Manual of Operations and Procedures for The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial

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This Manual of Operations and Procedures (MOP) was originally written with the assumption that most Recruitment, Consenting, Baseline – Visit 1(V1) and End of Treatment – Visit 2 (V2) would be done in person. With the advent of the COVID-19 epidemic, this was no longer a viable option. The current version of the MOP reflects this change through the addition of provisions for conducting the Recruitment, Consenting, Visits 1 and 2 and Follow-Up Visits online. However, it remains the consensus that, wherever possible, these visits be conducted in person.

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ACRONYMS

AE	Adverse Event
CBC	Complete Blood Count
CIC	Clean Intermittent Catheterization
Co-PI	Co-Principal Investigator
CRF	Case Report Form
DSMB	Data Safety and Monitoring Board
EMR	Electronic Medical Record
HIPPA	Health Insurance Portability and Accountability Act
HSIP	Human Subject Incentive Program
ICF	Informed Consent Form
IRB	Institutional Review Board
IRBMED	Institutional Review Board Michigan Medicine
IP	Investigational Product
MICHR	Michigan Institute for Clinical and Health Research
MOP	Manual of Operating Procedures
MS	Multiple Sclerosis
MSCIS	Michigan Spinal Cord Injury System
NTF	Note to File
PI	Primary Investigator
PM&R	Physical Medicine and Rehabilitation
QoL	Quality of Life (questionnaires)
RA	Research Assistant
SAE	Serious Adverse Event
SC	Study Coordinator
SCD	Spinal Cord Disease
SCI	Spinal Cord Injury
SCR	Scheduled Continuing Review
SF	Short Form
UA	Urine Analysis
UMHS	University of Michigan Health System
UP	Unanticipated Problem
UTI	Urinary Tract Infection

1.0 Introduction

The purpose of this document is to provide the readers and potential users of this information with a Manual of Operating Procedures (MOP) template for Principal Investigators and research teams of single site clinical trials, defined here as a trial that is conducted by a single funded institution or organization implementing a clinical trial.

The preparation of this MOP followed guidelines offered by the National Institute of Aging (NIA)[1] with respect to the organization and content of the document. The Principal Investigator should be aware of all requisites including regulatory to conduct such trial including reporting, data and safety monitoring, Institutional Review Board (IRBMED) approval and Federal Drug Administration documentation, in case of trial holding Investigational New Drug (IND) Application as required. All researchers and investigators participating in the conduct of this study should be trained by the Collaborative Institutional Training Initiative (CITI) program and have ready access to the MOP and be trained on its contents.

The study protocol, case report forms (CRFs), informed consent documents (ICFs), and administrative forms including screening and enrollment logs, protocol deviation log, follow up call logs, etc. should be finalized before the development of the MOP. When possible, the MOP should be drafted prior to the start of the trial. The MOP can be updated when changes to protocol or procedures are needed. Each new version developed and approved should be dated.

2.0 How to Use this MOP

The MOP for this clinical trial can serve as a cookbook and resource to investigators by serving as a reference that describes the study protocol and procedures. As such, this document offers guidance and recommendations for investigators and research teams interested in conducting similar types of clinical trials. Included are flow chart of activities, staff roles and training, timelines describing each activity and encounter with trial participants. Activities described here are based on the conduct and operations of this trial about the effect of Gentamicin intravesical instillations to decrease urinary tract infections (UTIs) after spinal cord injury (SCI). These activities and procedures are based on the study protocol (Appendix A). The purpose of this MOP is to ensure adherence to the study procedures consistent with federal regulations and good clinical practice.

3.0 Study Organization and Responsibilities

During the study planning phase, the Primary Investigator (PI) and research staff should develop a draft version of the complete study protocol to be approved by the institution's IRB and the study's Data Safety and Monitoring Board (DSMB), if applicable. All necessary forms (i.e., CRFs, informed consent forms (ICFs), dosing logs, study's questionnaires, templates of communications, screening and enrollment log, deviation of protocol logs, billing logs, etc.) should be drafted and completed during the first 6 months before the study starts. The PI should oversee the development of these forms and the study protocol. A pattern for communications with the DSMB, FDA (if applicable), and other regulatory bodies should be established by the PI in advance. Each study site can adapt these MOP guidelines to its needs. The information contained in this document reflects only this study's recommendations.

The following is a summary of responsibilities to be included while conducting study activities:

- Developing and updating study materials including study protocol, templates for questionnaires, forms, letters, reports, MOP, etc.
- Completing informed consent forms (ICFs) and appropriately archiving documentation
- Conducting participants' recruitment, screening, and enrollment
- Reporting and monitoring all adverse events (AEs) and serious adverse events (SAEs)
- Developing a study database and quality control procedures
- Collecting data and entering data into database
- Conducting baseline and follow up interviews with participants
- Overseeing the process of drug prescriptions and drug dispensing with pharmacy
- Ensuring compliance with study protocol
- Submitting reports to regulatory bodies (IRB, FDA)
- Maintaining and updating a study binder (electronic and/or hard copy)

The next sections provide an overview of the study, the scientific protocol, and the study flow.

4.0 Study Overview

4.1 Study Title

The Effect of Gentamicin Intravesical Installations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial

4.2 Objectives

Primary Objective: Evaluate efficacy of intravesical gentamicin in reducing the number of urinary tract infections (UTIs) during a 6-month period.

Secondary Objectives: Examine the effectiveness of gentamicin on decreasing associated bladder and bowel complications.

Tertiary Objective: Examine the effect of gentamicin on improving health-related quality of life (QoL) and community participation.

4.3 Design

A pre-post design study evaluating the efficacy of intravesical gentamicin on the occurrence rate of UTIs and bladder complications in patients after SCI, and to assess its effectiveness in preventing complications, promoting overall quality of life (QoL), community living, and social participation.

4.4 Primary Outcomes

Number of UTIs at 6 months (pre-treatment) and 12 months (after 6 months on-treatment) verified in electronic medical record (EMR)

Number of bladder/bowel complications in EMR

4.5 Methods

Treatment: gentamicin + saline

The study consists of a Screening Visit, a Baseline Visit (V1), an End of Treatment Visit (V2) and a Follow-Up Interview (V3). A post-trial survey was conducted to assess participants satisfaction with the trial and outcomes. Over the course of this study, these visits include urinalysis testing, UTI/adverse event (AE) check, investigational product (IP) compliance check/consolidation (ensuring compliance with study protocol including treatment dose, and availability of needed supplies), and completion of survey measures. These visits can be done in-person, on zoom, or on the telephone. Urine and blood collection can be done at clinic or participating laboratory. Participants receive bi-weekly phone calls to check for UTI/AE issues and to address any other issues or concerns as listed above or raised by participants.

4.6 Study Sample

Adults 18-80 years old with traumatic SCI or non-traumatic spinal cord disease (SCD) and with neurogenic bladder and history of recurrent UTIs. Based on statistical power analyses, a targeted sample size of 25 eligible participants is recommended.

5.0 Condensed Scientific Protocol

This study addresses a critical health issue affecting those living with spinal cord injury (SCI), that of recurrent UTIs and their effects on health, QoL, community living and participation. The full study protocol providing a detailed view of this trial is found in the Appendices (Appendix A). Although antibiotics have been used to treat UTIs, for those with recurrent infections, oral antibiotic treatment is not always effective and can lead to infections that are resistant to treatment. Intravesical (occurring within the bladder) instillation of a gentamicin solution (a generic antibiotic often used to treat UTIs) has been used clinically in adults with SCI for over 20 years.[2] The process is quite simple and requires flushing the bladder with the solution.[3] Yet, the effectiveness of intravesical gentamicin in prevention of UTIs has not undergone rigorous efficacy testing in SCI. This study proposes a clinical trial of intravesical gentamicin to reduce the incidence of UTIs in persons with SCI and to assess its effectiveness in promoting overall QoL, community living and participation.

Two important reasons guided the decision to study the effects of prevention of UTIs with gentamicin on QoL. First, informal discussions with colleagues and collaborators show that most persons with SCI/SCD who use gentamicin for prevention of UTIs are very satisfied with results. Second, there is a lack of clear evidence in the field for clinical trials showing the results of gentamicin instillations for those with UTI after SCI/D. Furthermore, there is a lack of clarity about the role of broad outcome measures, shown by the limited use of QoL and community participation measures, in clinical trials.

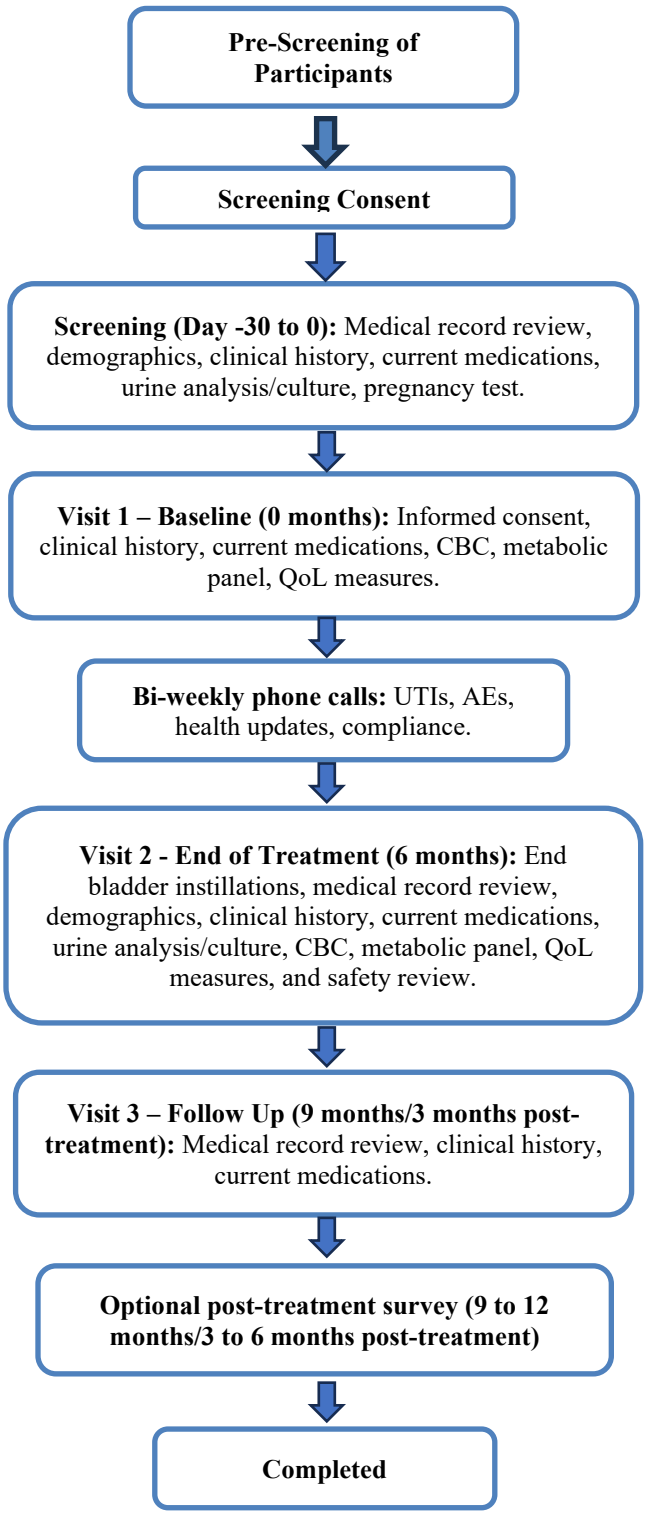
The primary goal of this study is to determine whether intravesical gentamicin is effective in reducing UTIs in persons with SCI/SCD. The secondary goal is to examine whether gentamicin is effective in decreasing bowel and bladder complications associated with SCI/SCD. Tertiary goals are to examine whether this treatment can help improve health related QoL and community participation.

6.0 Study Flow

This study is proposed as a controlled trial examining the effectiveness of intravesical gentamicin on the rate of UTI occurrence in approximately 25 patients with SCI or SCD. Potential subjects are screened for eligibility. Eligible individuals will receive a study treatment of gentamicin + saline. Participants are involved in study procedures over 9 months.

Study visits include a screening visit to ascertain eligibility, a baseline visit (V1) confirming eligibility and gathering initial medical and psychosocial data, an end of treatment visit (V2) after 6 months on treatment, and a follow-up data collection 3 months (V3) after the end of treatment. A 30-day window was considered in completing these visits. In addition to these study visits which could be in-person, on zoom, or on the phone, participants also complete bi-weekly telephone encounters with study staff to monitor potential AEs and IP compliance. After completing the trial, participants are be invited to participate in a voluntary post-trial survey. See study flowchart (Figure 1) below for more detail.

Figure 1: Study Flowchart



7.0 Informed Consent Process

For this single site study, two types of informed consents (ICFs) were developed: a screening consent (to determine if a participant is eligible to enroll in the study) and the study consent (to enroll eligible participants into the study and treatment.) The consent process for both the screening consent and the study consent follows the Institutional Review Board (IRBMED) template (it includes information about the process itself, when and where it will be obtained, description of the nature of the study, role of team members and participants, consent review and signatures and the reconsent process, if needed) and is a dialog between a member of the study team and the prospective participant. Typically, the study coordinator/research assistant (SC/RA) is responsible for guiding the discussion, and they are instructed to follow the standard format to ensure that all required elements are introduced. The dialog starts with an explanation of research and how it differs from clinical care, and then progresses to explanations of the study itself that are focused on the purpose, the activities involved, and a discussion of the risks and benefits. Subjects are informed that participation is voluntary and independent of one's regular clinical care. Each prospective participant is given time to read the ICF and discuss their options with family members. To ensure ample time to peruse the consent information, participants are provided with copies of a sample document.

During the screening consent process, the SC/RA contacts the potential subject to explain the study and email or mail the ICFs before the scheduled clinical office visit. This allows for the possibility that potential subjects could be enrolled in the study and complete their baseline visit at the same time as their scheduled appointment (if their schedule allows this). If this is not possible for some reason, the SC/RA explains the study and provides the ICFs at their clinic visit. For those who are screened on zoom or on via telephone, a verbal consent process is used. The screening consent process dialog follows the same steps outlined above when the process takes place in the clinic. Once an individual indicates that they are interested in participating and would like to proceed with the screening urinalysis/urine culture, they provide verbal consent for the screening process and the SC/RA signs and dates the "Consent to be Screened for a Research Study" ICF (Appendix B) and writes a Note to File (NTF) describing the Subject's Screening Verbal Consent. The NTF should record the date and time of the subject's verbal consent and note any concerns that were addressed for the subject. The screening consent should acknowledge that the subject had enough time to ask questions and they understood that their participation is completely voluntary. The SC/RA also signs and dates the NTF and files it in the participant's EMR. The SC/RA keeps the original screening consent form.

Whether the screening consent process takes place in-person or on zoom or telephone, potential subjects must be able to read and comprehend written documents and be able to follow instructions without influence or assistance from others. If the screening process is done in-person and a subject's paralysis prevents them from being able to sign or make their mark on the consent document, the same consent procedures outlined above are followed with the additional step of having a witness present to sign that the subject has verbally consented to be in the study. Once the screening consent has been obtained, the SC/RA will assign the subject a unique study ID in the form "GENT###" where the number will represent the order in which participants were enrolled in the study. For example, the first subject will be given the ID "GENT001," the second "GENT002," and so on.

Contingent upon confirming eligibility, the subject's first visit is scheduled, and the full study consent (Appendix C) is signed at the start of that visit, at the latest. During this time, participants can review the study in their own time and raise questions they may have to the study team. This strategy improves participants' comprehension and comfortability with the study, thus increasing chances of recruitment and retention. Once an individual has made the decision to participate in the proposed research, they will indicate intent by signing & dating the full informed consent document. The SC/RA will also sign and

date the document. He/she keeps the original ICF form to be filed in the study binder while participants are given a copy for their record.

Whereas the screening consent form allows for a verbal consent process that can be done over the telephone or zoom, the full ICF must be signed by the subject. If this cannot be done in person, the full consent form can be signed using the signNow process at "signNow Single Sign On" if the subject has access to a computer. This FDA and HIPAA[4] compliant electronic signature process permits informed consent materials to be uploaded to the signNow platform and routed via email for review and signature to the patient, LAR (Legally Authorized Representative), study team members, and any necessary witness. Signature lines (including date and time-stamps) are affixed to the consent forms within the signNow platform. Routing information is included during document set-up. Individuals access the document via email to complete the signature process.

The signNow process should not be used if the participant is using a cell phone due to technical difficulties. If the subject is not able to use the signNow process with a computer, then the full ICF should be sent to the participant with a self-addressed stamped envelope so they can sign and return the consent after the full discussion has taken place. The SC/RA then signs the ICF upon receipt and sends a copy of the fully signed consent back to the subject. If the subject is not physically able to sign the ICF, they can provide a witness present to the discussion who can testify and sign that the subject has verbally consented to be in the study.

All ICFs are prepared using templates from the IRB that ensures the process is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Participants authorize researchers to use their health information for the study by signing the full study consent.

8.0 Recruitment and Retention Plans

8.1 Participant Recruitment

Our target population are Adults 18-80 years old with traumatic SCI or non-traumatic SCD and with neurogenic bladder and history of recurrent UTIs.

This study will use a multi-pronged approach to recruitment that includes the following methods:

- Physician referral
- Weekly reviews of Michigan Medicine Outpatient Clinic Schedules (Urology and PM&R)
- Direct-to-patient marketing using established contacts with clinicians at UMHS
- Public advertisement using flyers (Appendix D) in UMHS hospitals and clinics
- Michigan Spinal Cord Injury System (MSCIS) database and UM SCI Research Registry
- Neurogenic Bladder Clinical Database
- Patient Reported Outcomes for Bladder Management Strategies in Spinal Cord Injury (SCI) project database.
- Study listing on UMHealthResearch.org (which may be linked to the patient's electronic health portal)
- Outreach to other related databases and patient advocacy groups in Ann Arbor and surrounding locales
- Recruitment letters (Appendix E)
    - Letters will be sent to potential participants who may or may not be seen within UMHS and are unable to take advantage of the above strategies.

8.2 Recruitment Details

Key criteria for targeting appropriate participants will include (more detailed inclusion/exclusion criteria are under Screening Components below)

- Age
- Presence of SCI and neurogenic bladder (evidenced by neurological classification when possible)
- Use of Clean Intermittent Catheterization (CIC) or catheterization through a stoma
- Experience with recurring UTIs (2 or more in the prior six months)
- Availability of regular physician for treatment of any UTIs who is affiliated with Michigan Medicine

Potential participants meeting this first pass at eligibility can be contacted in multiple ways:

- Approached in clinic by a referring physician.
- Sent an IRB approved introductory letter (Appendix E).
- Contacted via email with the same information as contained in the letter.
- Contacted via phone call.

Interested individuals are invited to a research interview at which time the consent dialog is initiated, and eligibility confirmed. This interview is conducted through secure, encrypted video conferencing, over the phone or in-person at a potential participant's clinic visit.

- Individuals are emailed or given an electronic copy of the ICF prior to the initial research interview. If the individuals do not have email access, physical copies will be mailed.
- Individuals are invited to review the study information on UMhealthresearch.org prior to the initial research interview.
- The study coordinator suggests that the individual share their intentions about potential participation with their family, caregiver, regular physicians, and/or care team prior to the initial research interview.
- Special efforts are made to recruit minority participants by ensuring that all potential eligible minority participants are contacted and invited to participate.

8.3 Retention

The study team strives for an empathetic relationship with participants to promote retention across the duration of this trial. Strategies for developing this type of relationship include:

- Engaging in active listening
- Using teach-back methods of communication and information sharing to ensure mutual understanding.
- Keeping individuals updated and aware of necessary and useful information.
- Allowing individuals to correct or add to study team responses.
- Engaging on a personal level, when appropriate
- Being culturally responsive and aware; assess personal implicit biases.
- Addressing questions participants may have about the study.
- Expressing appreciation for the subject's continued participation in the study.

Study team members will implement the above strategies in all participant encounters whether planned or ad hoc. All encounters also will be used to maintain and promote an ongoing relationship with study participants thus, facilitating retention.

8.4 Remuneration and Incentives

To aid study retention, participants receive a total of $90 for participating in the study. They receive $30 for each of the following study visits:

- Baseline visit (V1)
- End of treatment visit (V2)
- Follow-Up Interview (V3)

Payments are processed through the Human Subjects Incentive Program (HSIP) on a weekly or bi-weekly basis but no later than two weeks after any given participant's visit. The precise method of payment will default to check, with a cash or gift card option being offered upon request for a different method of remuneration.

The HSIP request form is accessed directly from Wolverine Access, the relevant information is put into the form, and the submission is done online. The information needed to complete the form is:

- the name and address of the subject,
- total amount of money to be paid to all subjects, and
- the study short code or grant account number

At each study visit, the SC/RA verifies the subject's address to ensure there is not a payment delay to the subject. Subjects typically receive a check in the mail within 3 or 4 days of the payment being processed through HSIP. They should be encouraged to contact the SC/RA if they have not received their payment within a reasonable amount of time after their visit to the study site.

9.0 Screening Components and Eligibility

9.1 Screening Overview

Screening is conducted to begin recruiting eligible participants and primarily to check for current UTI/pregnancy in the potential participant. The participant must agree and consent to the screening urine tests. Completing this step does not enroll the participant into the study, and they may choose not to enroll in the study even if they qualify based on these urine tests and the above criteria.

The screening/recruitment process should unfold as follows:

1. Conduct EMR screen for eligibility criteria.
2. Approach subject in clinic or by telephone and explain study completely.
3. Obtain subject's consent to be screened (shorter consent form not requiring subject's signature). A Note to File (NTF) should be done describing the screening consent process.
4. Obtain urine sample from subject or schedule subject for urinalysis at a clinic or laboratory. Urinalysis is done with reflex culture and, if subject is female with childbearing potential, includes a pregnancy test.
5. Once screening tests confirm eligibility, full informed consent is obtained and the participant's Baseline Visit (V1) will be scheduled within 30 days after screening.

Screening requires the collaboration of multiple departments and individuals, including the SC/RA & other members of clinic staff. The responsibilities are delineated below.

9.2 Screening Log

The screening log (Appendix F) will be maintained in REDCap[5]. Additionally, a screening/contact log (Appendix G) will be maintained in DROPbox[6] as a separate database containing subject data for the study. (DROPbox is a cloud sharing service that allows approved study staff to access, edit and share documents). The screening log serves several purposes: 1) to keep a record of accrual rates, reasons subjects are ineligible, etc., and 2) to maintain a record of patients who have been approached by the study team so that the study team does not contact or rescreen patients that have already refused or otherwise not met eligibility criteria.

The screening log will follow the basic form of the screening log CRF (Appendix H). Study staff may choose to fill out the CRF before entering the information into the REDCap database or may just enter it directly into REDCap. Patients who enroll in the study have either a paper source or electronic document for their screening eligibility result (Appendix I), which will be filed in their subject paper and/or electronic binder in Dropbox.

9.3 Pre-screening: EMR review

Pre-screening is performed by a trained SC/RA. The EMR review is the first level of screening. It should be a detailed review of most of the primary inclusion and exclusion criteria to target pitches to only the most qualified candidates. UTIs must be documented in the EMR to count towards eligibility. A positive urine culture or, if sample was not cultured, UAs positive for leukocyte esterase and/or bacteria (if analyzed) are deemed a UTI for eligibility purposes. In ambiguous cases, the study physician will be the final arbiter of whether there is active infection. Potential participants who are deemed ineligible after EMR pre-screening are only tracked

and documented (i.e., in an Excel spreadsheet) for study purposes, but are not to be entered into the screening log (as they have only been "pre-screened" and deemed ineligible).

9.4 Screening

Potential participants screened for this study come from various sources, but primarily from outpatient clinics (either PM&R or Urology). Those who are deemed eligible after EMR pre-screening move to the screening phase. Research staff approach potential participants in clinic, by phone call, or by email, explaining the study and reviewing primary eligibility criteria.

After confirming a potential participant's interest in the study, the SC/RA will complete the Screening Consent (Appendix B) and document the screening process in a NTF. Those who do sign the screening consent form will be invited to complete their screening UA and have their eligibility reviewed by the SC/RA. The SC/RA fills out the "Eligibility Criteria" Checklist (Appendix I) to determine eligibility, which must then be confirmed by the PI or Co-PI. The SC/RA also invites them to complete their screening UA. Patients who are approached for screening UA in clinic are entered into the screening log (REDCap database, Appendix F) for tracking purposes, even if they do not sign the screening consent form. These screening phases are summarized below.

Table 1. Screening Phases

	Eligibility criteria screened	Screening Log
Pre-screening	In Electronic Medical Record to check for eligibility and lab results	Not entered (tracked by SC/RA separately)
Screening (Phone or in person)	In person at patient's clinic visit or at visit to laboratory – Confirmed eligibility and lab results with participant	Entered into REDCap screening log (even if ineligible for the study)
Enrollment	N/A	Are already entered into REDCap screening log, file paper screening case report form in subject's study binder

9.5 Screening Visit

The screening visit may be conducted in person or over the phone. The potential participant needs to be given a complete explanation of the study. At this stage, the SC/RA should make sure to ask the participant questions that may not be easily gleaned from a medical record (i.e. intention to become pregnant, enrollment in other clinical trials/studies).

