canada. To be eligible, a patient must have a spinal cord injury and/or neurogenic bladder with urinary issues and be using one of the three bladder management treatments (CIC, IDC or urinary diversion). We plan to use the Neuro-QoL developed for PROMIS, a computerized adaptive test questionnaire to assess overall QoL and the Neurogenic Bladder Symptom Score (NBSS) to capture the impact of urinary specific issues and complications on QoL.

Baseline Visit: Patients at this visit will be approached regarding study participation. After providing consent and authorization, the patient will have about a 30 minute interview, with a clinician like a physician, nurse, or physician assistant, or a study coordinator who will obtain the medical history. We will gather the following information for our study: patient name, MRN, address, telephone, and email address. If the patient provides consent over the phone or remotely at our study website, the 30 minute interview will take place over the phone.

The patient will be asked very routine questions about his/her health, medication usage, surgical history, physical exam findings, and specifics related to bladder management, bladder health, and specifics regarding the treatments previously received for treatment of neurogenic bladder.

At the end of this 30 minutes, if the participant would like to complete the first set of questionnaires while he/she is in clinic, he/she will answer the questions on a tablet (or paper if the patient prefers) about his/her quality of life, pain and bladder management. These questionnaires should take about 10 minutes to complete. If the participant does not have the time at the current clinic visit to complete these questions, a link will be emailed to the participant, which when clicked, will take the participant to the Assessment Center, where the questionnaires will be completed. For participants who don't have a computer, who are not able to use a computer or prefer to have the questions read to them, study personnel will set up a time to call and the questions will be completed over the phone.

The patient will be asked to complete the same questionnaires that were completed at baseline, every 3 months for up to 1 year. This will be accomplished by either 1) sending the participant the questionnaire link via email 2) calling the participant and completing the questionnaire via phone 3) approaching the participant at his/her next standard of care clinic visit (if this visit falls within the 3 month window) to see if he/she would like to complete the next set of questionnaires either by paper or table. Also, there is an Exit Interview that will be given when the participant finishes the study. This Exit Interview can be sent to the participant via email with a link to the questions, or the participant can do the Exit Interview over the phone with study personnel; whichever method the participant prefers. The Exit Interview asks questions about any changes over the past year in bladder management, any surgeries that might have affected bladder management and any complications that resulted in a change of bladder management for the participants. The Exit Interview questions will take approximately 15 to 20 minutes to complete.

Data from participants that meet the study criteria and are enrolled in the study will be collected for research purposes only. A participant list will be placed on an excel spread sheet that will be stored in a secure folder on a secure drive. Access to this secure folder is only granted by the IT department upon request by the Research Manager. The excel database will contain the following information: Patient full name, medical record number, phone number, email, where consent was obtained, date of consent, date the questionnaires were sent, date questionnaires were completed and target date of future questionnaires. Data from the baseline assessment will be stored in REDCap and will include the participant's full name, address, phone number, medical record number, date of birth, email address, date of injury, previous medical history information, and current medical history information.

For the questionnaires done at baseline and then again every 3 months, the participants are sent a link, which is generated upon study enrollment with a unique participant identification number and is specific to each individual participant. The questionnaire link is sent to the participant via email, which takes them to the Assessment Center where the questionnaires are completed. Some participants will have difficulty completing these questionnaires themselves either because they don't have access to a computer or because of physical limitations. For these participants, study personnel will call them and read the questions to them over the phone. The Assessment Center

can only be assessed via the link that is sent to the participants, and no PHI is collected for the questionnaires at the Assessment Center. The participants are identified by their unique study ID only.

Termination of the project is contingent upon data analysis and manuscript preparation which should be completed in six years.

The University of Utah IRB will review this protocol and any modifications.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

The primary and secondary aims of this study are to compare total Neuro-QoL score and total NBSS score, respectively, across three common bladder treatments: CIC vs. IDC vs. Urinary diversion/bladder augmentation. While the total scores are our primary outcomes, we will also compare scores for the subdomains of these surveys, which include physical, mental and social function for the Neuro-QoL, and Incontinence, Storage and Voiding Symptoms, Complications, and a QoL item for the NBSS. We will also plan to report subgroup summaries to provide details specific to time since injury and/or treatment duration. The tertiary aim is to investigate whether the relationship between complication rate and total Neuro-QoL varies across treatment groups (i.e. is complication rate an effect modifier of the relationship between treatment group and Neuro-QoL). For this aim we will also describe and compare complication rates across bladder treatment groups.

Analysis Plan Overview:

The benefit of this longitudinal design is that it will allow us to capture QoL and complications data on a large cohort for a fairly rare condition. Furthermore, the subjects captured with this design resemble a typical patient population, where subjects present at various times since injury and with varying treatment durations. This is a typical patient population encountered in clinical practice, where the goal is to appropriately council these patients on their treatment options. Because treatment history, outcomes, and covariates are recorded only for a 12-month period and are not available prior to the baseline assessment, it is not possible under our proposed design to evaluate the causal effects of the patients' full bladder treatment histories. Rather, we will characterize the association of the QoL score and other outcomes with the patient's bladder management treatment at enrollment (CIC, IDC or urinary diversion/bladder augmentation) during the 12-month follow-up period for each patient, with adjustment for demographic factors and injury characteristics. Thus the goal for

our primary analysis for aims 1-3 is to summarize patient experiences over the 12-month period, defined by his/her treatment at enrollment (i.e., ignoring any changes in treatment). A secondary analysis for aims 1-3 will be to allow treatment group to be time varying for the 10-15% who are expected to change treatment during the course of the study. This latter type of analysis provides a more general characterization of QoL by treatment type, but it is limited in that it is more difficult to adjust for covariates -- more details are provided below.

