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

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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

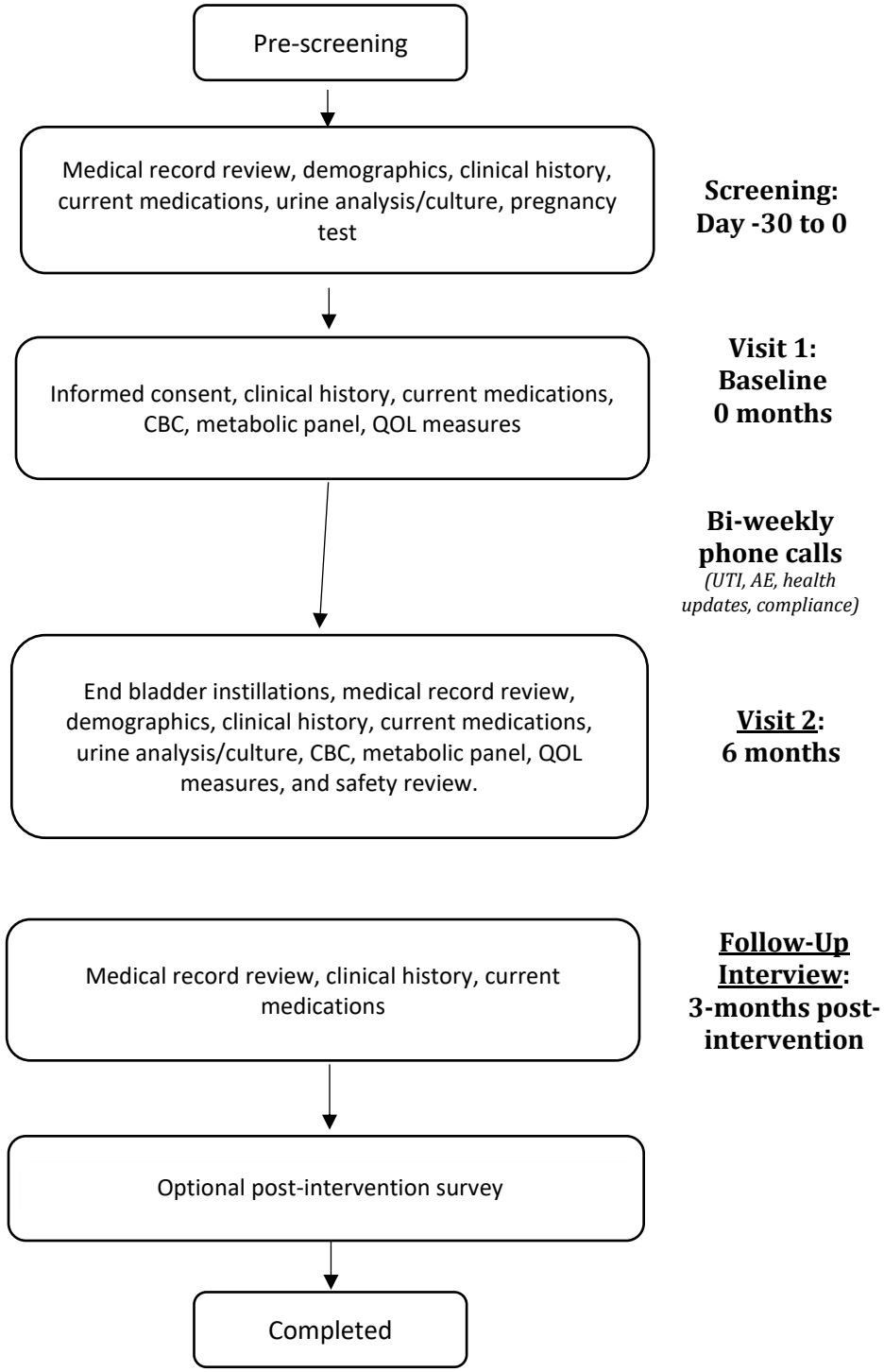

Figure 1. Study Flowchart; refer to Schedule of Activities (Table 1) for study procedures by visit

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Visit 1 (Baseline)[1]	Visit 2	Visit 3 (Follow-Up Interview)	Optional Post-Intervention Survey
	Day -30 to 0	D0	Day 180±30	Day 90 - 30 / + 90 post-intervention	Day 90 - 30/+365 post-intervention
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 (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.

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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