The inclusion/exclusion criteria are confirmed with the participant and, if the participant is still interested in the study, the SC/RA arranges for the participant to have a urine test and, if necessary, a urine pregnancy test. UA, culture, and pregnancy tests are preferably to be done within the study's health system so records are readily available. If this is not possible, the subject may arrange to have them done at their Primary Care Physicians office or a clinic close to them. It is the participant's responsibility to ensure that the results are forwarded to the SC/RA.

9.6 Urine Sample – Screening

After provision of the signed "Consent to be Screened for a Research Study" ICF (Appendix B), an order is placed for a urinalysis and urine pregnancy test (for females of childbearing potential) in the medical chart by the SC/RA. If the screening visit is done in person in clinic, the participant is instructed to provide a urine sample which can be tested in clinic with a urine dipstick. The urine sample provided by the participant should be at least 0.5 mL in volume. If the participant does not have a clinic appointment around this time, he/she can go to another health system clinic or other designated laboratory to provide the urine sample. If a participant has had a negative urinalysis in the past 30 days, they do not need another screening urinalysis. However, female participants of childbearing potential still need a urine pregnancy test. This process is designed to ensure the participant does not have an active UTI and is not pregnant, as well as to confirm eligibility based on previous EMR review.

9.7 Lab Reports

Results for dipstick urinalyses are immediately available. The tests must be negative (i.e. show no evidence of infection). The SC/RA will be responsible for reviewing the test results and informing the patient of the findings regardless of outcome (i.e. eligible vs. ineligible). Participants whose urinalysis tests positive at this stage undergo a reflex urine culture test (automatically done by the lab) and may be treated for their active UTI and undergo testing a second urine sample after their treatment and a post-treatment period of 10 days without symptoms. Treatment for a positive urine test needs to be ordered by the participant's physician.

The results of this second urine test will determine the patient's eligibility: (1) a "negative" UA indicates the patient is eligible for the study, or (2) a second "positive" UA will classify the patient as a screen-failure. Participants whose pregnancy test comes back positive are excluded from the study.

A screening log (Appendix F) is kept in REDCap of all potential participants who undergo this level of screening. REDCap is a secure web-based database to support clinical and research studies. The screening log denotes which eligibility criteria they may or may not meet, as well as any other reason they may not be eligible for participation in this study (i.e., history of non-compliance, refused to participate).

9.8 Lifestyle Considerations

In addition to meeting basic eligibility during screening as described above, other criteria are equally important to ensure a successful participation in the study.

Participants should show indications of health seeking behaviors and be able to consult with their personal physicians when noticing symptoms related to bladder complications and/or UTIs. Healthy behaviors related to hygiene when having to catheterize are also important. Compliance with the required steps of the study protocol for completing instillations into the bladder and disposal of remaining drug accordingly are critical considerations. Further, the ability and willingness to keep a daily dosing log (Appendix J) throughout the study is also important.

During this study, the management of all ongoing and new bladder or bowel issues continues to fall under the purview of the participant's treating physician or health care provider. The study team will not offer treatment for any new-onset UTIs. Participants are reminded that they are expected to contact their physician about any new symptoms or infections requiring treatment.

9.9 Screen Failures

Screen failures are defined as those individuals who consented to participate in the study, but who are subsequently deemed ineligible, usually after the baseline UA and culture. Those who test positive for a UTI at baseline may be re-assessed for eligibility after prescribed antibiotic use. Those who undergo a second positive urine test with UTI symptoms following treatment are ineligible for the study (i.e. categorized as a screen failure). Additionally, females of childbearing potential who have a positive screening pregnancy test will be categorized as a screen failure.

9.10 Eligibility Criteria

The full eligibility criteria are described below. Although the electronic medical record (EMR) is pre-screened for all eligibility criteria prior to contacting a potential participant for screening, confirmation of the criteria must be confirmed by the participant or caregiver at the Screening Visit and the Baseline assessment.

9.10.1 Inclusion Criteria

- Provision of signed and dated ICF.
- Male or female aged 18 to 79 at the time of enrollment.
- History of traumatic SCI or non-traumatic spinal cord disease (SCD), with sustained neurological dysfunction.
- At least 6-months post-initial hospital discharge following SCI/SCD onset.
- Neurogenic bladder.
- Ability to perform daily instillation by oneself or with help of others and willingness to adhere to the study regimen.
- Negative pregnancy test (for females of childbearing age) and expresses willing and ability to use appropriate contraception while enrolled in the study.
- History of at least 2 UTIs documented in the EMR during the previous 6 months (prior to screening).
- Have a designated physician or health care provider for routine urological care who is a member of the study's health system.
- Use of CIC or catheterization through a stoma (i.e. Mitrofanoff) as their primary method of bladder management.
- Agreement to adhere to Lifestyle Considerations throughout participation in the study. This includes agreeing to complete the daily dosing log as instructed by the coordinator.

9.10.2 Exclusion Criteria

- Concurrent use of *systemic* oral or intravesical antibiotic prophylaxis during the previous six months.
- EMR-documented or self-reported history of gentamicin allergy.

- Positive pregnancy test at screening or baseline.
- History of 8th cranial nerve disorder.
- Co-morbidities like cancer and chronic disease that could impact patient safety OR significantly affect the rate of UTIs and/or QoL substantially.
- Urological co-morbidities like bladder cancer and history of kidney disease. These include:
    - Patients with EMR-documented renal impairment (e.g. end-stage renal disease, documented glomerular filtration rate (GFR) less than 60 ml/min will be excluded (most recent result)
    - Patients with active pyelonephritis (patients with a history of pyelonephritis, which has been treated and is resolved, will be permitted in the study)
- Current UTI at screening visit, assessed via urine analysis, culture, and symptoms.
- Concurrent enrollment in a similar clinical trial.
- Concurrent use of contraindicated diuretics (ethacrynic acid, furosemide) or other contraindicated or disallowed concomitant medications or receiving treatments that may influence the results from this study.
- Otological symptoms at baseline (i.e., tinnitus, severe dizziness/vertigo).
- At the discretion of study team, individuals who are unable or unlikely to comply with procedures and/or for whom study participation is not recommended.
- Patients with a diagnosis of multiple sclerosis (MS) without cord involvement.

10.0 Study Intervention Description and Administration

10.1 Study Intervention Description

Eligible participants are mailed the investigational product (gentamicin + saline solute) immediately after the Baseline visit (V1). Upon the termination of treatment, they will complete a study visit (V2) consisting of a blood draw, urine sample, and self-reported QoL measures. The blood draw and urine sample can be completed at the health system's Lab or during the doctor's appointment in clinic. Additionally, a safety review is conducted 30 days after treatment termination by a member of the study team to assess for any adverse events (AEs).

The treatment period lasts 6 months, beginning at the time of the first bladder instillation. The daily treatment consists of each participant and/or caregiver flushing the bladder with the treatment drug via bladder or stoma catheterization in the evening, leaving it in overnight, and emptying it the next morning. This is to be done 7 days a week during the 6 months treatment. With each treatment, the participant is asked to record the date and time of treatment on the dosing log (Appendix J) as well as any issue with the treatment itself or, when appropriate, why they missed the daily treatment.

10.2 Study Intervention Administration

Ideally, the Baseline (Visit 1) and the End of Treatment (Visit 2) are conducted in person. However, due to COVID-19, the study visits were conducted via an encrypted, HIPAA-compliant video conferencing platform (e.g., Zoom for Health.) It was standard practice to conduct as many procedures remotely as possible to better protect subject/caregiver(s) and staff against the risk of COVID-19. However, in cases where a remote video interview was not possible, remote telephone interviews were conducted and the study followed the health system's guidelines for proper consenting. As the study progressed and COVID-19 precautions were no longer necessary, remote video interviews continued because it was found that participants preferred the convenience of remote visits over coming into the clinic.

10.3 Study Treatment

The study treatment consists of gentamicin, an aminoglycoside and saline. The drug is sent to participants by the health system's Research Pharmacy in a concentration of 60mg of the active product to 50ml of normal saline. With each shipment of study drug, participants receive catheters, syringe tips, daily dosing logs and a pamphlet describing the dosing procedure. The procedure entails participants withdrawing 25ml with their syringe, switch tips, instill, and dispose of the remaining 25ml of solution daily. Participants' shipments will be ordered every 28 days +/- 5 business days by the study team.

11.0 Study Activities and Procedures

A brief overview of study activities is provided in Table 2, followed by detailed descriptions of each study visit and their associated procedures. Note: reference numbers listed here refer only to this table and not to references.

Table 2: Schedule of Activities

Procedures	Screening	Visit 1 (Baseline)[1]	Visit 2	Visit 3 (Follow-Up Interview)[7]	Optional Post-Intervention Survey
	Day -30 to 0	D0	Day 180 ±30	Day 270/Day 90 post-treatment ±30	Day 360/Day 90 post-treatment ±30
Medical Record Review	X	X	X	X	
Informed consent		X			
Demographics	X				
Clinical History	X	X	X	X	
Current Medications	X	X	X	X	
Urine Analysis (UA; plus culture if needed)[2]	X		X		
Pregnancy test	X				
Complete Blood Count		X	X		
Comprehensive Metabolic Panel		X	X		
Self-report measures of QoL[3]		X	X		
Safety Review[5]			X		
Every 30 days +/- 2 business days: ship study product		←	→		
Schedule bi-weekly phone calls[4]		←	→		
Satisfaction survey[6]					X

1 Participation will commence once eligibility is confirmed via urine analysis (UA) (or culture for those individuals with a positive UA); an order for study product will be faxed/emailed to the Research Pharmacy; intervention start date will be the first dose listed on the dosing diary. If the dosing diary is not available, the intervention start date will be recorded as the date told to the study team by the participant and documented in the REDCap database.
[2] A rapid UA will be performed as part of standard of care at the time of screening; UAs at Visit 2 will be study-paid; positive tests will be followed with a urine culture; test results usually take about 4 days
[3] QoL measures include the following standardized surveys: Neurogenic Bladder Symptom Score; Neurogenic Bowel Dysfunction Score; SF-Qualiveen; SCI-QoL Measurement System's *Bladder Management Difficulties*, *Bladder Complications, Bowel Management Difficulties,* and *Satisfaction with Social Roles and Activities*; and Community Participation Indicators Scale (see Section 8.1, "Efficacy Assessments")
[4] Study team will make phone calls every two weeks +/- 3 business days to participants throughout the study period to ask about UTIs, adverse events, compliance and general health updates.
[5]Study team will conduct this visit, likely over the phone, within 30 days after the participant's final instillation in order to assess any adverse events or reactions while the study drug is washing out of the participant's system
[6]Study team will contact participants at least 60 days post-intervention for an optional survey to assess their perception of Gentamicin use, challenges and satisfaction with study participation. Participants may be contacted up to 1 year after the end of their participation.
[7]If Study team is unable to contact participants for the Visit 3, the data can be found in the participant's EMR.

12.0 Baseline Visit (Visit 1)

12.1 Overview

The purpose of this visit is to establish a baseline picture of the subject's health status, educate them on the proper way to administer the study drug, and administer baseline measures.

Participants need to complete the assessment questionnaires after signing the study ICF (Appendix C). They cannot start in the intervention until they have signed the study ICF.

Information from these visits will be recorded in the baseline visit CRF (Appendix K). As described in detail below, the components of this visit are as follows:

1. SC/RA greets subject (in person or on zoom or telephone)
2. SC/RA asks subject about their current medications and health status.
3. Urine sample (urinalysis with reflex culture) and blood sample (Complete Blood Count (CBC), metabolic panel) are obtained from the participant.
4. Participant, with assistance and guidance from SC/RA, completes self-reported QoL measures (Appendix L)
5. All information the SC/RA collects from the subject, including answers to the QoL measures, is recorded on the paper CRF or directly entered into the REDCap database. If the information is collected on paper first, it is entered into the REDCap database following the data collection. Paper CRF must be scanned and uploaded into the subject's binder in Dropbox or another safe data repository.
6. Participants are asked to complete a daily dosing log including dates and times of gentamicin dosing, whether the full dose was taken, as well as date and time of the subsequent catheterization to promote and record compliance with the treatment protocol. (see Study Compliance).
7. Participants are informed of the Washout Procedure (see Study Compliance).

12.2 Self-reported Medical History/Review of Health Problems

The SC/RA and participant fill out the medical history case report form (Appendix M) during this visit. It is important to capture each subject's medical history, both to categorize their SCI and associated complications, but also to record other co-morbid conditions they may be experiencing. The medical history information case report will be stored in REDCap. The CRF is reviewed during all subsequent visits and updated as needed.

Recent Medical History reflects any current diagnoses reported by the individual. It is not uncommon for older adults to present with a myriad of co-morbidities; however, this would not automatically exclude them from participation. For the most part, if the disease is well-controlled and the individual is on a stable regimen (medical, lifestyle, or otherwise) then they are still eligible for participation.

It is unlikely that a person will leave their screening with a new diagnosis. It is not the study's intent to diagnose or to treat the individuals who enroll in this study. Of course, if a situation arises where some other disease process is suspected, then the preferred course of action is to refer the individual to their primary health care provider. In more urgent situations (sudden sharp chest pain, loss of consciousness,

fainting, etc.) should they arise, the appropriate course of action for the study coordinator is to either contact a nurse or physician in the health system's clinic for medical advice or instruct the subject to call 911 (if talking to participant over the phone).

12.3 Complete Blood Count (CBC) and Comprehensive Metabolic Panel
The participant has a blood draw at the Baseline (Visit 1) and at the End of Treatment visit (Visit 2). This can be done at a clinic visit or the participant can go to a UM Laboratory. The results of the CBC and Comprehensive Metabolic Panel are made available in the subject's medical record.

12.4 Concomitant Medications (Prescription & Over-the-Counter Medication Use)
Concomitant drug information is collected and updated from the subject at each visit (including the bi-weekly telephone visits.) The information collected includes the drug name, dose, and date the participant started and stopped the medication (Appendix N).

Contraindicated therapies to gentamicin (i.e. furosemide, ethacrynic acid, and allergies to aminoglycoside antibiotics) are listed under the exclusionary criteria for this study. Concurrent use of *oral systemic* antibiotics is also not permitted during the study. However, topical antibiotic creams are permitted. Other medications should be discussed with the participant and the prescribing study physician in charge.

If a participant needs to take antibiotics for any reason, it is recommended that he/she discontinue the gentamicin flushes for the course of the antibiotic and for an additional seven days post-antibiotic before the subject can re-start the gentamicin.

12.5 Self-reported QoL Measures (Appendix L)
The following QoL measures are collected at this visit (V1) as well as at the six months end of treatment visit (V2). The surveys should be completed by the participant with or without assistance of a caregiver or SC/RA during the participant's scheduled visit. The surveys may be completed over the telephone or zoom if the visit is conducted over the phone or zoom, or if the subject is not able to fill them out during the visit.

- **Neurogenic Bladder Symptom Score (NBSS)**[7] (Appendix L1): 25 item validated measure that assesses symptoms across three domains (incontinence, storage & voiding, and consequences) plus one overall quality of life item.
- **Neurogenic Bowel Dysfunction Score (NBD)**[8] (Appendix L2): 10 item validated measure that assesses frequency, of defecation and methods of bowel management and complications.
- **SF-Qualiveen**[9] (Appendix L3): 8 item validated measure for urinary disorders that covers four domains (bother with limitations, frequency of limitations, fears and feelings). Participants respond to each item using a 5-point liker scale.
- **SCI-QoL Measurement System's Bladder Management Difficulties, Bladder Complications and Bowel Management Difficulties**[10] (Appendix L4): these reflect three scales within the SCI-QoL battery that is part of the NIH Patient Reported Outcomes Measurement Information System (PROMIS) initiative. The short-form (SF) for each scale is administered (range 5-9 items).
- **SCI-QoL Measurement System's Satisfaction with Social Roles and Activities**[10] (Appendix L5): is a 10-item short-form that is also part of the overall SCI-QoL battery.

- **Community Participation Indicators (CPI) Scale**[11] (Appendix L6): 20 item validated measure of the frequency and importance of involvement in various types of activities.

The SC/RA ensures that all the questions have been answered by the participant. The participant's ID and visit date are listed in ink at the top of each survey. The surveys are administered in the above order and are expected to take about 45 minutes. These surveys are considered source documents and are filed in the participant's study binder. The data collected is entered into the online REDCap database. If these surveys are administered over the telephone or zoom, then the SC/RA may directly enter the data into REDCap during the administration instead of on paper if preferred. The study project manager, biostatistician, and the independent study monitor review the database regularly and check for quality and accuracy of information.

12.6 Ordering the Study Treatment Drug

Orders are placed by the SC to the Research Pharmacy via a paper order document created specifically for this study by the Research Pharmacy at the start of the study. During or immediately after the Baseline visit, the SC should complete the order form and fax it to the Co-Primary Investigator (Co-PI) who has Medical License. Once the Co-PI has signed the order form it may be submitted to the Research Pharmacy. To ensure overnight shipping, the order should be placed before 2:30pm if possible. The faxed order and confirmation sheet will be kept in each subject's electronic study binder (EMR). The Research Pharmacy will maintain shipping and date of delivery records.

At the Baseline visit (V1), the SC/RA asks participants to let the study team know when they receive their first shipment of study drug and when they began their study treatment. The date they began study treatment is entered into the Medication List in each participant's REDCap file. This will ensure that the team has an accurate date for the start of study treatment, as well as whether there were any issues with the order being processed. If the SC/RA does not hear from the participant within a week of V1, they contact them, discuss problems, and re-order the IP (if necessary). This procedure is repeated each time drug shipment is required (i.e., every 28 days to re-supply subjects with IP).

12.7 Dosing and Administration Education (SC/RA)

The study treatment is either self-administered or administered by a caregiver. An educational sheet and/or brochure (Appendix O) for drawing up and administering the irrigation solution is included with the drug shipment. The information is also discussed with the participant prior to sending him/her the treatment drug. The study team answers questions and instructs the participant and his/her caregiver (if applicable) on the appropriate protocol for administration of the study drug (IP) at V1.

Participants are instructed to follow their normal catheter routine for bladder emptying at night, before bed. Once the bladder is empty, participants will attach the syringe containing the IP to the end of the catheter and slowly push the solution into the bladder. Once the full dose is instilled into the bladder, the participant removes the catheter and syringe leaving the IP in the bladder until, ideally, the following morning. Those who experience urine leakage or whose bladders are more overactive may need to empty their bladder during the night rather than wait until the next morning. They are instructed to keep the instillation in their bladder as long as possible, and for at least one hour (minimum time to be an effective dose per UM Urology nursing). In their dosing log (Appendix J), participants document the date and time of instillation and the date and time of bladder emptying, along with any other comments related to the process.

12.8 IP Dispensing and Storage

Participants are shipped parcels from the health system's Research Pharmacy monthly. These parcels include the IP in a IVPB bag, IVPB solutions, 18 g 1.5 needles (boxes of 100), syringe catheter tip, alcohol swabs, and sharps container (for needles), sufficient to cover at least 28 days of treatment.

Participants are instructed to contact the study team (who will contact the Research Pharmacy) if: 1) they receive a damaged parcel or contents, 2) they notice anything unusual about the syringes or contents, and/or 3) if they failed to receive an expected delivery. Participants will be advised to look for signs of a mishandled opened parcel; cracks or evidence of tampering with the mini bags; and distortions in the solution, e.g. cloudiness, particulates, etc.

The SC/RA informs participants of the appropriate storage protocols once they start the study treatment and reminds them throughout the course of their participation in the study during regular biweekly phone calls.

For unanticipated events that may cause lapses in treatment (namely, hospitalizations and vacations), specific procedures are followed. For example, when a participant is admitted to the hospital for any reason, they may not have immediate access to their study medication. An initial step is to inform the treating team that they are part of this study protocol and thus conducting intravesical bladder instillations with gentamicin daily. The physician in charge of care must approve the use of this study protocol and if needed, he/she should consult with the study's physician in charge, PI and/or the study team. If approved, participants should attempt to have a family member or friend bring their doses to the hospital where they may continue their treatment as usual. The study team needs to be notified of any hospitalizations ASAP.

When a participant goes on vacation, they should take an adequate number of syringes to cover the number of days to last them the duration of their time away from home as well as their dosing logs. In the case of airline flying, the study team will provide a letter, signed by the PI, for the purposes of informing relevant authorities that the medication should be allowed to be stored in the participant's baggage on the flight.

13.0 Biweekly Phone Encounters

13.1 Overview

The SC/RA conducts bi-weekly phone encounters with each participant during the trial. These encounters are meant to be brief (approximately 10 to 15 minutes) as compared to study visits 1 and 2. The bi-weekly phone encounters are primarily to ensure that participants are not experiencing any issues with their study drug adherence, with UTIs and other complications, and whether they have had any changes to their medications. If the participant reports AEs or medication changes, the SC will update the corresponding CRFs. The SC also asks about compliance with the dosing protocol and dosing log completion, along with any barriers to compliance at the bi-weekly phone calls. Information pertaining to these encounters can be recorded on the "phone encounter" CRF (Appendix P) and then entered into REDCap. The target dates for each encounter are populated automatically in OnCore upon the participant's enrollment in the study.

13.2 Structure of Encounter

The SC/RA calls participants and ensures that they are available for a few minutes to conduct their scheduled phone encounter. Questions asked should be open ended or general enough to avoid leading participants to specific responses. It is important that the interviewer obtain answers for questions regarding:

- participants' overall experience with the treatment and trial.
- any issues they may have with the study drug (positive or negative).
- any medication changes (if so, obtain dates and reason for change).
- any concerns they may have with the study protocol.
- participants' dosing log compliance.

Suggested questions include:
"Have you received enough doses of the study drug? Have you had any problems with giving yourself the medicine?"

"Have you seen a doctor or gone to the hospital since I spoke with you last? Do you remember what for?"

"Did you start or stop any of your medications?"

"Have you had any UTI symptoms? Have you had any other issues with your health?"

13.3 Process to Follow if Participant is Having UTI Symptoms

If a participant has UTI symptoms, their treating physician should be informed by the participant or his/her caregiver of these symptoms. Similarly, if the participant is being followed by a Urologist, the urologist should be contacted in the event the participant has a fever or flank pain.

If alarming symptoms are present and no physician or health care provider is available, the SC/RA advises the participant or caregiver to go to a local emergency department or urgent care. If no alarming symptoms are present, the SC/RA sends a medical chart note to the treating physician for medical decision making. As a reminder, this trial requires that the treating physician be within the study health care system.

13.4 Filling out the Case Report Form (CRF)

The following verbiage is used if the participant has no issues to report with either the study drug or their health status:

- "*No AEs/SAEs reported during this encounter."*
- *"No issues/concerns with IP administration reported during this encounter."*
- *"No medication changes reported during this encounter."*

If the participant reports any changes or issues, as much information as possible is obtained from the subject, and a detailed narrative is filled out in the appropriate section of the CRF (Appendix P).

In the case of AEs/SAEs, a detailed narrative is described on the CRF, and the event is reported appropriately as per the safety monitoring plan to the physician on the study (see section below for AE and SAE reporting) and the institution's IRB. All AEs, regardless of their severity, are listed on the AE log CRF (Appendix Q) for a given participant.

In the case of medication changes, a detailed narrative describing the changes and approximate dates of the changes is listed on the pertinent telephone visit CRF, and the concomitant medication CRF (Appendix N) is updated appropriately for the given participant. If he/she reports starting a new medication, the name of the medication and the approximate start date should be recorded on a new line on the CRF. Similarly, if the participant reports discontinuing one of their medications, the approximate end date (as reported by the subject) is recorded on the line of the medication which is being discontinued. All medication changes are updated in the REDCap database as well.

14.0 End of Treatment Visit (Visit 2)

14.1 Overview

The purpose of this visit is to collect information about subjects' health status, UTIs experienced, AEs or SAEs, and QoL measures after six months of study treatment. Data from these measures is compared to the data from Visit 1 (Baseline visit). Visit 2 can be done in-person, on the phone or using zoom. Information from Visit 2 is recorded on the End of Treatment V2 CRF (Appendix R) or directly into the REDCap database. As described in detail below, the components of this visit are as follows:

1. SC/RA greets participant.
2. SC/RA asks participant about any medication changes or changes to their health.
3. Urine sample (urinalysis with reflex culture) and blood sample (CBC, metabolic panel) are obtained from the participant. If visit done on zoom or telephone, participant goes to clinic or laboratory to provide urine and blood samples.
4. Participants, with assistance and guidance from SC/RA, complete self-reported QoL measures. This data can be directly entered into REDCap when the visit is completed via zoom or over the phone. If the visit is conducted in person, it is preferred that the QoL surveys (Appendix L) are completed on paper first to avoid errors.

14.2 Structure of encounter

The structure of Visit 2 is the same as for Visit 1. UA with reflex culture and blood work are collected at both Visit 1 and 2 in the same manner as during the screening laboratory tests. Additionally, the queries about AEs and investigational product compliance (as detailed above) will also be performed at Visit 2.

14.3 Review of Health Problems

The review of health systems will occur in the same manner as all the previous visits.

14.4 Concomitant Medication (Prescription & Over-the-Counter Medication Use)

Medication changes are captured as in the baseline visit. (See Visit 1)

14.5 Self-reported QoL Measures

The same QoL of life measures collected at baseline will be collected at the end of treatment visit.