Primary Analysis for Aims 1-2:

Our primary endpoints for aims 1 and 2 are the average of total QoL scores over time (total Neuro-QoL score and total NBSS score, respectively). For our primary analysis, these outcomes will be analyzed in a linear mixed effects regression framework, and our primary predictor variable will be the patient's baseline treatment type. Thus, even if a patient switches treatment during our study, we will ignore this change here and consider any change in QoL to just be part of a patient's typical one year experience starting from treatment X. Given that there are only five time points, it should be feasible to model within patient correlations using an unstructured covariance matrix. In these models we will evaluate the three possible pair-wise contrasts: CIC vs. IDC, CIC vs. Surgery and IDC vs. Surgery for statistical significance at the 0.017 Bonferroni-adjusted significance level. Key covariates that will be included in the aim 1-2 models are: time since injury at baseline (coded as a categorical variable with levels <1 year, 1-5 years, and >5 years), physical limitations severity (mild, moderate severe), time on bladder management strategy recorded at baseline (<6 months, 6m-1.5 years, >1.5 years), age at baseline (coded as <20, 20-30, 30-40, 40-50, >50), sex, follow-up time point and BMI. In addition, we hypothesize that interaction effects exist between treatment group at baseline and time on baseline treatment, time since injury, injury severity and patient age. This is because different treatments may have different complication rates, and longer times on a particular treatment may differ from shorter times on the treatment in terms of QoL. Similarly, patient satisfaction (and thus potentially QoL) with treatment type may vary with patient age, time since injury and injury severity. The possibility of additional pair wise interactions between treatment group and the covariates will be investigated in an exploratory fashion. Stata v.12 software will be used to extract the marginal coefficients, 95% confidence intervals (CIs) and p-values for each treatment group contrast in the presence of these interactions using the "margins" command (http://www.stata.com/stata11/margins.html). To summarize patient outcomes by treatment group, we will provide average QoL estimates and 95% CIs for some combinations of treatment group, treatment duration, time since injury, injury severity and age subcategories. While this corresponds to 3^5=243 possible different subcategory combinations, these descriptive results will be estimated from our model based on the full available sample size. Thus these results will provide a profile of expected outcomes for each treatment group given different combinations of patient and injury characteristics.

Secondary and Additional Analyses for Aims 1-2:

As a secondary analysis, we will allow treatment group to be a time-varying predictor given that patients can change treatment during the course of the study. This analysis will characterize the average relationship between treatment type and QoL. The key covariates will be the same as for the main analysis, except that we will not consider the interaction between treatment group and time on treatment at baseline, since it is no longer sensible in the context of a changing treatment group (given that time on treatment at baseline corresponds to one particular treatment).

It is also interesting to study patients who switch treatments during the 12m follow-up period. We will investigate potential predictors of switching treatment groups in an exploratory fashion, by modeling treatment change (yes/no) as an outcome and baseline treatment group as a main predictor. This will allow us to evaluate whether the rates of change during the 12 month follow-up period vary by baseline treatment group. Other potential predictors of treatment change will include time on baseline treatment, time since injury, injury severity, patient age, sex and BMI.

Finally, we will repeat the primary analysis model for each of the subscales of the two surveys (using treatment type at baseline as a primary predictor). For the subscale analyses we will plan to report the marginal coefficients, 95% confidence intervals CIs and p-values for each treatment group contrast (3 pair-wise comparisons), and statistical significance will be evaluated at the 0.017 level.

Analysis Plan for Aim 3

For our tertiary aim of evaluating cumulative complication rates (categorized as 0, 1-3, 3-5, >5) by treatment group on QoL, we will adopt a similar modeling framework as described for Aims 1-2, except that complications will be included in the model along with its interaction with treatment group. We will use a likelihood ratio test to evaluate the statistical significance of this interaction term, i.e. to answer our main question of whether or not the relationship between cumulative complications and QoL differs by treatment group. We will also provide average QoL estimates and 95% CIs for combinations of subcategories of complications, treatment group, treatment duration, time since injury, and age using Stata's margins command. We will also plan to implement the Aims 1-2 secondary analysis where treatment group is modeled as a time varying predictor. Again these models will include the additional interaction term between treatment group and cumulative complications.

While our original analysis for our PCORI grant funding specified data collection for 12 months follow-up, any additional longitudinal data follow-up would be useful and novel data for the field and will be collected as available.

A Note on Missing Data

One benefit of the mixed effects modeling framework is that our models will include all available patients even if a patient has a missing value for one or more time points. However, missing data is likely, and we will plan to use multiple imputation (MI) to investigate the sensitivity of our results to missing data (36, 37).