15.0 Follow-Up Visit (Visit 3)

A Follow-Up Visit (Visit 3) is conducted in the time period of 1 to 3 months post-treatment completion. Participants are asked if they have had any UTI occurrences since the end of their study treatment or if they have had any other AEs. If the participant is unable to be reached for this visit, then the SC/RA checks the participant's EMR for any UTIs or other AEs during the 3-month post-treatment time period and uses this information to complete visit 3 documentation. This visit is documented by the SC/RA in the Follow Up Visit V3 CRF (Appendix S) and filed in the participant's binder in Dropbox.

16.0 Voluntary/Optional Post-Intervention Survey

Study team contacts participants at least 60 days post-intervention for an optional survey (Appendix T) to assess their perception of gentamicin use, challenges they may have encountered while on the study, and their satisfaction with study participation. Participants may be contacted up to 1 year after the end of their participation.

17.0 Data Safety Monitoring Plan

All study personnel complete training in the protection of human research participants per guidelines issued by the U.S. Department of Health and Human Services, Office for Human Research Protection. Furthermore, the study team ensures that the study protocol is reviewed and approved by the IRBMED and other necessary regulatory and oversight entities, such as the FDA, prior to implementation.

The study team meets weekly to review data for adverse and other reportable events, with a primary aim of ensuring participant's well-being. The team maintains an updated record of protocol deviations and regularly reviews it for any unusual patterns and inaccuracies.

A Data Safety Monitoring Board (DSMB) comprised of a multidisciplinary team including a clinician, regulatory and biostatistician members meets annually to review all serious and unexpected adverse and other reportable events. The DSMB provides an unbiased written report to the sponsor, the PI, the FDA, and institutional review boards, if necessary. All events and trial activities are also reviewed by the clinical trial monitor provided by institution (or contracted outside, if needed) as part of their regularly scheduled monitoring visits.

Under the direction of the PI, the SC/RA is the primary liaison between the participant and the rest of the study team. The SC/RA routinely query the participants as to their well-being (at least bi-weekly, at regularly scheduled telephone encounters), and instructs them to call anytime something is amiss outside of these regularly scheduled interactions. This open line of communication is fostered through mutual respect and trust between the SC/RA and the participant, and results in our study team remaining current on all events concerning protection of human subjects via a bi-monthly report submitted to all collaborators by the front-lines research staff.

17.1 Adverse Event (AE) Reporting

The study team designed a study-specific reporting plan for adverse and other reportable events that is detailed in the protocol in Sections 8.3.4, 8.3.5, and 8.3.6. The purpose of the study-specific plan is to eliminate excessive paperwork and burden on the part of the oversight committees by allowing them to focus their efforts on serious and/or unexpected occurrences.

As the plan indicates, under the direction of the PI, the SC/RA administers the study procedures and collects information to monitor the safety and well-being of participants throughout their involvement with the study. The SC/RA makes every attempt to glean as much information about each event as possible (including, but not limited to: onset date, duration, and severity) and reports all events regardless of expectedness or seriousness to the PI and co-PI (IRB and DSMB, as required) at which time the PI, co-PI and/or DSMB assumes responsibility for further dissemination to the study's respective regulatory agencies (for example, the FDA).

The study specific monitoring and reporting plan cited in the protocol sections above broadly follows the standard AE reporting guidelines at the study's institution.

This study uses the FDA definition of SAE: An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

This study will classify AEs using the Common Terminology Criteria for Adverse Events (CTCAE)

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL; impact on ADLs will be considered within the context of the individual participant's usual capacity.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

17.2 AE Reporting Protocol

AEs not meeting SAE criteria are recorded on the subject's AE case report form (Appendix U) and stored in the subject's Dropbox. The SC/RA provides a narrative description of the AE which includes all relevant details at the top of the form. The forms are reviewed periodically by the PI or Co-PI who has a medical license, who rates and initials each AE in the appropriate spot, indicating that they have reviewed the AE. These reviews occur at a convenient time for both parties, but ideally not less than once a month. For the avoidance of doubt, if there is any question whether an AE could be classified as "serious," the SC/RA notifies the PI and Co-PI to make the final determination. Adverse Events are compiled as appropriate and submitted to the IRB with each Scheduled Continuing Review (SCR), per IRB reporting guidelines.

17.3 SAE Reporting Protocol

AEs meeting SAE criteria are reported to the DSMB within 48 hours of knowledge of the SAE, or the decision to reclassify an event not previously classified as an SAE as an SAE. The SC/RA fills out the SAE case report form (Appendix V) and sends to the DSMB team, the PI, and the institution's Investigator Assistance Team for triage. Most academic institutions offer investigators clinical trial support through their Clinical Trial Support Units or CTSUs. For events meeting FDA reporting criteria (serious, unexpected events related to the IP, see the section for **Unanticipated Problem (UP) Reporting** below.

The MedWatch Form 3500 is completed and submitted to the FDA under guidance and assistance from the Investigator's Assistance Team. In any case, the report contains only known information, even if there is little known information about the event – the study coordinator should report as much as possible, but it is not necessary to fill out every line on the SAE form if that information is not available. The participant's study ID number should be listed, as well as the assigned SAE case number. The SAE case number is assigned based on the year the event occurred, and the number of SAEs in that year, and it should follow this pattern: yyyy###. In other words, the SAE case number for the fourth SAE in the year 2018 (regardless of subject) would be 2018004.

17.4 Unanticipated Problems (UP)

The study team uses the IRBMED criteria to determine the occurrence of an unanticipated problem. All three of the following criteria must be met for an occurrence to be deemed an UP:

1. The occurrence is unexpected in terms of nature, severity, or frequency relative to what is written in the study protocol document and IRBMED application and considering the characteristics of the study population.

2. The occurrence is related or possibly related to participation in this study with "possibly related" defined as there being a "reasonable possibility that the incidence, experience, or outcome may have been caused by the procedures.
3. Suggests that participants or others are at greater risk than previously thought.

17.5 Unanticipated Problem (UP) Reporting

The following is to be considered when reporting UPs.

- Unanticipated problems that are also SAEs will follow the SAE reporting schedule and guidelines.
- Unanticipated problems that are not associated with an SAE will be reported to the DSMB, IRBMED, the Sponsor within 14 days of the study team becoming aware of the problem.
- Reports will include the following information:
    - Description of the problem, i.e., what occurred, how it occurred, any outcome, etc.
    - Discussion of why the event is considered an unanticipated problem.
    - Description of a corrective action plan.

17.6 Reporting Unanticipated Problems to Participants

Participants are notified forthwith about problems that directly impact their current risk level or potentially impact their decision to remain enrolled in the study. Examples of problems that require prompt reporting are:

- Contamination of IP.
- Problems leading to injury or illness related to study supplies (e.g. catheter tips or syringes).
- Breach of confidentiality.

Phone calls are the primary method of communication in these cases and will be documented in the study record.

18.0 Study Compliance

18.1 Institutional Review Board (IRB or IRBMED)

The IRB provides regulatory management for research studies at the institution and, as such, must approve all clinical trials before study recruitment can begin. Additionally, each year on the anniversary of the initial approval of the study application, a scheduled continuing review (SCR) must be completed and approved by the IRB before study procedures can continue. The SCR will include providing lists of all adverse events, serious adverse events and protocol deviations that have occurred during the previous year.

Any changes to the protocol must be submitted to the IRB for approval before any protocol changes can be implemented in the study.

18.2 Staff Responsibilities

It is the responsibility of the PI to delegate appropriate tasks to members of the study team, such as the Co-I, study coordinators, pharmacist, etc. These task delegations will be documented in the Delegation of Authority (DOA) Log (Appendix W) and filed in the site Regulatory Binder in Dropbox. The PI will sign the DOA log indicating they approve the delegation of given tasks to each study team member. Each study team member will also sign the DOA log indicating they accept the responsibilities associated with their delegated tasks.

It is also the responsibility of all study team members to maintain their familiarity with the study protocol and all CRFs. Therefore, study team members must be trained on all IRB-approved protocol amendments and CRF amendments. Staff protocol training will be documented in the Protocol Training Log (Appendix X), signed by the PI to confirm the training occurred, and filed in the site Regulatory Binder in Dropbox.

18.3 Washout Protocol

It is up to the participant and/or their caregiver to seek treatment for an active UTI. The study does not provide any medications other than the IP. Participants who experience a symptomatic UTI may be prescribed treatment by their treating physician. The name and dose of the antibiotic used for treatment is documented in the study record. The participant will discontinue the gentamicin study treatment while taking any prescribed antibiotic(s) and for a minimum 7-day washout period after they have finished the antibiotic(s) treatment. Participants may resume their study drug treatment after finishing their washout period and are asymptomatic. The SC/RA monitors this process via communications with the participant.

Likewise, it is possible that participants are prescribed an oral antibiotic for another reason (i.e. not for a UTI). Regardless of the reason, participants are instructed to pause their daily instillations while undergoing treatment with an oral antibiotic for any reason. They are then to resume their study treatment upon finishing their outside antibiotic and a 7-day washout period. The participants will document this pause in their dosing log and the information is maintained in the participant's research records. This issue will also be discussed at the biweekly phone calls.

18.4 Daily Dosing Logs

To promote and record compliance, the participant is reminded to maintain these logs during their biweekly phone calls. Participants are asked to share these logs during their six-month End of Treatment Visit (V2) or return the logs to the SC/RA to by mail, email or fax if V2 is not done in person.

18.5 Study Drug Return

Participants are requested to return any unused IP to the study site at the end of the treatment period for disposal. The SC/RA requests the Research Pharmacy to send shipping materials and label to each participant who has study drug to be returned.

18.6 Deviation Log

Protocol deviations are defined as any deviation, whether intentional or otherwise, from the protocol with respect to eligibility, study procedures and data collection arising from actions on the part of the participant, the study team or other entity (e.g. Labs run the wrong test). As with AEs, SAEs, and unanticipated problems (UPs), the occurrence of protocol deviations are routinely reviewed at regular study team meetings and entered in the study record according to the following steps:

- A Protocol Deviation Log (cumulative excel spreadsheet -- Appendix Y) is kept in Dropbox for each year of the study and submitted to the IRB with the annual Scheduled Continuing Review (SCR).
- The Protocol Deviation Log records the participant's ID, the date of the deviation, title, and description of the deviation.
- Appropriate corrective plans are developed and implemented where applicable.
- Deviations are reported according to the Event Reporting schedule and/or IRB standard reporting guidelines.
- Deviations are reviewed for frequency and degree of impact on participant safety and data integrity at regular study team meetings.

18.7 Lost to Follow-up

Every effort is made to maintain contact throughout a participant's enrollment. Standard practice for participant contact can involve telephone calls, routine emails, postal mail letters, and includes a review of the EMR to check health status prior to attempting contact. However, the nature of human subject studies involves the possibility of participants becoming lost to follow-up despite these efforts. When determining whether a subject should be classified as "lost to follow-up," study team discretion should be exercised with regards to knowledge of the participants, but rough guidelines to the number of attempted encounters are as follows:

18.7.1 Schedule baseline visit (V1)

- Initial introduction letter and 3 calls without contact
- Unlimited, yet practical, number of calls in context of contact with individual

18.7.2 Bi-weekly phone calls

- 3 encounter attempts (can use email if preferred by participant)
- Send letter asking for participant to call or email study team if no contact made after 3 attempts

18.7.3 Schedule End of Treatment Visit (V2)

- 3 phone calls in the month preceding the projected follow-up window to schedule V2 (can use email if preferred by participant)
- If no contact is made, the SC/RA sends a letter asking for participant to call or email the study team.
- Provide alternatives to facilitate completing outcome assessments: surveys over phone, urinalysis done at a clinic closer to home, etc.
    - Participants may use any of the health system's clinics that are convenient to them.
    - Outside laboratory certification documentation must be obtained if there is any plan to use non-study institutional laboratories.

All encounters are documented via source documents (CRFs) and in the REDCap database. Participants who are deemed "unreachable" at any time before Visit 2 will be withdrawn from the study and categorized as "Lost-to-follow-up." Efforts will be made to accommodate participant's preferred method of contact (i.e., email), where possible, if the subject indicates a preference.

18.7.4 Schedule Follow-Up Visit (V3)

The following efforts are made to reach the participant for the Follow-Up Visit (schedule for three months after V2). A participant is not considered "Lost to Follow-up" if he/she has completed V2.

- Phone calls in the month preceding the projected follow-up window (can use email if preferred by participant).
- Send letter asking for participant to call or email the study team if no contact is made.

19.0 Data Collection and Monitoring

19.1 Case Report Forms/Source Documentation

The case report forms (CRFs) are the primary source documents for capturing participants data throughout the study. As such, care is exercised to ensure that these forms are filled out clearly, legibly, and accurately. The CRFs for a given visit should be completed during the visit, with the information available at the time of the visit. Whoever performs the study visit (SC/RA authorized via the Delegation of Authority Log -- Appendix W) fills out the CRF. Data-related discrepancies or questions are resolved based upon what is recorded on the source document (which is, in most cases, the CRF). The CRFs are reviewed periodically by the PI and/or project manager, SC/RA as well as the Study Monitor for data quality and accuracy.

Case Report Forms are filled out with black ink (not pencil) and be signed and dated in the appropriate places by the SC/RA and filed in a subject-specific binder. If information needs to be changed on the CRF, the information to be changed is crossed out with a single line (do not “scribble out”). The SC/RA initials and dates next to the crossed-out section, and the correct or new information is then recorded on the CRF. A list is included in the appendix of CRFs that are used at each visit (Appendix Z).

This data may also be entered directly into the REDCap database at the time of data collection. (See database entry below.)

When there are medication changes, or in the case of AEs, a brief narrative is written describing the change or AE on the visit/encounter CRF. The change or AE is to be recorded on the participant’s medication log CRF (for med changes) or the participant's AE log (for AEs).

19.2 Database Entry

The data from the CRFs will be input into on online database maintained in REDCap. While it is not as critical to input participants data into the database immediately (as with the CRF), it is still helpful to fill out the online database as close to the participant’s visit/encounter as possible. Information listed in source documents (i.e., CRFs, surveys) should be considered accurate and correct. The data input into the REDCap database should reflect the information that is documented in the source documents. In the case changes need to be made to participant’s data (for example, errors or if new information is received) then the changes are first be made to the source document, and then to the REDCap database. All changes made to the source document are dated and initialed by person making the change.

The database generally follows the same outline as the CRFs to avoid confusion as much as possible. For data such as medications and AEs that will be tracked over the whole study (not linked to a specific visit), unlimited instances of the form are able to be added to the database. AEs and medication changes are to be reported in narrative format in the study visit instrument and also in these repeatable forms. The paper medication/AE CRFs for each participant is tracked by number as they happen in the appropriate column. This way the information is easily searchable in the REDCap database in case changes or updates must be made. Once a form is filled out in REDCap, the form should be marked as “complete” in the dropdown menu, and the form should be saved.

The database is reviewed periodically by the study team and Study Monitor for data quality and accuracy. The REDCap record ID is the same as the participant ID for each participant (i.e., GENT001, GENT002, etc.) Any data placed into other databases such as DROPBox, for example, should be migrated into REDCap for consistency of information.

19.3 Data Monitoring

Clinical site monitoring is conducted regularly by the institution independent clinical trial support unit. At this site, monitoring is conducted by the Michigan Institute for Clinical and Health Research Study Monitoring (MICHR) staff. The assigned monitor reviews study procedures and documentation to ensure the following:

- Participants' rights and well-being are protected.
- Reported data are completed, verified and accurate.
- Trial is being conducted in accordance with good clinical practice.
- Regulatory requirements (e.g., IRBMED and clincialtrials.gov) reporting requirements are up to date.
- The assigned monitor will review periodically at their discretion.
- As a rule, data generated from this study will be retained for future to-be-determined analyses in the development of additional research projects. At this site, the electronic and paper files will be housed at Michigan Medicine under the PI's oversight. Data will be stored and archived according to federal and institutional guidelines (https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/record-keeping-guidelines).
- In general, consent documentation (including HIPAA authorization) and all research records will be retained for 7 years from study completion or publication of the primary manuscript, whichever is later.
- Participants contact information and demographics are kept in the OnCore clinical trials management system and retained indefinitely. Individual subject identifiers are not stored in this system but are managed in a separate HIPAA-compliant database.
- The link between participant and their unique ID will be severed after publications of the primary manuscripts.
- Urine samples may be retained for subjects who opt-in (via the ICF). These samples may be used in future studies for analysis of the microbiome of the urine.

20.0 References

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7. Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic Bowel Dysfunction Score. Spinal Cord. 2006;44(10):625-31.

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9. Tulsky D et al. Overview of the Spinal Cord Injury Quality of Life (SCI-QOL) measurement system. J Spinal Cord Med, May,2015; 38(3)257-69.

10. Plow MA, Finlayson M, Gunzler D, Heinemann AW. Correlates of participation in meaningful activities among people with multiple sclerosis. J Rehab Med 2015 June; 47(6): 538-45.

11. DROPBOx: https://www.dropbox.com (2/28/2024)

Table 3: List of Appendices

A	Protocol
B	Screening Consent without Signature
C	Full Study Consent Form
D	PMR-UTI Flyer
E	PMR-UTI Letter
F	REDCap Screening Log
G	Screening & Enrollment Log
H	Screening (Visit 0) CRF
I	Eligibility Checklist
J	Dosing Log
K	Baseline (Visit 1)
L1	Neurogenic Bladder Symptom Score
L2	Neurogenic Bowel Dysfunction Score
L3	SF-Qualiveen
L4	SCI-QOL Bowel Management Difficulties Short Form 9a
L5	SCI-QOL Satisfaction with Social Roles and Activities Short Form 10a
L6	Community Participation Indicators
M	Medical History CRF
N	Concomitant Medications Log
O	Patient Instructions for Clean Intermittent Catherization
P	BiWeekly Telephone Encounter CRF
Q	Subject Adverse Event (AE) Log
R	End of Treatment (Visit 2) CRF
S	Visit 3 CRF
T	Post-Intervention Survey
U	Adverse Event (AE) CRF
V	Serious Adverse Event (SAE) Form
W	Delegation of Authority (DOA) Log
X	Protocol Training Log
Y	Protocol Deviation Tracking Log
Z	CRFs list by Visit

Appendix A

The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial

Protocol Number: 589-TATE (OnCore # 00137086)

National Clinical Trial (NCT) Identified Number: in03503513

IND Number: 138946

Principal Investigator: Denise Tate, PhD

Co-Principal Investigator: Anne Pelletier Cameron, MD

Co-Investigator: Gianna Rodriguez

IND Sponsor: Denise Tate, PhD

Funded by: National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR), Administration for Community Living, US Department of Health and Human Services

Version: 6.6

March 2023

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with good clinical practice, applicable United States (US) Code of Federal Regulations (CFR), and the NIDILRR Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed human subjects training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

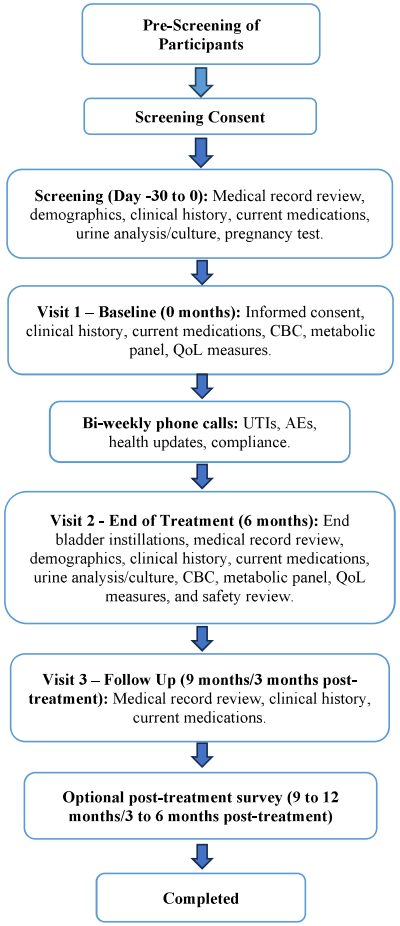
1.1 SYNOPSIS

Title:	The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial
Study Description:	A trial to assess the efficacy of intravesical gentamicin on the occurrence rate of urinary tract infections (UTIs) and bladder complications in patients after SCI, and to assess its effectiveness in promoting overall QOL, community living, and participation.
Objectives:	Primary Objective: Evaluate efficacy of intravesical gentamicin in reducing the number of urinary tract infections during a six-month period.[1] Secondary Objectives: Examine the effectiveness of gentamicin in decreasing associated bladder and bowel complications. Tertiary Objective: Examine the effect of gentamicin on improving health-related quality of life and community participation.
Endpoints:	Primary Endpoint: Number of UTIs Secondary Endpoints: Number of complications Tertiary Endpoints: Quality of life and participation scores
Study Population:	Adults with a traumatic or non-traumatic SCI with neurogenic bladder and recurrent urinary tract infections
Phase:	Phase 2/3
Description of Sites/Facilities Enrolling Participants:	Michigan Medicine (academic medical institution in southeastern Michigan affiliated with the University of Michigan) Department of Physical Medicine and Rehabilitation Department of Urology
Description of Study Intervention:	Intravesical gentamicin + saline instillations
Study Duration:	12 months
Intervention Duration:	6 months

[1] Throughout this document, six months refers to 180 days.

1.2 SCHEMA

Figure 1. Study Flowchart; refer to Schedule of Activities (Table 1) for study procedures by visit



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Visit 1 (Baseline)[1]	Visit 2	Visit 3 (Follow-Up Interview)[7]	Optional Post-Intervention Survey
	Day -30 to 0	D0	Day 180±30	Day 270/Day 90 post-treatment ±30	Day 360/Day 90 post-treatment ±30
Medical Record Review	X	X	X	X	
Informed consent		X			
Demographics	X				
Clinical History	X	X	X	X	
Current Medications	X	X	X	X	
Urine Analysis (UA; plus culture if needed)[2]	X		X		
Pregnancy test	X				
Complete Blood Count		X	X		
Comprehensive Metabolic Panel		X	X		
Self-report measures of QOL[3]		X	X		
Safety Review[5]			X		
Every 30 days +/- 2 business days: ship study product		←	→		
Schedule bi-weekly phone calls[4]		←	→		
Satisfaction survey[6]					X

1 Participation will commence once eligibility is confirmed via urine analysis (UA) (or culture for those individuals with a positive UA); an order for study product will be faxed/emailed to the Research Pharmacy; intervention start date will be the first dose listed on the dosing diary. If the dosing diary is not available, the intervention start date will be recorded as the date told to the study team by the participant and documented in the REDCap database.
[2] A rapid UA will be performed as part of standard of care at the time of screening; UAs at Visit 2 will be study-paid; positive tests will be followed with a urine culture; test results usually take about 4 days
[3] QoL measures include the following standardized surveys: Neurogenic Bladder Symptom Score; Neurogenic Bowel Dysfunction Score; SF-Qualiveen; SCI-QoL Measurement System's *Bladder Management Difficulties*, *Bladder Complications, Bowel Management Difficulties,* and *Satisfaction with Social Roles and Activities*; and Community Participation Indicators Scale (see Section 8.1, "Efficacy Assessments")
[4] Study team will make phone calls every two weeks +/- 3 business days to participants throughout the study period to ask about UTIs, adverse events, compliance and general health updates.
[5]Study team will conduct this visit, likely over the phone, within 30 days after the participant's final instillation in order to assess any adverse events or reactions while the study drug is washing out of the participant's system
[6]Study team will contact participants at least 60 days post-intervention for an optional survey to assess their perception of Gentamicin use, challenges and satisfaction with study participation. Participants may be contacted up to 1 year after the end of their participation.
[7]If Study team is unable to contact participants for the Visit 3, the data can be found in the participant's EMR.

2 INTRODUCTION

2.1 STUDY RATIONALE

This proposal addresses a critical health issue affecting those living with spinal cord injury (SCI), that of recurrent urinary tract infections (UTIs) and their effects on health, quality of life (QOL), community living and participation. While mortality due to urinary tract complications has decreased during the last several decades in persons with SCI, UTIs remain one of the eight leading causes of death among SCI patients,[1] and their effects on QOL and one's ability to function in the community are clearly documented in the literature.[2,3] Although antibiotics have been used to treat UTIs, for those with recurrent infections, oral antibiotic treatment is not always effective and can lead to infections that are resistant to treatment.[4] Intravesical (occurring within the bladder) instillation of a gentamicin solution (a generic antibiotic often used to treat UTIs) has been used clinically in adults with SCI for over 20 years.[5] The process is quite simple and requires flushing the bladder with the solution. Yet, the effectiveness of intravesical gentamicin in prevention of UTIs has not undergone rigorous efficacy testing in SCI. **This study proposes a clinical trial of intravesical gentamicin to reduce the incidence of UTIs in persons with SCI and to assess its effectiveness in promoting overall QOL, community living and participation**.

Two important reasons guided our decision to study the effects of prevention of UTIs with gentamicin on QOL. First, our discussions with colleagues and collaborators show that most SCI patients who use gentamicin for prevention of UTIs are very satisfied with results. Second, there is a lack of clear evidence in the field for broad outcome measures, shown by the limited use of QOL and community participation measures in clinical trials.

Due to its potential efficacy, a robust trial of intravesical gentamicin in person with SCI having recurrent infections is needed. The selection of gentamicin for this Clinical Trial (CT) has several reasons: 1) its ongoing use by patients with SCI and recurrent infections; 2) its potential efficacy as an antimicrobial treatment that shows good results in persons with neurogenic bladder; and 3) its apparent drug safety in this route of administration, with no expected systemic side effects per previous studies.

2.2 BACKGROUND

This study addresses a critical health issue for those living with SCI, that of recurrent UTIs and their effects on health, QOL, community living and participation. While mortality due to urinary tract complications has decreased during the last several decades in persons with SCI, UTIs remain one of the eight leading causes of death among SCI patients,[1] and their effects on QOL and one's ability to function in the community are clearly documented in the literature.[2,3] Although antibiotics have been used to treat UTIs, for those with recurrent infections, oral antibiotic treatment is not always effective and can lead to infections that are resistant to treatment.[4] Intravesical (occurring within the bladder) instillation of a gentamicin solution (a generic antibiotic often used to treat UTIs) has been used clinically in adults with SCI for over 20 years.[5]

Inappropriate bladder management can cause complications including recurrent UTIs, sepsis, and kidney damage due to chronic urinary retention.[6] The instillation process is quite simple and requires flushing the bladder with the solution. However, the effectiveness of intravesical gentamicin in prevention of UTIs has not undergone rigorous efficacy testing in SCI. This study will also contribute new knowledge by examining the associations between neurogenic bladder and bowel complications. It will also examine the impact of this treatment on QOL and community participation among persons with SCI.

Risk factors for UTIs include requiring catheterization by a caregiver,[7] build-up of urinary calculi in the bladder,[8] incomplete voiding, elevated intravesical pressure and catheter use.[9] There exists little consensus on treatment of UTIs in this population. While literature suggests the superiority of clean intermittent catheterization (CIC) for those who are able to perform it,[10,11] a 2012 systematic review suggested that no universal recommendations could be made.[12] The dose of gentamicin was selected based on similar protocols available in the literature.[5,13]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The overall risk of intravesical gentamicin for the management of recurrent UTIs in patients with neurogenic bladder is low. The method of daily bladder instillations is a common clinical strategy at Michigan Medicine, Department of Urology for specific patients (i.e. those with neurogenic bladder and frequent symptomatic UTIs), and it is one that is generally well-received by both patients and care givers. A retrospective analysis of Michigan Medicine patients showed mild and rare adverse events while using Gentamicin bladder instillations.[14] Likewise, Abrams et al.[15] and Defoor et al.[13] suggest that gentamicin as prophylaxis against recurrent UTIs is well-tolerated and of minimal risk.

Urinary tract infection (primary outcome) – Recurrent UTIs are a likely occurrence in this study population. Participants will be instructed to contact their physicians at U-M who provide urological care in the event of UTI symptoms and can expect to be managed according to standard clinical practice (e.g. a course of oral antibiotics). The study team will query participants bi-weekly for any UTI occurrences (including symptoms and treated cases) and prompt the participant to follow-up accordingly if they have not already done so.

Risks associated with regular bladder catheterization – There is *potential for trauma at the site of insertion* of the catheter. The risk associated with participation in this study is no greater than experienced by these patients as part of their typical catheterization process. Likewise, there is *a risk of contamination from using non-sterilized equipment*. Again, this risk is commensurate with participant's risk exposure during their typical catheterization process. Participants and/or their caregivers will typically be experienced in the proper and safe manner of clean intermittent catheterization, but all will receive education and guidance in proper and hygienic catheterization practices with their study materials.

Burden - Cox et al[14] describe daily gentamicin instillations as "minimally burdensome" as it only adds one additional step to the patient's normal nightly catheterization routine. The expected additional time is 1-3 minutes. This burden may be experienced by both the patient and a caregiver. Participants will be told that if the additional burden is too great they may withdraw from the study without repercussion to them or their normal clinical care.

Bladder spasms – Waites et al reported a small percentage (<5%) of patients with bladder spasms related to bladder irrigation using compounds other than gentamicin.[16] It is unclear whether these experiences were related to the process itself or to the product. There were no reports of bladder spasms in the Cox analysis.[14] To minimize the likelihood that the instillation process contributes to bladder spasms, we will provide standard patient and caregiver education on how to perform the instillation and on usual patient experiences. Participants will be told that withdrawal without repercussion is an option in the event the study proves more onerous than anticipated or desired.

Allergic reaction or sensitivity to study product – Individuals allergic to gentamicin or any component of the study product may experience allergic-type reactions including mild asthmatic episodes to anaphylaxis. The overall prevalence of reactive sensitivities is likely to be low (per product insert and clinical experience of Dr. Anne P Cameron, Associate Professor, Michigan Medicine Department of Urology, co-investigator on this study). Individuals with a noted and/or reported history of allergy or sensitivity to aminoglycoside antibiotics (including gentamicin) will be excluded.

Antibiotic resistance – It is unlikely that antibiotic resistance will be an issue in this study. The localized dosing (as opposed to systemic dosing via an oral or IV administration) used in this study will minimize the overall exposure and decrease the likelihood of altered urinary and urethral flora in response to antibiotic exposure. In fact, Cox et al actually demonstrated reduced antibiotic resistance while on gentamicin instillations.[14]

Confidentiality breach – The risk of research data or PHI being accessed without study or clinical care need is very low given the standard safeguards used by Michigan Medicine as an institution and by those on the study team. Access to study-related files is granted on the basis of need by the project manager. Electronic files, including electronic consents, are protected by the Michigan Medicine information technology infrastructure, which includes digital encryption, and paper files are stored in a secure environment including locked file cabinets and restricted access offices.

Toxicity – The likelihood that a participant in this study would experience toxicity is quite low, as toxicity as a side effect is more associated with high doses of prolonged systemic therapy and/or in patients with impaired renal function. While high doses of gentamicin and similar compounds can be associated with nephro- and ototoxicity, these risks are minimized in this study due to the exclusion of patients with renal impairment and because the systemic absorption via the bladder has been found to be negligible.[5,15] Using rats, canines and humans, Wan (1994) instilled gentamicin and evaluated serum

levels 30-minutes post-instillation.[5] Only the rat model showed measurable, yet low, non-toxic levels of serum gentamicin; neither canine nor human tests showed any detectable concentration. In studies with limited follow-up data, there were no clinically relevant side effects.[17] While unlikely based on these factors, gentamicin toxicity may manifest in the form of new onset and prolonged numbness, skin tingling, dizziness and vertigo. Other side effects include prolonged muscle twitching, tinnitus, roaring in the ears or hearing loss. Subjects will be instructed to remain well hydrated during study treatment, and to discontinue treatment if they experience any of these symptoms and to contact the study coordinator.

Overdosage – Overdosage may increase the risk of toxicity described above. The risk of this is minimal as long as subjects take study treatment as directed. As stated above, the localized dosing is unlikely to cause any increase in serum gentamicin levels and, additionally, the dose of gentamicin in each syringe is far below the threshold at which has been reported to cause adverse reactions.

Fetal Harm – Aminoglycosides such as gentamicin can cause fetal harm when administered to pregnant women. A pregnancy test will be administered to females of child-bearing potential at screening. Sexually active females of child-bearing age will also be asked to use appropriate contraception throughout the study while on the study treatment. Subjects who become pregnant after enrollment will be asked to discontinue the study treatment, but may remain in the study, tracking their UTIs and completing study interviews.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefits to patients include: a reduction in symptomatic UTIs, a reduction in use of oral antibiotics used to treat UTI, and an improved quality of life.[14] Successful treatment is likely to enable persons with SCI to live more active, independent and productive lives, contributing to the fabric of society. A 2009 study found that treatments leading to favorable urodynamic results correlated with better quality of life in those with SCI.[18] Neurogenic bladder in general and UTIs in specific lead to increased mortality and morbidity in the SCI population, along with greater incidence of hospitalizations.

Successful treatment can decrease morbidity, mortality and hospitalizations related to UTIs. With fewer medical complications associated with neurogenic bladder (i.e. incontinence and leakage) and bowel (i.e. constipation and incontinence), patients are more likely to live healthy, happy and fulfilling lives.

The potential for benefit extends to caregivers who might experience reduced stress or concern for UTIs, and to clinic staff who might experience fewer telephone encounters from patients related to UTI concerns.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk-benefit profile of using daily bladder instillations of gentamicin is favorable. In patients for whom frequent UTIs are a problem, intravesical treatment with gentamicin offers a minimally

burdensome strategy with minor increase over minimal risk.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The use of intravesical gentamicin reduces the incidence of UTIs during treatment	A reduction in the count of UTIs during the six months of treatment	Allows for verification of reduced UTIs during the intervention. UTIs are associated with major medical, psychological, social and economic consequences
Secondary		
Gentamicin treatment will decrease self-reported bladder complications	A reduction in scores of the Neurogenic Bladder Symptom Severity at six months of gentamicin use.	Allows for validated self-assessment of bladder symptoms in patients with SCI following the intervention.
Gentamicin treatment will decrease self-reported bowel complications	A reduction in scores of the Neurogenic Bowel Dysfunction at six months	Allows for a validated self-assessment of bowel dysfunction severity in patients with SCI following the interventions
Tertiary/Exploratory (other pre-specified analyses)		
The use of intravesical gentamicin will enhance overall quality of life	An increase in SF-Qualiveen scores at six months of gentamicin use	UTIs, associated bladder and bowel complications contribute to reduced QOL in patients with SCI manifesting in negative affect and psychological functioning
The use of intravesical gentamicin will enhance quality of life by decreasing bladder management difficulties	An improvement in SCI-QOL: Bladder Management scores at six months.	
The use of intravesical gentamicin will enhance quality of life by decreasing bladder complications	An improvement in SCI-QOL: Bladder Complications scores at six months.	
The use of intravesical gentamicin will enhance quality of life by decreasing bowel management difficulties	An improvement in SCI-QOL: Bowel Management Difficulties scores at six months.	
The use of intravesical gentamicin will increase overall community participation	An improvement in Community Participation Indicators Scale scores at six months.	Repeated UTIs, associated bladder and bowel complications negatively impact patients' interactions with their social environments
The use of intravesical gentamicin will increase subject's satisfaction with roles and activities scale	An improvement in SCI-QOL: Satisfaction with roles and activities scale scores at six months.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

KEY DESIGN DETAILS

- Hypothesis - The use of intravesical gentamicin will reduce the incidence of UTIs, bladder complications, bowel complications, and will enhance subject's quality of life.
- Pre-post study design, comparing participants number of UTIs during the six-month treatment period to the number they incurred during the six months[2] prior to treatment.
- Participants will begin with active treatment, using gentamicin + saline solution, after they have completed the baseline interview and required urinalysis and bloodwork.
- Phase 2/3
- Single-site - Michigan Medicine in Ann Arbor, MI.
- Dosing – Instillations of treatment solution will occur nightly after the subject's last evening catheterization.
- Interim analysis – The study design and intended sample size preclude meaningful interim analyses.

HYPOTHESES

The proposed study is a pre- post CT in which participants receive the study drug for six calendar months, and analysis compares their frequency of UTIs during this period to the frequency in the prior six months:

1. The incidence of UTIs will be lower during the treatment period than it had been during the previous six calendar months. Occurrence of UTIs throughout this study will be defined as having symptoms of a UTI, followed by a positive urine culture and prescribed treatment.
2. The number of bladder and bowel complications will be likewise decreased during the treatment period compared to what was reported during the baseline interview.
3. Reported health-related quality of life will be higher during the treatment period compared to the how it was reported during the baseline interview.
4. Satisfaction with social roles and activities and community participation will be higher during the treatment period than how it had been reported during the baseline interview.

[2] Throughout this document, six months refers to 180 calendar days.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study's pre-post design is selected because it provides substantially more statistical power than a parallel group design with a similar sample size and allows participants to serve as their own controls, without requiring them to use placebo for half of the study. Our prior project experience, using a cross-over design indicated that subjects are likely to drop out if they think that they are receiving placebo.

- Treatment (gentamicin plus saline) is administered to each study participant for six months.
- This design provides the benefit of a direct comparison within participants (the effect of no treatment vs. treatment).
- Superiority trial – this design allows one to determine a clinically relevant difference between no intervention and the study intervention.

4.3 JUSTIFICATION FOR DOSE

GENTAMICIN + SALINE

The research pharmacy will send participants premixed bags of 60mg of gentamicin in 50ml of normal saline. Participants will draw 25cc with their syringe, switch tips, instill this into the bladder after emptying of urine at their last evening catheterization, and discard the remaining 25cc of premixed solution. This is equivalent to the 30mg which had been used in the initial study protocol. The solution will remain in the bladder until the next catheterization. This is a standard dose that is easily tolerated by patients, and one that does not lead to leakage. It is based on the clinical expertise of Co-I, Dr. Cameron, and is appropriate for bladders sizes in patients with long-term use of indwelling catheterization.[16]

4.4 END OF STUDY DEFINITION

To be considered a "completer" of the study, a participant must:

1. Be placed into the study treatment.
2. Complete the 6-month intervention.
3. Complete both outcome assessments (baseline and 6-months).
4. Complete the follow-up assessments (3-months post-intervention).
5. Have available outcome data on UTI occurrences during the study period as well as during the six months prior to study participation.
6. Complete a safety review with a study team member within 30 days after administering last study drug dose to assess any adverse health/safety events, as required by the FDA.

The end of the study data collection will be when the last participant accrued completes their final assessment.

5 STUDY POPULATION

Participants who had previously been enrolled in this clinical trial and did not complete the intervention due to the study having been put on hold for an extended period will be allowed to re-enroll if they still meet the criteria for participation listed below.

5.1 INCLUSION CRITERIA

The electronic medical record (EMR) will be pre-screened for all inclusion criteria prior to the baseline interview and initial lab work. Criteria will be confirmed by patient or caregiver report at the screening assessment.

- Provision of signed and dated informed consent form.
- Male or female 18 years or older at time of enrollment.
- History of traumatic SCI or non-traumatic spinal cord disease (SCD), with sustained neurological dysfunction. Traumatic and non-traumatic SCI/D are defined according to the International SCI Standards and Datasets.[20]
- At least 6-months post-initial hospital discharge following SCI/D onset.
- Neurogenic bladder.
- Ability to self-perform daily instillation or with help of others and willingness to adhere to the study regiment.
- Negative pregnancy test (for females of childbearing age) and expresses willing and ability to use appropriate contraception while enrolled in the study.
- History of at least 2 UTIs documented in the EMR during the previous six months (prior to screening).
- Have a designated physician or health care provider for routine urological care who is a member of Michigan Medicine.
- Use of clean intermittent catheterization (CIC) or catheterization through a stoma (i.e. Mitrofanoff) as their primary method of bladder management
- Agreement to adhere to Lifestyle Considerations (see below) throughout participation in the study and to complete the daily dosing log as instructed by the study coordinator.

5.2 EXCLUSION CRITERIA

The EMR will be pre-screened for contraindications to participation based on medical history. Criteria will be confirmed by patient or caregiver report at the screening assessment. Final eligibility will be ascertained at the baseline assessment following confirmation of criteria by patient or caregiver report and a urine analysis.

- Concurrent use of *systemic* oral or intravesical antibiotic prophylaxis during the previous six months.
    - Localized antibiotic therapies (i.e. topical antibiotic creams) are permitted
- EMR-documented or self-reported history of gentamicin allergy.
- Patients who are 80 years old or older.
- Positive pregnancy test at screening (for female patients who are of childbearing age).
    - Subjects who are not pregnant and who are willing and able to use appropriate contraception while enrolled in the study intervention will be permitted.
- Patients with a history of 8th cranial nerve disorder.
- Co-morbidities like cancer and chronic disease that could impact patient safety OR significantly affect the rate of UTIs and/or QOL substantially.
- Urological co-morbidities like bladder cancer and history of kidney disease. Co-PI Cameron will review all cases where there is any question about possible inclusion of persons with a history of kidney disease. These include:
    - Patients with EMR-documented renal impairment (e.g. end-stage renal disease, documented glomerular filtration rate (GFR) less than 60 ml/min will be excluded (most recent result).
    - Patients with active pyelonephritis (patients with a history of pyelonephritis, which has been treated and is resolved, will be permitted in the study.)
- Current UTI at screening visit, assessed via urine analysis, culture, and symptoms.
- Concurrent enrollment in a similar clinical trial
- Concurrent use of contraindicated diuretics (ethacrynic acid, furosemide)
- Current use of other contraindicated or disallowed concomitant medications or receiving treatments that may influence the results from this study.
- Known allergy to aminoglycoside antibiotics.
- Otological symptoms at baseline (i.e., tinnitus, severe dizziness/vertigo).
- At the discretion of study team, individuals who are unable or unlikely to comply with procedures and/or for whom study participation is not recommended (e.g. unable to arrange transportation and/or reliable assistance to perform instillations, cognitive and/or behavioral challenges that preclude meaningful participation, poor health, etc.)

5.3 LIFESTYLE CONSIDERATIONS

Participants should show indications of health seeking behaviors (i.e. following bladder management procedures), and be able to consult with their personal physicians when noticing symptoms related to bladder complications and/or UTIs. They should have access to caregivers or family members, as needed, to assist them with instillations following regular catheterizations. Healthy behaviors related to hygiene when having to catheterize and during bowel management procedures are also important.

During this study, the management of all ongoing and new bladder or bowel issues will continue to fall under the purview of the participant's treating physician or care provider. The study team will not offer treatment for any new-onset UTIs, in their role on the study. This means that participants are expected to contact their provider about any new symptoms or infections. Since the physicians on the study team also provide treatment to SCI/D patients for urinary issues, in this clinician role, they may provide participants with care.

Participants or their assistants should be willing to follow study protocol for storage of the medication and preparation of dose for daily instillations as well as complete their dosing diaries.

Dietary restrictions and activity limitations are not required for participants while they are enrolled in this study. Should a participant start one of the contraindicated diuretics above, or become pregnant, they will discontinue the study treatment and notify the study team. Female participants will be asked about pregnancy and compliance with the use of contraception during their bi-weekly follow up visits.

5.4 SCREEN FAILURES

Screen failures are defined as those individuals who consented to participate in the study, but who are subsequently deemed ineligible, usually after the screening visit urine analysis and culture.

Individuals who test positive for a UTI at their screening visit may be re-assessed for eligibility after prescribed antibiotic use. Individuals who undergo a second positive urine tests with UTI symptoms following treatment are ineligible for the study (i.e.; categorized as a screen failure).

Additionally, females of childbearing potential who have a positive screening pregnancy test will be categorized as a screen failure.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

RECRUITMENT

This study will use a multi-pronged approach to recruitment that includes physician-referral, weekly reviews of the Michigan Medicine Urology and PM&R clinic schedules, use of MiChart Best Practice Alerts (BPAs) for satellite outpatient clinics, use of flyers for recruitment at clinics and community based agencies, use of UMhealthresearch.org (which may be linked to the patient's electronic health portal), the MSCIS database and UM SCI Research Registry, Neurogenic Bladder Clinical Database, Patient

Reported Outcomes for Bladder Management Strategies in Spinal Cord Injury project database, and outreach to other related databases and patient advocacy groups in Ann Arbor and surrounding locales. Key criteria for targeting appropriate individuals will include:

- Age
- Presence of SCI and neurogenic bladder (evidenced by neurological classification when possible)
- Use of CIC or catheterization through a stoma
- Experience with recurring documented UTIs (2 or more in the prior six months)
- Availability of regular physician for treatment of any UTIs who is affiliated with Michigan Medicine

The study team will pre-screen EMRs for pertinent eligibility criteria. The study team will also check individuals referred by physicians in clinic, or responses of patients to in-clinic flyers, for eligibility. Individuals meeting this first pass at eligibility can be contacted in multiple ways:

- Approached in clinic by a referring physician or by the study coordinator and/or her trained assistant.
- Sent an introductory letter about this trial.
- Contacted via email with the same information as contained in the introductory letter.

Interested individuals will be invited to a research interview at which time the consent dialog will be initiated and eligibility confirmed. This interview will be conducted through secure, encrypted video conferencing or over the phone.

- Individuals will be emailed a copy of the consent document and a study information sheet prior to the initial research interview. If the individuals do not have email access, physical copies will be mailed.
- Individuals will be invited to review the study information on UMhealthregistry.org prior to the initial research interview.
- We will suggest that the individual share their intentions about potential participation with their family, caregiver, regular physicians, and/or care team prior to the initial research interview.
- We anticipate the ability to screen at least 30-50 participants in order to obtain a sample of 25 potential participants following eligibility screening with the goal of enrolling and retaining a minimum of 15 participants..
- Special efforts will be made to recruit minority participants by ensuring that all potential eligible minority participants are contacted and invited to participate.

RETENTION

The study team will strive for an empathetic relationship with participants to promote retention across their study participation period. Strategies for developing this type of relationship include:

- Minimizing distractions and interruptions during research encounters (visits, phone calls, etc.)
- Being present in the moment.
- Engaging in active listening.

- Being aware of non-verbal cues, i.e. body language, that may turn off an individual.
- Using teach-back methods of communication and information sharing to ensure mutual understanding.
- Keeping individuals updated and aware of necessary and useful information.
- Allowing individuals to correct or add to study team responses.
- Engaging on a personal level, when appropriate.
- Being culturally responsive and aware; assess personal implicit biases.
- Addressing questions participants may have about the study.

Study team members will implement the above strategies in all participant encounters whether planned or ad hoc. In addition to regularly scheduled research phone calls or e-visits for outcome assessments, participants will be contacted bi-weekly via phone calls. These bi-weekly encounters, while ostensibly for the primary purpose of collecting information about UTI occurrences, adverse events, and other symptoms, will also be used to maintain and promote an ongoing relationship with study participants, thus facilitating retention.

REMUNERATION & INCENTIVES

Participants will be paid $90 for participating in the study, $30 at their baseline, six-month, and 3-month post-intervention assessments. Payments will be processed through the Human Subjects Incentive Program and will be conveyed via check or gift card. The precise method of payment will default to check, with the other option being offered upon request for a different method of remuneration.

6.1 STUDY INTERVENTION(S) ADMINISTRATION

Section 6.1 makes repeated references to remote interviews, which will be conducted via an encrypted, HIPAA-compliant video conferencing platform (e.g., Zoom for Health.) It will be standard practice to conduct as many procedures remotely as possible to better protect subject/caregiver(s) and staff against the risk of COVID-19. However, in cases where a remote video interview is not possible, remote telephone interviews will be conducted and the study will follow all UM guidelines for proper consenting.

6.1.1 STUDY INTERVENTION DESCRIPTION

Eligible participants will be given the investigational product (gentamicin + saline solute). Those who use "a closed system" for catheterizing will also be provided with catheters to insert the investigational product into their bladders. Upon the termination of treatment, they will complete a study visit consisting of a blood draw, urine sample, and self-reported quality of life (QOL) measures. Additionally, a safety review will be conducted within 30 days after treatment termination by a member of the study team to assess for any adverse events. Approximately three months following the termination of treatment, participants will complete a final study visit to assess current Gentamicin use and UTI occurrences. Those interested will complete a brief survey about their perceptions of this treatment and

trial during or following the 3 months follow up. The treatment period lasts six months, beginning at the time of the first bladder instillation. Data collection will occur at baseline, at the biweekly visits, at the end of the treatment, and three-months post-treatment. Participants will be monitored bi-weekly throughout the trial through remote video interviews, and/or phone calls. The daily treatment consists of each participant and /or caregiver flushing the bladder with the treatment drug via bladder or stoma catheterization in the evening, leaving it in overnight, and emptying it the next morning.

Treatment

Consists of Gentamicin, an aminoglycoside antibiotic indicated for a variety of gram-negative bacterial infections and saline. The drug will be sent by the Michigan Medicine Research Pharmacy in a concentration of 60mg of the active product to 50ml of normal saline. Participants will receive catheters and syringe tips and will withdraw 25ml with their syringe, switch tips, instill, and dispose of remaining 25ml of solution daily. Participants' shipments will be ordered every 28 days +/- 2 business days by the study team.

6.1.2 DOSING AND ADMINISTRATION

The study treatment will either be self-administered or administered by a caregiver. During treatment participants will be instructed to follow their normal catheter routine for bladder emptying at night, before bed. Once the bladder is empty, participants will attach the syringe containing the study product to the end of the catheter and slowly push the solution into the bladder. Once the full dose is instilled into the bladder, the participant will remove the catheter and syringe, leaving the study product in the bladder until the following morning. Participants will be asked to document the date and time of instillation and the date and time of bladder emptying the next morning in their daily dosing log, along with any other comments related to the process or related observed complications. In summary the process involves:

1. Emptying the bladder as usual at night, before bed
2. Attaching the catheter tip to the syringe
3. Flushing the bladder with the solution
4. Discarding the catheter tip and disposing of used syringe
5. Leaving the solution in place until next routine bladder emptying
6. Emptying the bladder with catheter as usual at next routine bladder emptying the next morning

Treatment condition: gentamicin + saline

- Instillation dose of 25mL solution every day; gentamicin dose = 30mg.
- Instillation to occur at night after the last bladder emptying of the day before bed.
- Self or caregiver administered via catheter.
- To remain in the bladder until next catheterization.

To ensure proper administration, participants and their caregivers will receive training on how to conduct the daily instillations. This training and printed information that includes contact information

for the study team will be provided to participants. A blank copy of the daily dosing log will be included as well. The process will also be explained to them when they enter the study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Michigan Medicine Research Pharmacy will maintain study medication supply (both active and control products) and be responsible for dispensing the medication and study supplies (syringes, needles, catheter tips, and dosing logs) directly to the participant. Participants will receive their study medication in the mail via ground delivery. A signature at delivery is preferred. The Research Pharmacy will maintain shipping records and the study team will follow-up with participants to ensure receipt of study materials at the appropriate bi-weekly visit. The study participants will be asked to maintain a dosing log and review educational materials supplied by the study team. They are not required to save the used syringes but should refrain from re-using the syringes.

The Research Pharmacy and Study Team shall retain records of the following:

- Product shipped date.
- Product received date.
- Quantity of product shipped.
- Batch/serial numbers of products.
- Product expiration dates.
- Participant compliance.

The study team will call participants to confirm receipt of study product. Accommodations will be made for vacations and other travel away from home.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The individual mini bags sent to participants will be labeled with study identification, participant identifier, a “use-by date”, and contact information for study team. A patient education sheet for drawing up and administering the irrigation solution will be included with the shipment. The immediate package shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

6.2.3 PRODUCT STORAGE AND STABILITY

Active products should be stored at room temperature in the packaging they were shipped in.

Participants will be instructed to contact the study team (who will contact the Research Pharmacy) in the event that: 1) they receive a damaged parcel or contents, 2) they notice anything unusual about the syringes or contents, and 3) if they failed to receive an expected delivery. Participants will be advised to look for:

- Signs of a mishandled opened parcel.
- Cracks or evidence of tampering with the mini bags.
- Distortions in the solution, e.g., cloudiness, particulates, etc.

6.2.4 PREPARATION

The active study product (Gentamicin+ saline) will be obtained by the Research Pharmacy from Baxter. This is a premixed solution of 60mg of gentamicin in 0.9% NaCl 50 mL. Participants will be shipped parcels from the Research Pharmacy every 30 days +/- 2 business days. These parcels include the study product in a IVPB bag, IVPB solutions, 18 g 1.5 needles (boxes of 100), syringe catheter tip, alcohol swabs, and sharps container (for needles), sufficient to cover at least 28 days of treatment.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

RANDOMIZATION

Not Applicable.

UN-BLINDING

Not Applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Participants will be asked to complete a daily dosing log to promote and record compliance with the treatment protocol. The participants will share these logs during their 6-month outcome assessment. This will generally be done by emailing them to the Study Coordinator. Data captured will include dates and items of dosing, as well date and time of the subsequent catheterization (to estimate duration of instillation), and any challenges or problems encountered. Participants will be requested to return any unused investigational product to the study site at the end of the treatment period for disposal.

Additionally, the Study Coordinator will ask about compliance with the dosing protocol and study log completion, along with any barriers at the bi-weekly phone calls. The dates, times, and content of these calls will be documented in the study record.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

During each bi-weekly call, participants will be asked about any changes in medications.. Changes will be entered into the CRF.

Concomitant use of ethacrynic acid and furosemide is not permitted in this protocol due to the increased risk of neurotoxicity. Additionally, concurrent use of systemic antibiotics for any reason is not permitted. Subjects prescribed a course of systemic antibiotic therapy will discontinue study treatment for the duration of their antibiotic course.

6.5.1 RESCUE MEDICINE

Participants experiencing a symptomatic UTI may be prescribed an oral antibiotic by their treating physician. The name and dose (if available) will be documented in the study record. It is up to the participant and/or their caregiver to seek treatment for an active UTI. The study will not provide any medications other than the study products.

Likewise, it is possible that participants might be prescribed an antibiotic for another reason (i.e. not for a UTI). Regardless of the reason, participants will be instructed to pause their daily instillations while undergoing treatment with an antibiotic for any reason. They are then to resume their study treatment upon finishing their outside antibiotic. The participants will document this in their dosing diaries and the information will be maintained in the subject's research records. This issue will also be discussed during the bi-weekly phone calls.

Participants may use non-pharmacologic strategies to help manage their urinary health, such as cranberry juice. The use of these types of treatments will be documented at the study visits, and during the bi-weekly phone calls.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants may elect to discontinue the study intervention for any number of reasons (not inclusive list): burden of study procedures, side effects, caregiver limitations, etc. They will be educated on signs and symptoms of toxicity (see Section 8.2) and instructed to notify the study team and their physician for advice on discontinuation of study treatment. If a participant develops COVID-19 while participating in this study, the study team will make every effort to keep the participant in the trial. Participants with COVID-19 will remain in the study unless, for medical reasons, they can no longer participate. Participants will be asked about the reasons for withdrawal from the study when self-initiated.

Regardless of the reason, discontinuation of the study treatment does not mean withdrawal from the study since the study uses an intent –to-treat design. If a participant decides to stop using the study product, and they are willing, they will remain enrolled in the study. This means that study procedures, including bi-weekly phone calls and study visits will go on as scheduled. No drug taper is required when subjects discontinue the study treatment – they may stop immediately. These subjects will also complete the study's final assessments, if willing.

Regarding the discontinuation of treatment, the following information will be documented in the study record:

- Reason for discontinuation of intervention (i.e. treatment).
- Date of last dose.
- Willingness to continue in the study.

If a participant decides to discontinue the study intervention in light of a new or exacerbated clinical finding, we will report the finding on the Adverse Event case report form, and report to the necessary entities as outlined in the Events Reporting Schedule.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw from the study at any time; likewise, the study team can withdraw a participant from the study given any of the following reasons:

- Individual expresses desire to stop participation.
- A new or exacerbated clinical occurrence or adverse event that precludes safe and meaningful participation in the remaining study activities (note: while it may be necessary for a participant who experiences an adverse event to discontinue study treatment, they do not necessarily need to be withdrawn from the study).

  - This criterion can include, but is not limited to, an adverse event, disease progression, other medical condition or lab finding.
- Individual fails to comply with study requirements (e.g., unable or unwilling to complete lab exams, outcome assessments, lost-to-follow up, maintain appropriate communications with the study team, etc.)
- Study team discretion that continued participation is unlikely to be safe and/or meaningful.
- Participant status changes such that an individual no longer meets eligibility criteria.

The reason for withdrawal will be documented in the study record (i.e., CRFs and REDCap database). Participants will be informed that they have been withdrawn from the study by the study team.

Replacements

- Participants who sign the informed consent form but do not receive the study intervention (for whatever reason, e.g., if they change their mind) will be replaced.
- Participants who sign the informed consent form, *and* receive the study intervention, *and* subsequently are *withdrawn or discontinued from the study*, may be replaced at the discretion of the PI and Co-Is.

7.3 LOST TO FOLLOW-UP

Every effort will be made to maintain contact throughout an individual's enrollment. Standard practice for participant contact can involve telephone calls, routine emails, and snail mail letters, and will include a review of the EMR to check health status prior to attempting contact. The exact number of encounters will be based on study team discretion and knowledge of the participants, with consideration of the following guidelines:

Schedule baseline visit

- Initial introduction letter and 3 calls without contact.
- Unlimited, yet practical, number of calls in context of contact with individual.

Bi-weekly phone calls

- 5 encounter attempts made at different times.
- Can use email if preferred by participant.
- Send letter asking for participant to call or email study team if no contact made after 3 attempts.

Second Visit

- Phone calls in the month preceding the projected follow-up window.
- Can use email if preferred by participant.
- Send letter asking for participant to call or email the study team if no contact is made.
  - Provide alternatives to facilitate completing outcome assessments: surveys over phone, urine analysis done at a clinic closer to home, etc.

Since some of the information to be collected for this follow-up may be available in participants' medical records, e.g., documentation of treatment for a UTI, study staff will review records before contacting subjects and query subjects if discrepancies are observed. If the follow-up cannot be completed with the subject, data from their medical record may be entered into the study database. All encounters will be documented in the study record. Individuals who are deemed "unreachable" will be withdrawn from the study and categorized as "Lost-to-follow up."

Participants will be asked if they would like to participate in a brief survey about their experience in the trial. When possible, these questions will be asked at the end of their follow up. For those who already completed their third follow up, the study team will contact them via phone or e-mail asking the same questions. Three to four contact attempts will be made to participants to gauge their interest in completing this post-intervention survey. Email may be used if preferred by participant. If a participant cannot be reached after these attempts they will be considered uninterested in the survey. All participants will be thanked for their participation in the study either verbally or by letter.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Section 8.1 refers to lab visits and study interviews. It will be standard practice to conduct as many procedures remotely as possible to better protect subject/caregiver(s) and UM staff against the risk of COVID-19. However, in cases where a procedure cannot be conducted remotely (e.g., required in-person lab visits for blood draws), the study coordinator will educate study participants/caregivers on all of Michigan Medicine's safety guidelines for entering and being in UM buildings (e.g., COVID screenings, PPE, social distancing, etc.).

Demographics, Clinical History and Current Medications will be abstracted from the electronic medical record and confirmed with participant and caregiver during study interviews. Co-morbidities, bladder and bowel symptoms, and current medications will be recorded. Elements specific to SCI include age at injury and level and completeness of neurological impairment. Changes in health status and medication use will be updated during each interview.

Urine analysis – Prior to any MLabs visit, the study coordinator will remind the participant of Michigan Medicine's policies regarding COVID-19 as they relate to the participant and any person whom they might need to accompany them. Participants will provide urine samples according to MLabs (Michigan Medicine Pathology Handbook) specifications. A clean urine analysis is required for enrollment. Minimum volume required is 0.5ml collected in a non-sterile plastic urine cup. Dipstick analysis may be performed in the clinic at the time of the baseline visit; results are usually available within 10-15 minutes. Tests that come back positive will be sent to the lab for a urine culture. Specimens can be stored at room temperature if received in lab within 2 hours of collection; otherwise the sample should be refrigerated for up to 24hr. Results are usually back within 4 days for a culture.

Self-reported quality of life measures will be collected twice: at baseline and after the treatment period (approximately six months). Several disease-specific and overall quality of life measures will be used, including several scales from the SCI-QOL Measurement System. The SCI-QOL system builds on the PROMIS and Neuro-QOL initiatives were developed to address a dearth of valid patient-reported outcome measures for patients with spinal cord injury.

- *Neurogenic Bladder Symptom Score (NBSS):* 22 item validated measure that assesses symptoms across three domains (incontinence, storage & voiding, and consequences) plus one overall quality of life item.
- *Neurogenic Bowel Dysfunction Score (NBD):* 10 item validated measure that assesses frequency, of defecation and methods of bowel management and complications.
- *SF-Qualiveen:* 8 item validated measure for urinary disorders that covers four domains (bother with limitations, frequency of limitations, fears, and feelings). Participants respond to each item using a 5-point Likert scale.

- SCI-QOL Measurement System's *Bladder Management Difficulties*, *Bladder Complications* and *Bowel Management Difficulties*: these reflect three scales within the SCI-QOL battery that is part of the NIH Patient Reported Outcomes Measurement Information System (PROMIS) initiative. The short form for each scale will be administered (range 5-9 items).
- SCI-QOL Measurement System's *Satisfaction with Social Roles and Activities* is a 10-item short-form that is also part of the overall SCI-QOL battery.
- *Community Participation Indicators Scale:* 20 item validated measure of the frequency and importance of involvement in various types of activities.

UTI Query and Adverse Event Occurrences – Study staff will review the participant's EMR and communicate with them to query for UTI symptoms and occurrences, and any adverse events and side effects every 2 weeks throughout the study. These contacts also serve to promote protocol adherence and compliance with the study schedule, and will occur through remote video interviews, or over the phone. In addition, participants are instructed to contact the study team at any time during the trial to report UTIs, UTI symptoms, AEs, and any other concerns (e.g. transportation challenges or schedule conflicts). Each contact, whether scheduled or ad hoc, will be documented in the study record. Study staff will also query for UTI occurrences at Visit 3 (three months after the end of treatment).

8.2 SAFETY AND OTHER ASSESSMENTS

- The bi-weekly phone encounters and EMR reviews are the primary means of monitoring the occurrences of side effects and participant tolerability of the Gentamicin treatment. If a participant reports a UTI or UTI symptoms, they will be advised to follow-up with their personal provider for management. Any potential manifestation of gentamicin toxicity will also be assessed during these phone encounters. These include new onset and prolonged numbness, skin tingling, dizziness, and vertigo. They also include prolonged muscle twitching, tinnitus, roaring in the ears or hearing loss. The study team will recommend subjects with these symptoms be seen by a physician for otological assessment and possible study treatment discontinuation.
- A complete blood count and comprehensive metabolic panel will be administered at baseline and six months when treatment is concluded.
- If a study-ordered urine analysis (atscreening, and approximately 6-months later, defined here with a window of plus or minus 30 days) reveals an infection, participants will be instructed to follow-up with their personal provider to treat the current infection. The results of the urine test will be included in the EMR and be available to providers across institutions with EPIC access.
- During the follow-up interview (3-months post-treatment), the participant will also be asked if they have used any gentamicin instillations since being off the study drug. If they have used gentamicin, they will be asked if they are still using it. If they have not used gentamicin, they will be asked why not.

- After the follow-up interview, participants will be thanked for their participation in the trial and asked to participate in a final optional survey. If willing, they will be asked about their perceptions of the benefits and/or challenges of using Gentamicin instillations and whether they thought their participation in this trial was worthwhile. This information will be recorded in their CRFs. This option will be offered to participants at the end of their 3-months post-treatment interview and/or at a different time following this interview, depending on their availability and interest in participating.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

This study's definition of AE will align with the FDA definition: "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." In practice, this means we will consider and document any experience or unfavorable and unintended sign, symptom, or disease that arises while an individual is participating in the study. This interpretation includes positive test results on urine analysis and urine culture (both those provided by the study and those ordered by the participant's treating physician) and reports of UTI symptoms (e.g., malodorous and cloudy urine, fatigue, fever, chills, etc.)

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Similarly, this study will use the FDA definition of SAE:

> "An adverse event or suspected adverse reaction is **considered "serious"** if, in **the view of either the investigator or sponsor**, it results in any of the following outcomes: **Death**, a **life-threatening** adverse event, **inpatient hospitalization or prolongation of existing hospitalization**, a **persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**, or **a congenital anomaly/birth defect**."

This definition goes on to i**nclude any other "important medical events"** that may not result in death, be life-threatening, or require hospitalization, but may be considered serious when deemed as such by medical judgment. These **events may jeopardize the participant** and **may require** medical or surgical **intervention to prevent one of the outcomes listed above**. Examples of such medical events include hospitalization for complications from a UTI (e.g., kidney infection, sepsis), allergic response requiring intensive treatment, other side effects or complications that require intensive or ongoing treatment and/or admission to the hospital.

AE occurrences can be caused by any of the study products themselves, other aspects of the interventions like reactions to the catheter supplies, research procedures, the underlying health status of the participant, and any concurrent treatments or therapies not necessarily associated with the study. There might be other causes of AEs that we haven't considered.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The PI, and Co-Is Dr. Cameron and Dr. Rodriquez will be the final arbiters of AE classification.

8.3.3.1 SEVERITY OF EVENT

This study will classify adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 from 2009:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL; impact on ADLs will be considered within the context of the individual participant's usual capacity.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL*.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

Under this classification system, UTIs are a "disorder characterized by an infectious process involving the urinary tract, most commonly the bladder or the urethra." The severity classification begins with grade 2:

- Grade 2 - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)
- Grade 3 - IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

DEFINITELY RELATED

- The event is a known effect of the drug, or procedure (e.g., listed in the protocol documents, consent, publications).
- The event follows an obvious sequence of time, from the drug's administration, or procedure, for which the event is directly attributed to the administration, implantation, activation, or procedure.
- The event ceases with discontinuation of the drug, or procedure (and reoccurs on restarting).
- The event includes data that was only collected for the study.
- The event included disturbing or upsetting questions that the subject was asked for the purpose of the research.

PROBABLY RELATED

- The event is a lesser known or suspected effect of the drug, or procedure (listed in the protocol documents including consent, publications, etc.)
- The event follows a reasonable sequence of time from the drug's administration, or procedure, for which the event may be attributed to the administration, or procedure.
- The event ceases or diminishes with discontinuation of the drug, or procedure.

POSSIBLE RELATED

- The event is a lesser known or possible effect of the drug, or procedure.
- The event occurred within a sequence of time from the drug's administration, or procedure, for which the event may be attributed to the administration or procedure.
- The event could be explained by the characteristics of the population under study.

UNLIKELY RELATED

- The event is NOT a previously known or suspected effect of the test drug, or procedure.
- The event does NOT follow a sequence of time from drug administration, or procedure, for which the event could be attributed to the administration, or procedure.
- The event can be readily explained by the characteristics of the population under study.

NOT RELATED

- The event is NOT known to be an effect of the test drug, or procedure.
- The event does NOT follow a sequence of time from drug administration, or procedure, for which the event could be attributed to the administration, implantation, activation, or procedure.
- The event can be readily and easily explained by the characteristics of the population under study.
- Subject never received study drug or underwent research study procedure.

8.3.3.3 EXPECTEDNESS

The determination of expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention. An AE will be considered "expected" if any of the following conditions are met:

- The event is listed on the informed consent document.
- The event is documented in the proposal to the National Institute on Disability, Independent Living and Rehabilitation Research, this protocol document or IRB application.
- The event is listed as a side effect in the respective drug information materials for gentamicin and saline.
- The event is identified in published literature or otherwise related to the study population (for example, UTIs would be expected, pressure sores would be expected, heart attack would not necessarily be expected given the characteristics of the study population, etc.).

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

- Study staff will call or otherwise contact participants and/or their caregivers to assess for side effects, adverse events, UTI symptoms, etc. every two weeks for the duration of the study intervention.
    - Staff will ask about changes in health status since enrollment in the study.
    - Study staff will ask directed questions regarding specific side effects or difficulties related to the bladder instillation.
- The reporting period for AEs will begin when the participant signs the main consent and end 30 days after the end of treatment.

8.3.5 ADVERSE EVENT REPORTING

This study will follow the standard Institutional Review Boards of the University of Michigan Medical School (IRBMED) reporting schedule for AEs. Refer to https://az.research.umich.edu/sites/default/files/Adverse%20Event%20Reporting%20Guidelines%20for%20INTERNAL%20AEs%20Occurring%20at%20UM_1152018%20OUTWARD%20facing.pdffor a printable version.

Briefly, this reporting schedule precludes reporting to IRBMED all expected non-serious events regardless of relatedness. These events will be recorded in the study record and evaluated for occurrence rates. If any event seems to occur in greater numbers than expected or are more severe than previously known, we will file a report with IRBMED and DSMB.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

- All SAEs will be reviewed and evaluated by the PI and Dr. Cameron, and reported to the following groups: DSMB, IRBMED, and the Sponsor
- SAEs or new clinical findings which meet the reporting requirements under the Federal Food, Drug, and Cosmetic Act and/or the Code of Federal Regulations will be reported to the FDA.
    - Any unexpected fatal or life-threatening suspected adverse reaction to the study product will be reported no later than 7 calendar days after initial receipt of the information.
    - Any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction will be reported no later than 15 calendar days after determining that the information qualifies for reporting.
- The study team will notify the participant's treating physician of any study product-related SAE.

- All SAEs will be followed until satisfactory resolution or until Dr. Cameron and/or the participant's treating physician deem the event to be chronic or that the participant is stable.
- The PI and study team will notify all parties of any unexpected fatal or life-threatening suspected adverse reaction to the study product as soon as possible, but no later than 7 days after becoming aware of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

In general, the occurrence of adverse events throughout the study will not be reported back to the participants. Exceptions to this general policy include:

- SAEs that are related to the study product.
- Findings of the DSMB related to patterns of AE/SAE occurrence that might impact one's decision to continue participation.

Phone calls will be the primary method of communication in these cases and will be documented in the study record.

8.3.8 EVENTS OF SPECIAL INTEREST

We will document any challenges, difficulties or complaints associated with the following:

- Delivery of study product.
- Stability of study product.
- Usability of study product and supplies.

8.3.9 REPORTING OF PREGNANCY

Pregnancy is not considered an adverse event, but it is an exclusion criterion for the study. Individuals reporting a new pregnancy will discontinue their study intervention and will be withdrawn from the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

We will use the IRBMED criteria to determine the occurrence of an unanticipated problem. All three criteria must be met for an occurrence to be deemed an UP. More guidance from IRBMED regarding UPs can be found at the following link: https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-and-other-required-reporting/unanticipated-problems-involving-risks-subjects-or-others

1. The occurrence is **unexpected** in terms of nature, severity or frequency relative to what is written in this protocol document and IRBMED application *and* considering the characteristics of the study population.
2. The occurrence is **related or possibly related** to participation in this study with "possibly related" defined as there being a "reasonable possibility that the incidence, experience, or outcome may have been caused by the procedures.
3. Suggests that participants or others are **at greater risk than previously thought**.

8.4.2 UNANTICIPATED PROBLEM REPORTING

- Unanticipated problems that are also SAEs will follow the SAE reporting schedule and guidelines.
- Unanticipated problems that are not associated with an SAE will be reported to the DSMB, IRBMED, the Sponsor within 14 days of the study team becoming aware of the problem.
- Reports will include the following information:
    - Description of the problem, i.e., what occurred, how it occurred, any outcome, etc.
    - Discussion of why the event is considered an unanticipated problem.
    - A corrective action plan.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be notified forthwith about problems that directly impact their current risk level or potentially impact their decision to remain enrolled in the study. Examples of problems that would require prompt reporting:

- Contamination of study product.
- Problems leading to injury or illness related to study supplies (e.g. catheter tips or syringes).
- Breach of confidentiality.

Phone calls will be the primary method of communication in these cases, and will be documented din the study record.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Our primary hypothesis (H1) is that during the six-month treatment period, incidence of UTIs will be significantly lower than it had been during the six months prior to the treatment period. Our Secondary Hypothesis (H2) states that there will be significantly fewer bladder and bowel complications as reported on the various patient-reported outcome measures at the end of treatment than there had been on the baseline interview, just prior to the start of treatment.

Our tertiary hypotheses (H3 and H4) center on health-related quality of life and community participation. We expect that at the end of the treatment period, QOL will be significantly higher than it had been at the time of the baseline interview, prior to treatment (H3). Similarly, we expect that at the end of the treatment period, community participation will be significantly better than it had been at the time of the baseline interview (H4).

9.2 SAMPLE SIZE DETERMINATION

Power calculations were conducted based on the **primary hypothesis that incidence of UTIs will be significantly lower during the treatment period (gentamicin + saline) than during the prior six months**.

In calculating power, we assume that during the study period, there will be a 50% reduction in UTIs from the number that participant experienced during the prior six months, which serves as the control period. These assumptions are based on the findings of a six-month retrospective study of gentamicin.[22] Calculations of power were conducted assuming that paired samples t-tests will be used to assess the first hypothesis. While we may consider using other additional ways of determining differences in UTIs between the baseline and trial periods, paired samples t-tests will be used at least initially. Because we are working with count rather than continuous data, the t-tests will be conducted using natural log-transformed infection rates rather than the raw rates. Based on our assumptions, the sample size needed to have a power of at least 80% will be 15. This is the necessary sample size of participants who complete the study. SPSS version 28 was used to conduct this power analysis.

9.3 POPULATIONS FOR ANALYSES

The primary analyses will be conducted including those participants who have used Gentamicin flushes for at least half of the days during their 6-month intervention period if data is available for the number of UTIs that they experience during the period when they are using these flushes. Additional analyses will be conducted using an intent-to-treat orientation, using all participant data that is available.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All data will be examined for completeness and outliers before hypothesis testing. Categorical data will be summarized in terms of frequencies, presented as n (%), and continuous data will be summarized in terms of means (standard deviations). Participant demographics and clinical status will be evaluated using descriptive statistics. These analyses will be conducted after all data has been collected. All efforts will be made to recruit a balanced sample representative of persons with SCI/D. Missing data will be handled using common statistical methods such as multiple imputation and the estimation maximization approach.

All statistical procedures will be run using either SPSS[28] or the statistical package R.[29] Statistical significance will be set at $p < 0.05$ for group comparisons and all models.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

To test for significant differences in the incidence of UTIs across periods, as mentioned above, paired samples t-tests will be conducted using log-transformed infection rates rather than the raw rates. We may than subsequently re-analyze this data using a Generalized Linear Mixed Model (GLMM) with log link and a Poisson distribution, as is appropriate for count outcomes data.

9.4.3 ANALYSIS OF THE SECONDARY AND TERITIARY ENDPOINT(S)

To assess the impact of the study intervention on our Secondary Endpoint, bladder, and bowel complications (Hypothesis 2), and Tertiary Endpoints, QOL (Hypothesis 3), and Participation (Hypothesis 4), a similar analytic approach will be used as was used for Hypothesis 1. The outcomes for these hypotheses are all continuous and therefore paired t tests or GLMM will be used. Our plan for handling missing data across all study analyses will include the use of common statistical methods to handle missing data such as multiple imputation and the estimation maximization approach. As appropriate, we may employ sensitivity analysis to assess the effect of data that is not missing at random such as when participants stop using the research treatment but continue to be willing to participate in the study's assessments.

9.4.4 SAFETY ANALYSES

The study team will ask about adverse events at the bi-weekly phone calls. The frequency of events will be monitored by the study coordinator and reported to the PI and co-Investigators at regular meetings. Instances in which the frequency of total events or of any event seem higher than expected will be referred to the DSMB for further review.

In the event that any participant dies during their study participation, the investigators will determine if this is related to the study intervention and document the cause of death regardless. The DSMB will be provided with this information along with that about other adverse events.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Participants will be characterized using standard demographic variables (e.g. age, sex, etc.) and clinical status (age at injury, level of injury, completeness of injury, etc.)

9.4.6 PLANNED INTERIM ANALYSES

The use of our study design results in no complete data being ready to be analyzed until at least six months into the conduct of the intervention. Given this, the timeframe for all data collection and the intended sample size, meaningful interim analyses will not be viable to conduct.

9.4.7 SUB-GROUP ANALYSES

Again, given the small sample size, planned group analyses are unlikely except for review of characteristics associated with completion vs. non-completion of the study.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Available participant data from each time point will be retained in the study dataset.

9.4.9 EXPLORATORY ANALYSES

We do not have any exploratory analyses planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Section 10.1 makes repeated references to remote interviews, which will be conducted via an encrypted, HIPAA-compliant video conferencing platform (e.g., Blue Jeans, Zoom for Health, etc.) It will be standard practice to conduct as many procedures remotely as possible to better protect subject/caregiver(s) and staff against the risk of COVID-19. However, in cases where a remote video interview is not possible, remote telephone visits will be conducted and the study will follow all UM guidelines for proper e-consenting. Baseline interviews may also be completed at U-M clinics, if participants prefer, following all U-M COVID-19 guidelines.

10.1.1 INFORMED CONSENT PROCESS

The informed consent process will center on providing sufficient and usable information that allows an individual to make a choice about whether to participate in the study. A copy of the consent document will be provided (e.g., mailed or emailed) prior to the remote or in-person baseline interview. Individuals will be encouraged to discuss the merits of participation with their caregiver, families, and physician. The actual consent dialog will occur during the remote baseline interview. Baseline visits can also be conducted in person, at U-M clinics adjacent to patient appointments, if participants prefer, following all U-M COVID-19 guidelines.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Participants will be provided with either an electronic or physical copy of their signed and dated consent document. If consent is obtained using a mailed copy of the consent, which participants send back after signing, they will be resent a physical copy after all signatures are included. If consent is provided electronically, a physical copy will be mailed to participants, upon their request. The signed consent will be uploaded to the participants' electronic medical record.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be obtained prior to the beginning of the baseline visit. The dialog will follow the IRBMED-approved consent document and cover sheet with an emphasis on participant responsibilities, the risk-benefit profile, and the voluntary nature of research participation (including the right to withdraw without prejudice). A member of the study team will lead the discussion, allowing time for and encouraging questions along the way. Visual materials (such as mock study supplies and written materials) will be available during the consent dialog to assist the patient and their caregiver in deciding about participation. Electronic informed consent signatures will be collected using SignNow. All procedures will adhere to the IRBMED Guidance for use of SignNow for Electronic Informed Consent Procedures. If subjects are unable to use SignNow for consenting, e.g., if they do not have a computer for this purpose, of if they do not wish to, a physical version of the consent document can be mailed to them to sign and return, in a provided, stamped envelope. Also, if participants choose to do the baseline

interview at a U-M clinic location, e.g., prior to or following a clinic visit, the consent will be provided to them at that time, though a copy may be sent to them prior to this appointment to review.

Individuals can elect to withhold informed consent without prejudice and can be rescheduled for another baseline appointment if desired. Regardless, study procedures will not be administered without a valid documented consent document.

The original electronically signed and dated consent document (or physically singed consent) will confirm the provision of voluntary and informed agreement of the participant to enroll in the study. For individuals who are unable to sign the consent electronically or physically due to upper extremity paralysis, a witness who is unassociated with the study will be made available during the consent process. This person will electronically or physically sign the consent document, verifying that they have witnessed the individual providing assent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

If suspension of study activities or a premature end to the study is necessary, relevant parties will be notified in writing, and/or via a phone call. For example, the research team will notify participants by phone, e-mail and/or letter in the event the study is terminated for any reason prior to its conclusion. It will be the PI's responsibility working with his/her study team to follow-up with other invested entities, e.g., IRBMED and Sponsor, the FDA, etc., and will provide the reason(s) for the termination or suspension.

Circumstances that might result in early termination of the study include:

- Occurrence of unexpected, significant, or unacceptable risks.
- Demonstration of efficacy suggesting further observation is unnecessary.
- Insufficient compliance to protocol rendering insufficient or invalid data for analysis of primary outcome.
- Demonstration of futility (e.g., inability to recruit and retain participants).
- Lack of key resources needed for the trial (i.e. drug supply) and funding challenges.

The study may resume provided reason(s) for early termination have been adequately addressed and approved by the relevant oversight agencies.

10.1.3 CONFIDENTIALITY AND PRIVACY

This study will follow all national and institutional regulations and safeguards to protect participant confidentiality and privacy. An individual's research data (e.g., outcome assessments like surveys and lab results), clinical data and demographics (information abstracted from the EMR and patient-report), and contact information (e.g. telephone number, address, etc.) are all protected by institutional confidentiality practices.

- Access to study data is granted based on the need for completion of job-role responsibilities and to uphold patient safety. The types of data accessible will include but are not limited to data collected for research purposes (e.g., patient-reported outcomes), results of urine analysis in the EMR, other relevant medical records, Research Pharmacy records, and contact information, etc.
    - Data or other participant information will not be released to an unauthorized individual or entity (i.e., agents not listed Section 9 of the consent document) without approval from the PI and/or participant.
- Research procedures, including the consent process, will be conducted in as private a setting as possible. Likely locations include private rooms dedicated to research and exam or conference rooms located within the clinic.
- Participants will be assigned a unique alphanumeric code to identify their research records. Case report forms will be labeled with this identifier rather than an individual's name. The link between an individual and their code will be stored in a HIPAA-compliant database (e.g., REDCap, OnCore Clinical Trials Management System, etc.) Both systems allow for role-based restrictions on data access and download.
- All files will be in electronic form, unless otherwise specified.
- All electronic files will be maintained behind Michigan Medicine firewalls and require passwords for access.

The individuals who are most likely to access all or some of the research data and information include:

- Study team members involved in the day-to-day operations (e.g., project manager, study coordinator, PI, research assistant, etc.) will be responsible for maintaining study databases and research files in a manner conducive to preserving participant confidentiality and privacy.
- Research Pharmacy staff - will require access to participant contact information.
- Members of the Data Safety Monitoring Board (DSMB) - will have full access to participant information and research data. Specific data will be prepared and provided by the study team for review at the DSMB's request.
- Study Monitor (MICHR staff) – will also have widespread access upon request.
- Data analysts & statisticians - will primarily use coded data sets in their day-to-day work, unless identifying information is required to evaluate safety endpoints.
- Co-investigators - will have access to full study records upon request.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

As a rule, data generated from this study will be retained for future to-be-determined analyses in the development of additional research projects. The electronic and paper files will be housed at Michigan Medicine under the PI's oversight. Data will be stored and archived according to federal and institutional guidelines (https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/record-keeping-guidelines).

- In general, consent documentation (including HIPAA authorization) and all research records will be retained for 7 years from study completion or publication of the primary manuscript, whichever is later.
- Participant contact information and demographics will be preserved in the OnCore clinical trials management system and will be retained indefinitely. Individual subject identifiers will not be stored in this system but will be managed in a separate HIPAA-compliant database.
    - The link between participant and their unique ID will be severed after publications of primary manuscripts.
- Urine samples may be retained for subjects who opt-in (via the consent). These samples may be used in future studies for analysis of the microbiome of the urine.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**DSMB**
Denise Tate, PhD	Michael Geisser, PhD (chair); Kate Kraft, MD; Shokoufeh Khalatbari, MS
Study Physicians, Prescribers, & Co-Investigators	
Anne Cameron, MD	
Gianna Rodriguez, MD	
Patricia Maymi-Castrodad, MD	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the following expertise and/or qualifications:

- Clinical knowledge of patient population and study intervention products, e.g., urologists, pharmacists, PM&R physicians treating patients with SCI, etc.
- Statistics
- Independent from the day-to-day study conduct

- Generally free of conflicts of interest (COI)
    - In the case of appearance of a COI or potential COI, we will put in place adequate measures and practices to minimize bias.

The DSMB will meet on an enrollment-based schedule. For every ten subjects which complete their 6-month intervention, the DSMB members will convene to assess safety and efficacy when appropriate, comparing data from the six-month period prior to enrollment with that obtained during the treatment period. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study team and the Sponsor, when appropriate. They will be provided with periodical updates on study participants, AEs and SAEs as well as other issues encountered during the conduct of this trial.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted by Michigan Institute for Clinical and Health Research Study Monitoring staff. The assigned individual will review study procedures and documentation to ensure the following:

- Participants' rights and well-being are protected.
- Reported data are completed, verified and accurate.
- Trial is being conducted in accordance with good clinical practice.
- Regulatory requirements (e.g., IRBMED and clincialtrials.gov) reporting requirements are up-to-date.
- The assigned monitor will review periodically at their discretion.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The responsibility for upholding quality assurance and control practices will involve an engaged PI and project manager in close concert with other study staff. Regular meetings and documented routine communications will provide a record of study activities. Meetings of the study team (e.g., PI, Co-Investigators, project manager and coordinator/research assistants) will focus on accrual and withdrawal updates, challenges and problem-solving related to recruitment, AE/ORIO/UP updates, and any other issue relating to the day-to-day operations of the study. Full details of study procedures and quality control practices will be described in the Manual of Operations. Minutes will be generated for all weekly meetings.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Day-to-day data collection and management will be the responsibility of the study coordinator(s) or other study staff, with the project manager (Martin Forchheimer, MPP) providing managerial and statistical oversight. Source data are defined as:

- Survey responses of participants whether via electronic direct-entry or using paper and pencil

- EMR for enumeration of UTIs documented on appropriate case report form (CRF).
- Participant dosing log for compliance with medication protocol.
- Participant-report of clinical status updates and data regarding concomitant medication will be recorded on the appropriate case report form.
- Adverse events as reported by participant or as indicated in the EMR will be documented on the appropriate case report form.

All CRFs and study documents will be completed electronically except for participants dosing logs, reviewed for accuracy, and stored in the participant research record within the secured database.

All study data (e.g., outcome data, encounter records, adverse events, etc.) will be stored in a REDCap database supported by the Michigan Medicine IT infrastructure. Data base quality checks will be conducted by the project manager and/or study coordinator to determine missing information, and data inconsistencies.

10.1.9.2 STUDY RECORDS RETENTION

Data will be stored and archived according to federal and institutional guidelines (https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/record-keeping-guidelines).

- In general, consent documentation (including HIPAA authorization) and all paper research records will be retained for 7 years from study completion or publication of the primary manuscript, whichever is later.
- Electronic files will be retained indefinitely, though participant identifiers (participant ID, MRN, clinic visit dates, etc.) will deleted or adjusted to ensure anonymity after the publications of primary manuscripts.

10.1.10 PROTOCOL DEVIATIONS

For the purposes of this study, a protocol deviation is defined as any deviation, whether intentional or otherwise, from the protocol with respect to eligibility, study procedures and data collection arising from actions on the part of the participant, the study team or other entity (e.g., MLabs runs the wrong test). Details related to protocol deviations documentation and reporting will be included in the Manual of Operations. As with AEs, SAEs and unanticipated problems (Ups), the occurrence of protocol deviations will be routinely discussed at regular study team meetings.

- Deviations will be documented in the study record.
- Appropriate corrective plans will be developed and implemented where applicable.
- Deviations will be reported according to the Event Reporting schedule and/or IRBMED standard reporting guidelines.
- Deviations will be reviewed for frequency and degree of impact on participant safety and data integrity at regular study team meetings.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will abide by FDA, NIH and IMJE requirements to share information about this study via timely registration, updates, and results reporting in clinicaltrials.gov. The informed consent document will include statements to inform participants of this fact. The results of the primary analyses will be submitted to a peer-reviewed journal for digital archiving in PubMed Central upon acceptance for publication.

10.1.12 CONFLICT OF INTEREST POLICY

The study team will follow the Michigan Medicine policies on conflict of interest. Conflict of interest management plans will be developed and upheld for any member of the study with an actual or apparent conflict. Management plans will include appropriate disclosure and mitigating practices to minimize effects on participant well-being and data integrity.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CIC	Clean Intermittent Catheterization
CRF	Case Report Form
CBC	Complete Blood Count
CT	Clinical Trial
DSMB	Data Safety Monitoring Board
EMR	Electronic Medical Record
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IND	Investigational New Drug
IRB	Institutional Review Board
IRBMED	Institutional Review Boards of the University of Michigan Medical School
MIAP	Michigan Institute for Clinical and Health Research Investigator Assistance Program
MICHR	Michigan Institute for Clinical and Health Research
MOP	Manual of Procedures
NCT	National Clinical Trial
NIDILRR	National Institute on Disability, Independent Living and Rehabilitation Research
NIH	National Institutes of Health
PI	Principal Investigator
QOL	Quality of Life
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCD	Spinal Cord Disease
SCI	Spinal Cord Injury
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UA	Urinalysis
UP	Unanticipated Problem
US	United States
UTI	Urinary Tract Infection

10.4 PROTOCOL AMENDMENT HISTORY

Date	**Affected Section(s)**	**Summary of Revisions Made**	**Rationale**
14 MAR 2018	6.3, 10.1.3, 10.1.7	Added language on clinical monitoring	This study is now an FDA IND trial and will require clinical monitoring
14 MAR 2018	8.3.6	Added language on FDA reporting	FDA reporting is required for the same reason as above
11 JUN 2018	6.1.2	Clarified order of instillation process	Was unclear per MICHR safety monitoring group
09 JUL 2018	2.3.3, 5.1, 5.5, 6.1.2, 7.3	Changed assessment of risk, clarified inclusion criteria, training materials, recruitment methods	IRB comments
09 JUL 2018	6.3, 7.2	Clarified using blocking randomization, treatment discontinuation	FDA comments
25 OCT 2018	4.4, 5.2, 10.1.5, 10.1.6	Clarified washout period, Clarified eligibility criteria, Listed DSMB members names, revised DSMB meeting schedule	Per DSMB request
3 SEP 2019	4.3	Clarified dosing instructions	FDA comments
28 May 2020	1.3, 6.1.1, 6.2.4	Clarified shipping frequency window	Per MICHR monitor's suggestion
13 July 2020	6.1, 8.1, 10.1	Included COVID-19 procedures/precautions	Per Michigan Medicine, U of M, IRB requirements
13 October 2020	1.3, 7.1	Assigned superscript number to schedule of activities SOA), added language regarding continued study participation of COVID-19 patients	FDA comments
17 March 2021	4.1-4.4, 5.1, 6.1, 6.3	Change in study design	Change the study design from a randomized cross-over trial to a pre- post design in which all participants receive the active study drug. The study will assess the difference in the number of UTIs during treatment to the number that occurred in the six months prior to their start in the trial.
30 November 2021	1.3, 3, 4.4, 5.2, 6.1	Addition of study event	Added 3-month post-intervention follow-up interview
6 July 2022	1.3, 8.1	Remove special contact of participants to do COVID screening by study staff prior to conduct of laboratory assessments	Such screening is part of standard practice for of all in-person clinical contact and thus, does not need to be conducted by the study team.
3 October 2022	10.1	Allow for informed consent and study visits to be conducted in person	Adding these options may reduce burden for study participants
5 December 2022	1.2, 1.3, 5.2, 5.4, 6.5, 7.3	Allow for follow up information to be collected from participants' medical records. Clarify screen failure assessment.	Necessary data may be collected even if participants are lost to follow up
1 March 2023	1.2, 6.1.1, 8.1, 8.3.4, 10.1.5	Reconcile discrepancies in the calendar, provide a timeline for AEs, addition of a co-investigator	Clarified which assessments will be performed at each visit and when AEs will be recorded

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Appendix B

UNIVERSITY OF MICHIGAN
CONSENT TO BE SCREENED FOR ELIGIBILITY IN A RESEARCH STUDY

NAME OF STUDY AND RESEARCHERS

Title of Project: The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial

Principal Investigator: Denise Tate, PhD

GENERAL INFORMATION

We're doing a study to learn more about the effect of intravesical instillation (added to the bladder drop by drop, and leaving in place overnight) of a gentamicin solution (a generic antibiotic often used to treat urinary tract infections on the occurrence of urinary tract infections (UTIs) and bladder complications in patients after SCI, and to assess its effectiveness in promoting overall quality of life. Gentamicin, an antibiotic, is commonly taken orally to treat a variety of infections, including UTIs. Using gentamicin by putting it directly into the bladder is not an approved use by the U.S. Food and Drug Administration, and is considered to be experimental in this study.

Before you can join the study, we'll need to make sure you qualify. To find out whether you qualify, we'll take a sample of your urine to perform laboratory tests to check for the presence of any active bacteria. If you are a female capable of having children, we will also administer a pregnancy test. Your medical records will be used to verify required medical history. Once your medical records and the results of your urine test have been reviewed the study team will determine if you qualify to be enrolled in this clinical trial of intravesical gentamicin.

If you do qualify and are interested in joining, we will give you another consent form to read and sign. That form will explain the rest of the study in detail.

Providing this urine sample to find out whether you qualify for our study is voluntary. You don't have to take part if you don't want to. Choosing not to take part won't affect your medical care in any way. Even if you do qualify for the study and decide to join, you can change your mind later and leave the study.

Determining whether you qualify for the study won't benefit you directly.

You or your insurance may be charged for some of the screening procedures, but only if they are used as part of your clinical care.

Like the information in your medical record, the records we create in this study will remain confidential and protected.

AUTHORIZATION TO RELEASE PROTECTED HEALTH INFORMATION

Agreeing to participate in this screening gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by contacting the researchers listed below (under Contact Information).

Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

It's possible that the researchers or others will need access to information about you during or after this study. For example:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- The University of Michigan or a government agency may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors, funders, safety monitors or committees, may need the information to, make sure the study is done safely and properly, learn more about side effects, or analyze the results of the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular Michigan Medicine medical record.
- Federal or State law may require the study team to give information to the Food and Drug Administration (FDA) or other government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

As a rule, the researchers will continue to use information about you until the study is over and will keep it secure until it is destroyed. Limited information about you may continue to be used after the study is over, for other research, education, or other activities. But use of this information would not reveal your identity.

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information see http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

A description of this clinical trial may be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

If you agree to participate in this study screening, you will receive a copy of this "Consent to Be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

CONTACT INFORMATION

To find out more about the study, to ask a question or express a concern about the study, or to talk about any problems you may have as a study subject, you may contact one of the following:

Principal Investigator: Denise Tate, PhD Mailing Address: 325 E Eisenhower Pkwy, Lower Level, Ann Arbor, MI 48108 Telephone: (734) 763-0971 Email: dgtate@med.umich.edu	Study Coordinator: Elizabeth Sullivan BGS, CCRP Mailing Address: 325 E Eisenhower Pkwy, Lower Level, Ste 4, Ann Arbor, MI 48108 Telephone: (734) 276-0460 Email: elizsull@umich.edu

You may also express a concern about a study by contacting the Institutional Review Board:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
734-763-4768
E-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study, you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

FOR OFFICE USE ONLY

I have explained the research to the subject and answered all of his/her questions. The subject understands that by verbally agreeing to be screened for this study, he/she is providing consent to participate in the screening procedures. The participant has received a copy of this Information Sheet for his/her records.

Name of Interviewer (printed)	Screening ID#
Signature of Interviewer	Date

Appendix C

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

Study title: The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial

Company or agency sponsoring the study: DHHS – Administration for Community Living/National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)

Names, degrees, and affiliations of principal investigator and study coordinator:

Principal Investigator: Denise Tate, PhD. Department of Physical Medicine and Rehabilitation
Study Coordinator: Elizabeth Sullivan, BGS, CCRP. Department of Physical Medicine and Rehabilitation

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

2. PURPOSE OF THIS STUDY

2.1 Study purpose: This study addresses a critical health issue for those living with spinal cord injury (SCI), that of recurrent urinary tract infections (UTIs) and their effects on health, quality of life (QOL), community living and participation. Complications from UTIs remain a leading cause of death among SCI patients, and their effects on QOL and one's ability to function in the community are well known. Although antibiotics have been used to treat UTIs, for those with recurrent infections, oral antibiotic treatment does not always work and can lead to infections that are resistant to treatment. Intravesical instillation (added to the bladder drop by drop, and leaving in place overnight) of a gentamicin solution (a generic antibiotic often used to treat UTIs) has been used clinically in adults with SCI for over 20 years. Yet, the effectiveness of intravesical gentamicin in prevention of UTIs has not been well tested in SCI. Using gentamicin by putting it directly into the bladder is not an approved use by the U.S. Food and Drug Administration, and is considered to be experimental in this study. **This study proposes a clinical trial of intravesical gentamicin to reduce the incidence of UTIs in persons with SCI and to assess its effectiveness in promoting overall QOL, community living, and participation.**

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adults with SCI who self-catheterize, consent to be screened for current UTIs via urine analysis, and are found to be free of infection, may volunteer to take part in this study. All new participants must have a designated physician who will manage any UTIs the subject may get throughout the duration of the study.

3.2 How many people (subjects) are expected to take part in this study?

About 25 people are expected to be enrolled in this study at the University of Michigan.

Consent Subtitle: _____
Consent Version: _____

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

*All study procedures will follow the University of Michigan's COVID-19 safety guidelines***.**

Interviews: After signing this consent document, the study will begin with a baseline interview. This will be done remotely by video conference. We will use an encrypted, HIPAA-compliant video conferencing platform (e.g., Zoom for Health). A link will be sent to your email to access the video conference. You will click on this link, and will be taken to the video feed. If the visit cannot be done through video conferencing, it will be completed over the phone. The purpose of this visit is to establish your current health status before beginning the study drug. You will be asked about your past and present spinal cord disease or conditions, as well as any medications you currently take. You will also be educated on the proper way to administer the study drug, and will complete surveys. In addition to this visit, there will be one other follow-up visits (at 6-months), where we will ask you about any updates to your health, problems or issues with the study medication, and complete a survey.

Lab visits: You will have your blood drawn for a couple tests at Michigan Medicine's MLabs. You will also supply a urine sample to check for a current UTI. These visits are expected to take 30 minutes to an hour. Per Michigan Medicine policies, if you or a person whom you need to accompany you to these visits has g any COVID-19 symptoms, you will have to reschedule your lab visit.

Surveys: During each of the three video conference/telephone study interviews, you will complete surveys. These surveys will ask questions about any symptoms you are experiencing, as well as aspects of your quality of life. It should take you 30 minutes to an hour to complete each of the surveys.

Bi-weekly phone encounters: In addition to the interviews and lab visits, the study team will call you every two weeks while you are enrolled in the study. The purpose of these calls is primarily to ensure there are no issues with receiving or using the study drug, as well as to query for any adverse events such as UTIs. These phone encounters are expected to take about five minutes.

Study drug: The dosage of gentamicin will be 30 mg of gentamicin per every 25 mL of solution. Participants in this study will receive gentamicin solution for six months.

Retention of urine specimens: Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your urine samples and medical information for future research.

If you give us your permission, we will use your urine samples and medical information for future research. Even if you give us permission now to keep some of your urine samples and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your urine samples, we may not be able to take the information out of our research.

We may share your urine samples and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your urine samples and medical information with other researchers, we will not be able to get it back.

Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your urine samples. Allowing us to do future research on your urine samples and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Throughout the duration of the study, you will administer the study medication each night before bed. The medication will be delivered to your house at no charge to you or your insurance. The instillations are able to be done along with your normal nightly catheterization routine. The instillation of the medication involves the following:

1. Emptying the bladder as usual at night, before bed
2. Withdrawing 25ml of the solution using the syringe
3. Attaching the catheter tip to the syringe
4. Flushing the bladder with the solution
5. Discarding the catheter tip and disposing of used syringe
6. Leaving the solution in place until next routine bladder emptying
7. Emptying the bladder with catheter as usual at next routine bladder emptying, typically the next morning

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments, take your study medication as directed, and report any adverse reactions you may have during the study.

4.2 How much of my time will be needed to take part in this study?
There are two lab visits and three interviews. Each interview, as well as each lab visit, is expected to take about 30 minutes to an hour. The interviews will be completed from your home using remote video conferencing or telephone. Lab visits will be completed in-person at a Michigan Medicine lab. Bi-weekly phone encounters will take approximately five minutes each. The nightly study drug instillations may be done as part of your normal nightly catheterization routine and will not require a significant time investment.

4.3 When will my participation in the study be over?
After you have completed all doses of study drug instillations, the second interview will take place. A third interview, similar to the first two, will then take place approximately three months later. After you have completed this, your participation in the study will be over. Provided that you complete all the study procedures, your participation will last approximately 9 months from the time you enroll in this study.

You may be discontinued from the study medication before the study drug schedule is completed. This may be brief (for example, in the case you are prescribed a course of an oral antibiotics), or permanent. If this happens, we request that you continue in the study, without taking any study medication, for protocol specified procedures at regularly scheduled labs and interviews until the study is completed.

As with any study, your participation may end at any point should you decide you would like to withdraw from the study.

4.4 What will happen with my information and/or biospecimens used in this study?
Your information may be shared with the NIDILRR (sponsor).

With appropriate permissions, your collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The overall risk of intravesical gentamicin for the management of recurrent UTIs in patients with neurogenic bladder is low. The method of daily bladder instillations is a clinical strategy at Michigan Medicine, Department of Urology for specific patients (i.e. some of those with bladder issues and frequent UTIs), and it is one that is generally well-received by both patients and care givers.

Urinary tract infection (primary outcome) – Recurrent UTIs are a likely occurrence in this study population. You will be instructed to contact your treating physician in the event of UTI symptoms and will be managed according to their expertise (e.g. they may prescribe you a course of oral antibiotics). The study team will regularly ask if you are having any UTI occurrences (including symptoms and treated cases) throughout the study.

Risks associated with regular bladder catheterization – There is *potential for trauma at the site of insertion* of the catheter. The risk associated with participation in this study is no greater than experienced as part of your typical catheterization process. Likewise, there is *a risk of contamination from using non-sterilized equipment*. Again, this risk is no different than it is with your typical catheterization process. You and/or your caregivers will receive education and guidance in proper and hygienic catheterization practices with your study materials.

Burden – This method is minimally burdensome as it only adds one additional step to your normal nightly catheterization routine. The expected additional time is 1-3 minutes. This burden may be experienced by both the you and a caregiver. If the additional burden is too great you may withdraw from the study without repercussion to you or your normal clinical care.

Bladder spasms – A small percentage (<5%) of patients report bladder spasms related to bladder instillations using compounds other than gentamicin. This has not been reported when using gentamicin. It is unclear whether these experiences are related to the process itself or to the product. We will provide you with standard patient and caregiver education on how to perform the instillation and on usual patient experiences. You may withdraw from the study at no penalty to you in the event the study proves more difficult than anticipated or desired.

Allergic reaction or sensitivity to study product – It is possible that you have an unknown allergy to gentamicin or similar antibiotics. Individuals allergic to gentamicin or any component of the study product may experience allergic-type reactions including mild asthmatic episodes to anaphylaxis. The overall prevalence of reactive sensitivities is likely to be low.

Antibiotic resistance – It is unlikely that antibiotic resistance will be an issue in this study. The localized dosing (as opposed to systemic dosing via an oral or IV administration) used in this study will minimize the overall exposure and decrease the likelihood of altered urinary and urethral flora in response to antibiotic exposure.

Confidentiality breach – The risk of research data or your health information being accessed without study or clinical care need is very low given the standard safeguards used by Michigan Medicine as an institution and by those on the study team. Access to study-related files is granted on the basis of need by the project manager. Electronic files are protected by the Michigan Medicine information technology infrastructure, which includes digital encryption, and paper files are stored in a secure environment including locked file cabinets and restricted access offices.

Toxicity – Gentamicin toxicity as a side effect is more associated with high doses of prolonged systemic therapy and/or in patients with impaired renal function. While high doses of gentamicin and similar compounds can be associated with kidney and neurotoxicity, the dose used in this study is low. Due to the exclusion of patients with kidney problems and because the negligible absorption of gentamicin via the bladder, this risk is minimized in this study. While unlikely based on these factors, gentamicin toxicity may occur in the form of new onset and prolonged numbness, skin tingling, dizziness and vertigo. Other side effects include prolonged muscle twitching, tinnitus, roaring in the ears or hearing loss. You should remain well hydrated while on the study drug to reduce some of these risks

Overdosage – Overdosage may increase the risk of toxicity described above. The risk of this is minimal as long as you take your study drug as directed. As stated above, the localized dosing is unlikely to cause any increase in serum gentamicin levels and, additionally, the dose of gentamicin in each syringe is far below the threshold at which has been reported to cause adverse reactions.

Fetal Harm – Gentamicin may cause fetal harm when administered to pregnant women. If you are a sexually active female of child-bearing age you will be asked to use contraception (see below) throughout the study. If you become pregnant during the study you will be asked to discontinue the study drug, but may remain in the study to document your UTIs and complete study interviews.

Women:
If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use one of these types of birth control listed below. These birth control methods must be used from the time of enrollment, during the entire instillation period including during temporary breaks from instillations, and for at least one week after the instillations have stopped. The following methods are considered acceptable birth control methods:

- tubal sterilization (tubes tied)
- partner's vasectomy
- intrauterine device
- hormonal contraceptives (includes transdermal patch, injectables, implantables)
- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide
- vaginal sponge (contains spermicide)

Any birth control method can fail.

Men:
Men must agree to either abstain from sexual activities that could result in pregnancy or use an acceptable form of birth control while taking part in the study. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy.

Blood Draw: A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of

puncture. There is also a slight chance of infection. About 45 ml (about 1.5 oz) of blood will be collected throughout the duration of the study.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any UTIs, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study. Enrollment in other studies about UTIs, or which involve the use of systemic antibiotics should generally be avoided. If you are unsure whether another study might conflict with this one, please contact the study team listed in section 10.1.

5.4 How could I benefit if I take part in this study? How could others benefit?
It is possible that your condition or health may improve because of your taking part in this study. However, there is no guarantee that you will benefit in any way. Information from this study may help other people in the future.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
You do not have to be in this study and your decision on whether to participate will not influence the standard care that you receive. Instead of taking part in this study, following discussion with your doctor, you may choose to receive treatment with other antibiotics that have been approved for use in this country and which follows the current standard of care for treating urinary tract infections in people with spinal cord injury.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

You are free to stop participating in this study at any time. If you stop, you will not lose any medical benefits except for any benefits that you might have been receiving in connection with this study. All information and samples collected from you before you stop the study may still be used by the study team to understand more about the effectiveness of the study drug. If you want to stop participating in the study, please tell a member of the study team. He/she can tell you about stopping all or part of the study activities and what other care is available for you.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.
- ✓ You become pregnant

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you will have to arrange for treatment on your own, as the study will not provide medical treatment or provide any compensation to you. You or your insurance provider will be billed for all costs of treatment for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will be paid $30 for completing each of the three interviews. The study site will reimburse you by mailed check after each completed interview.

8.3 Who could profit or financially benefit from the study results?
Gentamicin is a cheap, and readily-available generic drug. It is unlikely that any company or the University of Michigan would profit in any substantial way from this study. Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. The Privacy Rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you.

If you enroll in the study, you will be given a unique study ID which will not be linked to any personally identifying information. Your study information will be tracked with this study ID only. The only link between your personal information and your study ID will be kept in a secured database accessible only to certain members of the study team.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. However, if you do not, you will not be able to take part in the study.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.

- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:
- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or instillations
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Denise Tate, PhD
Mailing Address: 325 E Eisenhower Pkwy, Lower Level, Ann Arbor, MI 48108
Telephone: (734) 763-0971

Study Coordinator: Elizabeth Sullivan, BGS, CCRP
Mailing Address: 325 E Eisenhower Pkwy, Lower Level, Suite 4, Ann Arbor, MI 48108
Telephone: (734) 276-0460
Email: elizsull@umich.edu

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- A copy of this "Consent to be Part of a Research Study" document, once signed and dated. (*Note: In addition to the copy you receive, electronic and/or paper copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Investigational Product Dosing Diary

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information in this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time that I sign it or shortly thereafter. If I receive an electronic copy initially, I may request a paper copy of this signed form. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to electronically re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

☐ Check here if subject is not able to sign due to paralysis

Date of consent: _____ Witness to consent:_____

Name (Print): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Witness

I observed that the above subject, who is unable to write his or her signature has verbally consented to participate in this study and my signature below serves to document this.

Legal Name: _____

Title: _____

Signature: _____

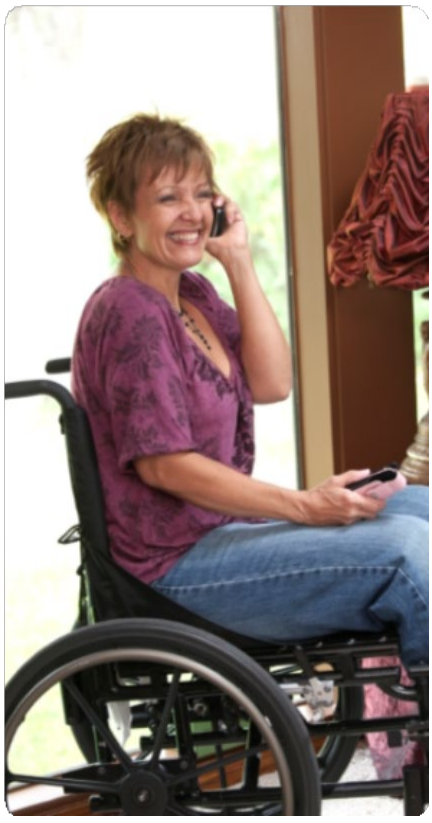
Date of Signature (mm/dd/yy): _____

Appendix D

HAVE YOU HAD A SPINAL CORD INJURY OR HAVE SPINAL CORD DISEASE?

Do you suffer from recurrent Urinary Tract Infections (UTIs)?

IRBMED: HUM00137086



We are currently recruiting individuals with spinal cord injury and spinal cord disease to participate in a clinical trial looking at reducing the recurrence of UTIs.

WHO CAN PARTICIPATE?

- Have a traumatic spinal cord injury or non-traumatic spinal cord disease with sustained neurological dysfunction
- Are at least 18 years of age
- Currently using intermittent catheterization to empty your bladder
- Have problems with recurrent UTIs

WHAT IS INVOLVED?

This study is done primarily over the phone, but two virtual visits and two lab visits will be required.

Participants in the study will receive monetary compensation upon completion of study tasks.

The Effect of Intravesical Gentamicin on Decreasing Urinary Tract Infections Clinical Trial

Funding provided by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)

FOR MORE INFORMATION call:
734-936-2817
email: gentamicin-RCT@umich.edu

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

gentamicin-RCT@umich.edu 734-936-2817
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gentamicin-RCT@umich.edu 734-936-2817
gentamicin-RCT@umich.edu 734-936-2817

DO YOU HAVE A SPINAL CORD INJURY OR SPINAL CORD DISEASE?

Do you have recurrent Urinary Tract Infections (UTIs)?

The Effect of Intravesical Gentamicin on Decreasing Urinary Tract Infections
Clinical Trial

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Department of Physical Medicine & Rehabilitation
University of Michigan
325 E. Eisenhower Parkway, Lower Level, Suite 4, Ann Arbor, Michigan 48108

Appendix E

IRBMED: HUM00137086

We are contacting you because we are currently recruiting individuals with spinal cord injury and spinal cord disease to participate in a clinical trial looking at reducing the recurrence of urinary tract infections (UTIs). You may be eligible to participate in this study.

This study is done primarily over the phone, but two virtual visits and two lab visits will be required. You are under no obligation to participate and a decision not to participate does not affect your access to health care.

Who can participate in this study?
You meet the basic eligibility criteria to participate in this study if the following are true:
- **Have a traumatic spinal cord injury or non-traumatic spinal cord disease with sustained neurological dysfunction**
- **Are at least 18 years of age**
- **Currently using intermittent catheterization to empty your bladder**
- **Have problems with recurrent UTIs**

If you DO NOT want us to contact you, please let us know in one of the following ways:
- **Call a research team member at (734) 936-9474 and tell them that you are not interested in participating in the study. You may leave a confidential voice mail message if you do not reach someone**
- **Send a letter declining to be contacted to the Gentamicin Trial study team at: 325 E. Eisenhower Parkway, Lower Level, Suite 4, Ann Arbor, MI 48108.**

Participants in the study will receive monetary compensation for completing the study. To find out more about the study and whether you qualify, please contact Adrienne Roth (734) 936-9474 or email adbpo@med.umich.edu. If we do not hear from you, we will attempt to contact you to see if you are able and interested in participating. You can ask any questions that you have when we call.

Thank you for your consideration and we hope to hear from you!

Sincerely,

Denise Tate, PhD

Appendix F: Screening Log

	_____
Patient Info	
MRN (if UM patient)	_____
First Name	_____
Last Name	_____
Did subject consent to undergo screening urinalysis?	◯ Yes ◯ No (If yes, report results below)
If yes, assign patient a subject ID	_____ (Alphanumeric ID in the format "GENT###")
Inclusion Criteria	
Is the subject 18-80 years old?	◯ Yes ◯ No
Does subject have a history of traumatic SCI or non-traumatic SCD?	◯ Yes (SCI) ◯ Yes (SCD) ◯ No
If yes, did this occur/were they discharged from the hospital at least six months prior to their intended date of enrollment?	◯ Yes ◯ No
Patient has neurogenic bladder?	◯ Yes ◯ No
Has the subject had at least 2 UTIs documented in the EMR during the previous six months, or at least 3 UTIs in the past year?	◯ Yes ◯ No
Patient uses clean intermittent catheterization?	◯ Yes ◯ No
Patient has a designated treating physician for any UTIs?	◯ Yes ◯ No
Does subject have a current UTI (via urinalysis?)	◯ Yes ◯ No ◯ Not obtained

If yes, has patient already been treated for a current UTI during the screening process?	◯ Yes (screen failure) ◯ No

Exclusion Criteria

Patient currently taking antibiotics?	◯ Yes ◯ No
Documented aminoglycoside allergy?	◯ Yes ◯ No
Is the subject pregnant?	◯ Yes ◯ No
Does the subject plan on becoming pregnant and does not agree to take contraceptive measures while in study?	◯ Yes ◯ No
Renal impairment?	☐ None ☐ Documented end-stage renal disease ☐ GFR less than 60 ml/min ☐ Documented pyelonephritis
Patient currently taking contraindicated diuretics?	☐ No ☐ ethacrynic acid ☐ furosemide (Lasix)
Other reasons for exclusion?	☐ None ☐ 8th cranial nerve disorder ☐ Persistent current UTI (2x pos. screening UA) ☐ Cancer/other chronic disease substantially affecting QOL ☐ Enrollment in a similar protocol ☐ Vertigo/other otological symptoms at baseline ☐ Not interested/refused

Eligibility

Is subject eligible for the study based on the above criteria?	◯ Yes ◯ No
F/U needed?	◯ Yes ◯ No
Comments	_____

Appendix G: Screening and Enrollment Log

Study Name: Gentamicin in SCI	**IRB HUM #: 00137086**
Principal Investigator: Denise Tate, PhD	

IRB approved number of subjects to be enrolled: _____

Screening Number	**Assigned Participant ID # (if enrolled)**	**Date Screened** *(MM/DD/ YY)*	**Eligibility Criteria Met** *(Yes/No)*	**Participant Initials**	**Informed Consent Signed: (Date or N/A)** *(Copy to Subject Y/N)*	**Reason for Exclusion** (Screen Fail, Refused to Participate, etc.)	**Randomization ID Assigned**	**Additional Comments**

PI Signature: _____ Page _____ of _____

Appendix H

GENIIUs-SCI **Screening Visit (Visit 0)**

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

Informed Consent

Informed Consent Obtained (Date): _____

Screening Consent approval date: _____

□ Patient Enrolled in OnCore

Laboratory

Urine Sample (Date): _____

□ Urinalysis

□ Pregnancy Test (only applicable for women of childbearing age)

 CRC Signature & Date: _____

Appendix I

HUM00137086: Randomized Clinical Trial of Gentamicin to Decrease Urinary Tract Infection after SCI	Principal Investigator: Denise Tate, PhD

Participant ID: _____ **Date Consent Signed:** _____

Protocol Version Consented to: _____

ELIGIBILITY CRITERIA

The electronic medical record (EMR) will be pre-screened for all inclusion criteria prior to the baseline interview and initial lab work. Criteria will be confirmed by patient or caregiver report at the baseline assessment.

Inclusion Criteria	Yes	No
Provision of electronically signed and dated informed consent form.		
Male or female of 18 years or older at time of enrollment.		
History of traumatic SCI or non-traumatic spinal cord disease (SCD), with sustained neurological dysfunction. Traumatic and non-traumatic SCI/D are defined according to the International SCI Standards and Datasets.		
At least 6 months post-initial hospital discharge following SCI/D onset.		
Neurogenic bladder		
Ability to perform daily instillation oneself or with help of others and willingness to adhere to the study regiment.		
Negative pregnancy test (for females of childbearing age) and willing and able to use appropriate contraception while enrolled in the study		
History of at least 2 UTIs documented in the EMR during the previous 6 months (prior to screening)		
Have a designated physician or health care provider for routine urological care who is a member of Michigan Medicine.		
Use of clean intermittent catheterization (CIC) or catheterization through a stoma (i.e. Mitrofanoff) as their primary method of bladder management.		
Agreement to adhere to Lifestyle Considerations (see below) throughout the study duration.		

The EMR will be pre-screened for contraindications to participation based on medical history. Final eligibility will be ascertained at the baseline assessment following confirmation of criteria by patient or caregiver report and a urine analysis.

Exclusion Criteria	Yes	No
Concurrent use of systemic oral or intravesical antibiotic prophylaxis during the previous six months. Localized antibiotic therapies (i.e. topical antibiotic creams) are permitted.		

Exclusion Criteria (continued)	Yes	No
EMR-documented or self-reported history of gentamicin allergy.		
Patients who are 80 years old or older.		
Positive pregnancy test at baseline (for female patients who are of childbearing age). Subjects who are not pregnant and who are willing and able to use appropriate contraception while enrolled in the study will be permitted.		
Patients with a history of 8th cranial nerve disorder.		
Co-morbidities like cancer and chronic disease that could impact patient safety OR significantly affect the rate of UTIs and/or QOL substantially.		
Urological co-morbidities like bladder cancer and history of kidney disease. These include: • Patients with EMR-documented renal impairment (e.g. end-stage renal disease, documented glomerular filtration rate (GFR) less than 60 ml/min will be excluded (most recent result)). • Patients with active pyelonephritis (patients with a history of pyelonephritis, which has been treated and is resolved, will be permitted in the study).		
Current UTI at baseline visit (assessed via urine analysis and culture and symptoms).		
Concurrent enrollment in a similar clinical trial.		
Concurrent use of contraindicated diuretics (ethacrynic acid, furosemide).		
Current use of other contraindicated or disallowed concomitant medications or receiving treatments that may influence the results from this study.		
Known allergy to aminoglycoside antibiotics.		
Otological symptoms at baseline (tinnitus, severe dizziness/vertigo).		
At the discretion of study team, individuals who are unable or unlikely to comply with procedures and/or for whom study participation is not recommended (e.g. unable to arrange transportation, cognitive and/or behavioral challenges that preclude meaningful participation, poor health, etc.).		

If any answers to inclusion criteria are 'no' or exclusion criteria 'yes', then participant is not eligible to be enrolled.

Subject is: **Eligible** **Not Eligible**

Confirmed by:

Signature of Investigator

Date (MM/DD/YYYY)

Appendix J: Dosing Calendar

Date (mm/dd/yy)	Full dose taken	Dose skipped – taking antibiotics for UTI	Dose skipped – other reason	Notes
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
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	☐	☐	☐	
	☐	☐	☐	

Appendix K

GENIIUs-SCI **Baseline (Visit 1)**

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

Informed Consent

Informed Consent Obtained (Date): _____

Consent approval date: _____

Investigational Product Counseling

□ Subject has received investigational product counseling from the Investigator or Designee

□ Subject was given a chance to ask questions regarding the investigational product, and all of the subject's questions have been answered appropriately by Investigator or Designee

Has subject used antibiotic bladder instillations in the past? □ yes □ no

Laboratory

Labs Drawn (Date): _____

□ Complete Blood Count
□ Comprehensive Metabolic Panel

 CRC Signature & Date: _____

GENIIUs-SCI **Baseline (Visit 1)**

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

Standard Measures

Subject has completed and understood the following surveys:

□ Demographics
□ NBSS
□ NBDS
□ Community Participation Indicators
□ SCI-QOL
□ SF-Qualiveen

_____
_____
_____
_____

Other Visit Information

□ Review for AE's and SAE's

Comments (add appropriate concerns to AE/SAE log):

_____
_____
_____
_____

□ Concomitant Medication Review

(Note changes on Con.Med. log for subject)

Comments:

_____
_____
_____
_____

 CRC Signature & Date: _____

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

□ Contraception Check

- □ The subject is a female of childbearing age
  - □ The subject is using an appropriate contraception device
  - □ The subject is not using an appropriate contraception device
- □ The subject is not female or is not of childbearing age

_____

_____

_____

_____

Appendix L1: Neurogenic Bladder Symptom Score (NBSS)

1.	I usually manage my bladder or urine function:
	• With a catheter in all the time, or a urostomy bag
	• With a condom catheter
	• With an intermittent catheter
	• By just urinating in the toilet
2.	During the day, how often do you have urine leakage (including leakage around a catheter or stoma):
	• More than once a day
	• About once a day
	• A few times a week
	• Rarely
	• Zero – don’t have urine leakage
3.	During the day, the amount of urine leakage (including leakage around a catheter or stoma):
	• Requires 3 or more pads
	• Requires 2 pads
	• Requires 1 pad
	• Is minimal and doesn’t require pads
	• Is zero – I don’t have urine leakage
4.	During the day, the amount of urine leakage (including leakage around a catheter or stoma) is:
	• Large (clothes/pads are soaked)
	• Medium (clothes/pads are wet)
	• Small (clothes/pads are damp)
	• Minimal
	• Zero – I don’t have urine leakage
5.	When I am asleep, the amount of urine leakage (including leakage around a catheter or stoma) is:
	• Large (it makes things soaked)
	• Medium (it makes things wet)
	• Small (it makes things damp)
	• Minimal
	• Zero – I don’t have urine leakage

6.	Urine leakage has changed the amount of liquid I drink
	• Agree – I reduce my liquid intake all the time
	• Agree – I reduce my liquid intake some of the time
	• Disagree – Leakage hasn’t caused me to change my liquid intake
	• Disagree – I don’t have any urine leakage
7.	Urine leakage has caused skin problems.
	• Agree – I see a doctor for the skin problems
	• Agree – I am able to manage the skin problems myself
	• Disagree – Leakage doesn’t cause any skin problems
	• Disagree – I don’t have any urine leakage
8.	Urine leakage limits the activities I enjoy.
	• Agree – It limits all my activities
	• Agree – It limits some of my activities
	• Disagree – It doesn’t limit any of my activities
	• Disagree – I don’t have any urinary leakage
9.	The sudden urge to urinate, (or bladder spasm) occurs:
	• Many times a day
	• A few times a day
	• Rarely
	• Never
10.	When I need to urinate or use an intermittent catheter:
	• I have to do this right away or I may leak urine
	• I can only delay this a few minutes or I may leak urine
	• I can do this when it is convenient without leaking urine
	• I don’t think about urinating. I have a catheter or stoma bag
11.	During my nighttime sleep, I need to urinate, use a catheter, or fix my catheter or stoma bag:
	• Three or more times
	• Twice
	• Once
	• Rarely
	• Never

12.	During the day, the longest I can go between urinating, using a catheter or emptying my urine bag is:
	• Less than an hour
	• About 1–2 hours
	• About 2–3 hours
	• More than 3 hours
13.	During the day, the longest time I can stay dry without any urine leakage is:
	• Less than an hour
	• About 1–2 hours
	• About 2–3 hours
	• More than 3 hours
	• This isn’t an issue for me. I don’t have urine leakage
14.	Urinating or using urinary catheters cause me pain or discomfort:
	• Most of the time
	• Sometimes
	• Rarely
	• Never
15.	When I am done urinating or using a catheter, my bladder or urinary reservoir still feels full.
	• Agree – This happens most of the time
	• Agree – This happens some of the time
	• Disagree – This doesn’t happen after I urinate
	• This isn’t an issue for me. I don’t feel my bladder, or I use a catheter or stoma bag
16.	When I urinate my urinary stream:
	• Drips out
	• Comes out with a weak stream
	• Comes out with a strong stream
	• This isn’t an issue for me. I use a catheter or stoma bag
17.	When I urinate I have to strain or push to empty my bladder or urinary reservoir.
	• Agree – This happens most of the time
	• Agree – This happens some of the time
	• Disagree – I don’t do this when I urinate
	• This isn’t an issue for me. I use a catheter or stoma bag

18.	I have a urinary tract infection with symptoms (for example pain, foul smelling urine, fever):
	• Once a month, or more
	• Once every few months
	• A few times a year
	• About once a year or less
	• Never
19.	For me, urinary tract infections:
	• Often require me to be admitted to hospital
	• Require me to take antibiotics all the time
	• Can be treated at home with antibiotics when necessary
	• Can be treated without antibiotics
	• Do not occur
20.	I have kidney stones:
	• More than once a year
	• Less than once a year
	• A long time ago
	• Never
21.	I have had bladder stones:
	• More than once a year
	• Less than once a year
	• A long time ago
	• Never
22.	I need to take pills or medications for my urination or bladder.
	• Agree – However I don’t take them
	• Agree – They cause significant side effects for me
	• Agree – They cause minimal or no side effects for me
	• Disagree – No pills or medications are needed for my bladder
23.	I find the pills or medications I use for my urination or bladder are:
	• Effective
	• Partially effective
	• Not very effective
	• I don’t take pills or medications for my bladder

24.	If you had to live the rest of your life with the way your bladder or urinary reservoir currently works, how would you feel?
	• Unhappy
	• Mostly unsatisfied
	• Mixed: equally satisfied and unsatisfied
	• Mostly satisfied
	• Pleased
25.	All things considered, how satisfied are you with the way your bladder or urinary reservoir currently works?
	• Very unsatisfied
	• Mostly unsatisfied
	• Mixed: equally satisfied and unsatisfied
	• Mostly satisfied
	• Very satisfied

Appendix L2: Neurogenic Bowel Dysfunction Score (NBD)*

1. How often do you defecate?
   ☐ Daily(0) ☐ 2-6 times per week(1) ☐ Less than once per week(6)
2. How much time do you spend on each defecation?
   ☐ Less than 30 minutes(0) ☐ 31-60 minutes(3) ☐ More than an hour(7)
3. Do you experience uneasiness, sweating or headaches during or after defecation?
   ☐ Yes (2) ☐ No (0)
4. Do you receive medication (tablets) to treat constipation?
   ☐ Yes (2) ☐ No (0)
5. Do you receive medication (drops or liquid) to treat constipation?
   ☐ Yes (2) ☐ No (0)
6. How often do you use digital evacuation?
   ☐ Less than once per week(0) ☐ Once or more every week(6)
7. How often do you have involuntary defecation?
   ☐ Daily(13) ☐ 1-6 times per week(7) ☐ 3-4 times per month(6)
   ☐ A few times per year or less(0)
8. Do you receive medication for fecal incontinence?
   ☐ Yes(4) ☐ No(0)
9. Do you experience uncontrollable flatus?
   ☐ Yes(2) ☐ No(0)
10. Do you have peri-anal skin problems?
    ☐ Yes(3) ☐ No(0)

Please rate your general satisfaction with you bowel management on a scale from 0–10, with 0 representing total dissatisfaction and 10 representing Perfect satisfaction.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10

NBD score Bowel dysfunction
0–6 Very minor
7–9 Minor
10–13 Moderate
14 or more Severe

* Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic bowel dysfunction score. *Spinal Cord.* 2006;44(10):625-631. http://dx.doi.org/10.1038/sj.sc.3101887

Appendix L3: SF Qualiveen

Are you bothered by:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1. The time spent passing urine or in catheterization?	0	1	2	3	4
2. In general, do your bladder problems complicate your life?	0	1	2	3	4
Are you restricted:	**Never**	**Rarely**	**From time to time**	**Often**	**Always**
3. Can you go out without planning anything in advance?	4	3	2	1	0
4. Is your life regulated by your bladder problems?	4	3	2	1	0
Do you worry about:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
5. Smelling of urine?	0	1	2	3	4
6. Your bladder problems worsening?	0	1	2	3	4
Do you feel:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
7. Embarrassed because of your bladder problems?	0	1	2	3	4
8. Worried because of your bladder problems?	0	1	2	3	4

Appendix L4: Bowel Management Difficulties– Short Form 9a

Please respond to each question or statement by marking one box per row.

	Lately…	**Not at All**	**A Little Bit**	**Somewhat**	**Quite a Bit**	**Very Much**
rToiletBO_33	I was frustrated by repeated bowel accidents…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_Com25	I worried that my social activities would be interrupted by a bowel accident…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_27	I worried I would have a bowel accident...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_4	Bowel accidents limited my independence……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_7	A bowel accident has affected my self-esteem……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_29	I was upset by problems with my bowel functioning…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_12	I worried about performing my bowel program……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Lately…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
rToiletBO_46	Bowel accidents have disrupted my daily activities…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
rToiletBO_52	I had bowel accidents…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix L5: Satisfaction With Social Roles and Activities– Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
SRPSAT10	I am satisfied with my current level of social activity.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT23	I am satisfied with my ability to do leisure activities.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT25	I am satisfied with my current level of activities with my friends.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT48	I am satisfied with my ability to do things for fun at home (like reading; listening to music; etc.).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT49	I am satisfied with my ability to perform my daily routines.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very Much
NQSAT02	I am disappointed in my ability to meet the needs of my family.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT03	I am bothered by my limitations in regular family activities.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT13	I am disappointed in my ability to socialize with friends.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT39	I am disappointed in my ability to take care of personal and household responsibilities.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT40	I am bothered by limitations in performing my work (include work at home).	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix L6

Community Participation Indicators

CaseId # ☐☐☐☐

This survey is voluntary. If you choose to participate, your information will be kept private. Your name will never be linked to any of the information you share.

Shade circles like this: ●
Not like this: ⊗ ⊘

The statements below describe many of the ways that people participate in society. For each item, tell us:

1) How often you do the activity,
2) If the activity is important to you, and
3) If you feel you are doing the activity enough, too much, or not enough.

1. How often? --> 2. Important? --> 3. Doing enough?

In a typical week, how many days do you:	None	1-2 Days	3-4 Days	5-6 Days	7 Days	Is this activity important to you?		Are you doing this activity:		
						No	Yes	Enough	Not Enough	Too Much
Get out and about	○	○	○	○	○	○	○	○	○	○
Spend time with family	○	○	○	○	○	○	○	○	○	○
Keep in touch with family by phone or Internet	○	○	○	○	○	○	○	○	○	○
Spend time with friends	○	○	○	○	○	○	○	○	○	○
Keep in touch with friends by phone or Internet	○	○	○	○	○	○	○	○	○	○
Go to parties, out to dinner, or other social activities	○	○	○	○	○	○	○	○	○	○
Spend time with a significant other or intimate partner	○	○	○	○	○	○	○	○	○	○

Community Participation Indicators

Shade circles like this: ●
Not like this: ⊗ ⊘

For each item, tell us:

1) How often you do the activity,
2) If the activity is important to you, and
3) If you feel you are doing the activity enough, too much, or not enough.

1. How often? --> 2. Important? --> 3. Doing enough?

In a typical week, how many hours do you:	None	1-4 Hours	5-9 Hours	10-19 Hours	20-34 Hours	35 or more Hours	Is this activity important to you?		Are you doing this activity:		
							No	Yes	Enough	Not Enough	Too Much
Work for money	○	○	○	○	○	○	○	○	○	○	○
Cook, clean, and look after your home	○	○	○	○	○	○	○	○	○	○	○
Manage household bills and expenses	○	○	○	○	○	○	○	○	○	○	○
Look after children or provide care for a loved one	○	○	○	○	○	○	○	○	○	○	○
Go to classes or participate in learning activities	○	○	○	○	○	○	○	○	○	○	○
Volunteer	○	○	○	○	○	○	○	○	○	○	○

Community Participation Indicators

CaseId # | | | | |

Shade circles like this: ●
Not like this: ⊗ ⊘

For each item, tell us:

1) How often you do the activity,
2) If the activity is important to you, and
3) If you feel you are you are doing the activity enough, too much, or not enough.

1. How often? --> 2. Important? --> 3. Doing enough?

In a typical month, how many times do you:	None	Once	2 Times	3 Times	4 Times	5 or More Times	Is this activity important to you?		Are you doing this activity:		
							No	Yes	Enough	Not Enough	Too Much
Participate in religious or spiritual activities	○	○	○	○	○	○	○	○	○	○	○
Go to support groups or self-help meetings	○	○	○	○	○	○	○	○	○	○	○
Engage in hobbies or leisure activities	○	○	○	○	○	○	○	○	○	○	○
Go to movies, sporting events or entertainment events	○	○	○	○	○	○	○	○	○	○	○
Exercise, participate in sports or active recreation	○	○	○	○	○	○	○	○	○	○	○
Participate in community clubs or organizations	○	○	○	○	○	○	○	○	○	○	○
Participate in civic or political activities	○	○	○	○	○	○	○	○	○	○	○

Appendix M: Medical History

Patient ID: _____

Number	Medical Event	Date of Onset	Resolved (date) or Ongoing?	Comments
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

CRC Signature & Date: _____

CRC Initials _____

Appendix N: Concomitant Medications

Patient ID: _____

Medication #	Medication Name	Date Started	Date Stopped	Comments

CRC Signature & Date: _____

Appendix O

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Gentamicin Bladder Instillations: Instructions for Clean Intermittent Catherization (CIC)

1. Wipe injection port of bag of study drug with alcohol swab three times in the same direction.
2. Peel open the packaging of the syringe and attach a sterile needle.
3. Using the syringe, withdraw 25 mL of solution from the bag of study drug through the injection port.
4. Remove (unscrew) the needle from the syringe and dispose of it in sharps container.
5. Attach (screw on) blue catheter tip onto the syringe.
6. Drain your bladder with your usual self-catheter, once it is empty do not remove the catheter
7. Push catheter tip syringe into the catheter drainage port until it fits snugly and slowly push the solution through the catheter into your bladder
8. Remove catheter and catheter tip syringe from the bladder together (do not detach them) leaving the solution in your bladder (do not drain it out, it will come out at your next catheterization)
9. Discard syringe with catheter tip and the partially filled bag of study drug.

Supplies:

◆Gentamicin/Placebo in 0.9% NaCl 50 mL IVPB bag ◆luer-lok syringe ◆18 g 1.5 in needles (boxes of 100) ◆syringe catheter tip◆ alcohol swab ◆sharps container (for needles)◆

Appendix P

GENIIUs-SCI **Telephone Encounter**

(Week: 2/4/6/8/10/12/14/16/18/20/22/24/28/30/32/34/36/38/40/42/44/46/48/50)

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

IP Compliance Check

□ Participant compliant with investigational product administration

_____

_____

_____

Other Visit Information

□ Review for AE's and SAE's

Comments (add appropriate concerns to AE/SAE log):

_____

_____

_____

_____

□ Concomitant Medication Review

Comments: (Note changes on Subject's Concomitant Medication log -- Appendix G4)

_____

_____

_____

_____

□ Contraception Check

- □ The patient is a female of childbearing age
  - □ The patient is using an appropriate contraception device
  - □ The patient is not using an appropriate contraception device
- □ The patient or patient's partner is not of childbearing age

_____

_____

 CRC Signature & Date: _____

Appendix Q

Gentamicin in SCI RCT: Adverse Event/Serious Adverse Event Log

Patient ID: _____

AE #	AE Description	SAE? (Y/N)	Start Date/Time	Severity 1-Mild 2-Moderate 3-Severe	Relationship to IP 1-Not Related 2-Unlikely Related 3-Possibly Related 4-Related	Action Taken 1-Dose not changed 2-Dose Increased 3-Dose Reduced 4-Drug Interrupted 5-Drug Withdrawn 6- Not Applicable 7-Unknown	Other Action Taken 1-None 2-Medication 3-Non-Drug Therapy 4-Hospitalized 5-Other	Outcome 1-Not Recovered/Not Resolved 2-Recovered/Resolved with sequelae 3-Recovering/resolving 4-Recovered/resolved 5-Unknown 6-Fatal	Expectedness 1-Expected 2-Unexpected	CTCAE Grade	PI Initials

CRC Signature & Date: _____

Appendix R

Gentamicin in SCI RCT **Follow-up Visit (Visit 2/Visit 3)**

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

Standard Measures

Patient has completed and understood the following surveys:

□ Demographics
□ NBSS
□ NBDS
□ Community Participation Indicators
□ SCI-QOL
□ SF-Qualiveen

_____
_____
_____
_____

Laboratory

Labs Drawn (Date): _____

□ Complete Blood Count
□ Comprehensive Metabolic Panel

Urine Sample (Date): _____

□ Urinalysis

 CRC Signature & Date: _____

Patient Initials: _____ **Patient Number: _____**

Date of Visit: _____

Other Visit Information

□ Review for AE's and SAE's

Comments (add appropriate concerns to AE/SAE log):

_____

_____

_____

_____

□ Concomitant Medication Review

(Note changes on Subject's Concomitant Medication log – Appendix G4)

Comments:

_____

_____

_____

_____

IP Compliance Check

□ Participant compliant with investigational product administration

_____

_____

_____

□ Contraception Check

□ The patient is a female of childbearing age

□ The patient is using an appropriate contraception device

□ The patient is not using an appropriate contraception device

□ The patient or is not of childbearing age

_____

_____

_____

 CRC Signature & Date: _____

Appendix S: Visit 3

Record ID	_____
Gentamicin ID	_____
Date Interview	_____
Have you used gentamicin bladder irrigations since you stopped using them as a part of the study?	◯ Yes ◯ No
Are you currently using gentamicin bladder irrigations?	◯ Yes ◯ No
On average, how many times per week have you been doing the Gentamicin flushes since the end of your study participation?	_____
Have you received a prescription for Gentamicin since completing the 6 month study?	◯ Yes ◯ No
Since you completed using Gentamicin bladder irrigations as a part of the study on (provide date), have you had any urinary tract infections for which you were treated?	◯ Yes ◯ No
How many urinary tract infections have you had?	_____
If you are not using gentamicin bladder irrigations, why are you not using them? [Interviewer Note: Common reasons may be: lack of interest, perceived lack of effectiveness, unwillingness of insurance to cover Gentamicin, and that they found the process to be annoying. Clarify if any of these are true along with any other reasons respondents may have for not taking Gent.]	_____

Appendix T

Gentamicin Trial: Post-Intervention Satisfaction Survey

This optional survey is being offered to participants who are at least 90 days post completion of participation in *The Effect of Gentamicin Intravesical Instillations on Decreasing Urinary Tract Infections in Patients with Neurogenic Bladder after SCI: A Clinical Trial.* Participants will be informed that the survey is completely voluntary, and that by declining participation they will not lose any rights or benefits to which they are otherwise entitled. Participants will be asked if they agree to participate prior to any survey questions being asked. Those who decline participation will be thanked for their time and effort while participating in this trial. Those who agree to participate will be read the following instructions and questions:

Instructions: Thank you for participating in this brief survey. We would like to know your thoughts and comments about your participation in this Gentamicin Instillation Trial.

Do you feel that your participation in this clinical trial to decrease urinary tract infections (UTIs) has been worthwhile to you?

Yes_____ No_____ Not sure_____

Can you tell me about the benefits you encountered when using Gentamicin instillations in your bladder during this trial? Were you happy with the results? Did your symptoms improve? Did you feel better?

Can you tell me about any challenges you encountered when using Gentamicin instillations in your bladder during this trial (i.e., difficulties doing the installations, not having the drug on time, becoming ill and unable to continue with treatment)? Was it hard to do these instillations?

Did you dispose your remaining gentamicin after the treatment period ended?

Yes_____ No_____

If yes, how did you dispose of the gentamicin?

Are you still using Gentamicin instillations?

Yes_____ No_____

Have you had any issues using it lately?

Yes_____ No_____ N/A_____

If Yes, can you tell me about these issues?

Do you plan to continue to use Gentamicin in the future?

Yes_____ No_____ Not sure_____

If yes, is having access to the medication (Gentamicin) an issue for you? Is it covered by your insurance?

Do you have any final questions for the study team?

We wish to thank you for your participation in this brief survey and in this Gentamicin study and wish you well. If you have any symptoms related to UTIs or possible adverse events related to the use of this medication, please contact your physician in charge of your care right away. If you have questions about this study please contact the study principal investigator at dgtate@umich.edu.

Appendix U

GENTAMICIN STUDY ADVERSE EVENT

GENT30XX — [Event Title]

Severity

- ☐ 1—Mild
- ☐ 2—Moderate
- ☐ 3—Severe

Relationship to IP

- ☐ 1—Not Related
- ☐ 2—Unlikely Related
- ☐ 3—Possibly Related
- ☐ 4—Related

Action Taken

- ☐ 1—Dose Not Changed
- ☐ 2—Dose Increased
- ☐ 3—Dose Reduced
- ☐ 4—Drug Interrupted
- ☐ 5—Drug Withdrawn
- ☐ 6—N/A
- ☐ 7—Unknown

Other Action Taken

- ☐ 1—None
- ☐ 2—Medication
- ☐ 3—Non-drug therapy
- ☐ 4—Hospitalized
- ☐ 5—Other

Outcome

- ☐ 1—Not Recovered/Not Resolved
- ☐ 2—Recovered/Resolved w/ Sequelae
- ☐ 3—Recovering/Resolving
- ☐ 4—Recovered/Resolved
- ☐ 5—Unknown
- ☐ 6—Fatal

Expectedness

- ☐ Unexpected
- ☐ Expected

CTCAE Grade

- ☐ 1—Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- ☐ 2—Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
- ☐ 3—Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- ☐ 4—Life-threating consequences; urgent intervention indicated
- ☐ 5—Death related to AE

Physician Signature: _____

Date of Signature: _____

Appendix V

National Center for Complementary and Integrative Health

Serious Adverse Event (SAE) Report Form

GENTAMICIN IN SCI

Protocol Number:_____

SAE #:_____

Pt ID:_____

Date Participant Reported:

__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

1. SAE onset date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
2. SAE stop date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
3. Description of SAE:_____
4. Brief description of participants with no personal identifiers:
   Sex: ☐ F ☐ M Age: _____
   Diagnosis for study participation:_____
   _____
5. Brief description of the nature of the SAE (attach description if more space is needed):
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____

6. Category of the SAE:

- ☐ Date of death ___/_____/_____ (dd/mmm/yyyy)
- ☐ Life threatening
- ☐ Hospitalization – initial or prolonged
- ☐ Disability/incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Required intervention to prevent permanent impairment
- ☐ Other:_____

7. Intervention type:

- ☐ Medication or nutritional supplement (specify):_____
- ☐ Device (specify):_____
- ☐ Surgery (specify):_____
- ☐ Behavioral/lifestyle (specify):_____

8. Relationship of event to intervention:

- ☐ Unrelated (clearly not related to the intervention)
- ☐ Possible (may be related to intervention)
- ☐ Definite (clearly related to intervention)

9. Was study intervention discontinued due to event? ☐ Yes ☐ No

10. What medications or other steps were taken to treat the SAE?

_____

11. List any relevant tests, laboratory data, and history, including preexisting medical conditions:

_____

12. Type of report:

- ☐ Initial
- ☐ Follow-up
- ☐ Final

13. Signature of principal investigator or designee: _____ Date: _____

Appendix X

National Center for Complementary and Integrative Health

Tool Summary Sheet

Tool: Delegation of Authority Log

Purpose: To record all study staff members' significant study-related duties

Audience/User: Principal investigators (PIs), study coordinators, other site staff, clinical monitor

Details: This log should provide a comprehensive list of study staff members and the duties that have been delegated to them by the PI. It is required for both observational and interventional clinical research studies.

Best Practice Recommendations:

- List the names of study staff members and record the responsibilities that have been assigned to them using the boxes under the responsibilities header.
- Revise the Responsibilities Header as needed to reflect study-specific needs, such as signing CRFs and reviewing/signing laboratory reports.
- Each study staff member listed should initial and sign to indicate understanding of the responsibilities assigned.
- The site PI should initial and date each line of the form as entries are recorded. The PI's signature at the bottom of each form is required at the conclusion of the study.
- Update the log as needed following any change in site study personnel.
- Number each page and maintain this log in the Essential Documents Binder, behind the Delegation of Authority Log tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File [ISF], and Study File.)
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.
- Remove this Tool Summary Sheet before use of the log.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	20Apr2012	First approved version
2.0	24Apr2013	Added Tool Summary Sheet

Delegation of Authority Log

STUDY NAME

Site Number:____

The purpose of this form is to: a) serve as the Delegation of Authority Log and b) ensure that the individuals performing study-related tasks/procedures are appropriately trained and authorized by the investigator to perform the tasks/procedures. This form should be completed prior to the initiation of any study-related tasks/procedures. The original form should be maintained at your site in the study regulatory/study binder. This form should be updated during the course of the study as needed.

Please Print	Obtain Informed Consent	Source Document Completion	Case Report Form (CRF) Completion	Assess Inclusion and Exclusion Criteria	Physical Examination	Medical History	Medication History / Concomitant Medication	Collect Vital Signs	Review Vital Signs and Labs for Clinical Significance	Laboratory Specimen Collection/Shipping	AE Inquiry and Reporting	AE/SAE interpretation (severity/relationship to IP)	Administration of Investigational Product (IP)	IP Accountability	Regulatory Document Maintenance	Administrative	
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	OTHER (specify):
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	OTHER (specify):
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	OTHER (specify):
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	OTHER (specify):
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	OTHER (specify):
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:

I certify that the above individuals are appropriately trained, have read the Protocol and pertinent sections of 21CFR 50 and 56 and ICH GCPs, and are authorized to perform the above study-related tasks/procedures. Although I have delegated significant trial-related duties, as the principal investigator, I still maintain full responsibility for this trial.

Investigator Signature: ____ **Date:** ___________________________________

Appendix X

Instruction Page: Protocol Training Log

Study Stage: Set-up - Termination

Purpose: When conducting a clinical trial it is the Investigator's responsibility to ensure each member of the study team is trained on the protocol as it applies to their job function. This template can be used to keep track of protocol training.

Useful to: Investigators, Project Managers, Research Coordinators, and Monitors

Instructions:

- The log should be completed during the start-up stage of the study, prior to study initiation.
- Each column of the log should be filled out as completely as possible.
- A legible printed name is required in addition to the signature of each participant.
- Columns such as the study role may be completed in advance by the study coordinator or PI.
- Whenever a new study team member is added, protocol training for the new member should be added to this document.
- Whenever a substantive change to the protocol or a procedure is made and approved by the IRB, training of all study staff to this new change should be documented.

Best Practice Recommendation:

- The log is recommended for all studies (including investigator-initiated studies that are non-FDA regulated).
- File in an appropriate location to be easily accessible for monitoring visits, internal auditing and in order to have complete study records.

Template History:
Last updated: January 27, 2016
Version: 2.1

Reference(s):
ICH GCP 4.2.4
http://ichgcp.net/4-investigator

Protocol Training Log

Study Name:	**IRB HUM #**
Principal Investigator:	

Printed Name and Signature	Study Role	Date Trained	Method	Topics (see key)

Topics (Examples):

1: Protocol overview
2: Inclusion/exclusion Criteria
3: Database Entry Training
4: Scheduled visits and windows
5: AE and UA reporting
6: Protocol deviations and reporting
7: Screening, Examination, and End of Study Visits
8: Study Objectives

By signing below I affirm that each staff member verifies that s/he has had the opportunity to review the relevant study materials and that s/he agrees to conduct the study in accordance with the current protocol

PI signature: _____ Date: _____

Appendix Y

Instruction Page: Protocol Deviation Tracking Log

Study Stage: Set-up, Conduct, Termination

Purpose: This template lists all of the protocol deviations from a particular study. The template may also be used to submit accumulated deviations to the IRB at the time of a continuing review for a study.

Useful to: Principal Investigators, Co-Investigators, Project Managers, Research Coordinators and study team members

Instructions:

- Complete each column of the log as thoroughly as possible, documenting all study protocol deviations on the study.
- See the IRBMED website for a definition of protocol deviations and when to report (see in Reference section below).

Best Practice Recommendation:

- If a sponsor (funding entity of the study; NIH, Industry, coordinating site etc.) provides a Protocol Deviation Log, complete as instructed. Otherwise, the log should be completed throughout the study, as protocol deviations occur.
- File in an appropriate location to be easily accessible for monitoring visits, internal auditing and in order to have complete study records. It is recommended to update this log using an excel spreadsheet.
- It is recommended to have a section of your binder/file where sponsor correspondence and CAPA (corrective action and preventative action) plans in response to deviations are kept as well.

Template History:
Last updated: Feb 25, 2016
Version: 2.2

Reference(s)
Protocol Deviations Definition: ICH GCP 10.2 pg.13
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf
Reporting Protocol Deviations to the IRBMED -
http://medicine.umich.edu/medschool/sites/medicine.umich.edu.medschool/files/res_irbmed_IRBMED_ORIO%20Table%20View%2010-20-11-Protocol%20Deviation.pdf

Protocol Deviation Tracking Log

Study Name:	**IRB HUM #:**
Principal Investigator:	

	Study Participant related Y/N	If Y, Participant ID	Date of Deviation[a]	Date Identified	Type of Event or Information	Description[b]	Date Reported to IRB	Date IRB Acknowledged	Date Sponsor Notified
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									

Appendix Z

Case Report Forms by Visit

Appendix	Screening (Visit 0)
B	Screening Consent
C	Full Study Consent
H	Screening CRF
I	Eligibility Checklist
M	Medical History CRF
N	Concomitant Medications Log

Appendix	Baseline (Visit 1)
C	Full Study Consent
K	Baseline (Visit 1) CRF
M	Medical History CRF
N	Concomitant Medications Log
J	Dosing Log
O	Patient Instructions for Clean Intermittent Catherization
L1	Neurogenic Bladder Symptom Score
L2	Neurogenic Bowel Dysfunction Score
L3	SF-Qualiveen
L4	SCI-QOL Bowel Management Difficulties Short Form 9a
L5	SCI-QOL Satisfaction with Social Roles and Activities Short Form 10a
L6	Community Participation Indicators

Appendix	BiWeekly Telephone Encounters
P	BiWeekly Telephone Encounter CRF
M	Medical History CRF
N	Concomitant Medications Log
Q	Subject Adverse Event Log

Appendix	End of Treatment (Visit 2)
R	End of Treatment (Visit 2) CRF
M	Medical History CRF
N	Concomitant Medications Log
Q	Subject Adverse Event Log
L1	Neurogenic Bladder Symptom Score
L2	Neurogenic Bowel Dysfunction Score
L3	SF-Qualiveen
L4	SCI-QOL Bowel Management Difficulties Short Form 9a
L5	SCI-QOL Satisfaction with Social Roles and Activities Short Form 10a
L6	Community Participation Indicators

Appendix	Follow-up Visit 3
S	Visit 3 CRF

Appendix	Voluntary/Optional Post Interview
T	Post-Interview Survey