Study Title: Nitrofurantoin Administration for the Prevention of Short-Term Catheter Associated Urinary Tract Infection After Pelvic Surgery (NAUTICA): A Randomized Controlled Trial

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STUDY OBJECTIVES

Primary Objective

To evaluate the efficacy of administration of nitrofurantoin prophylaxis after catheter discontinuation for the prevention of catheter-associated urinary tract infections in patients with postoperative short-term catheterization following pelvic reconstructive surgery. The primary outcome will be the treatment of clinically suspected and/or culture-proven UTI within 30 days of surgery.

Secondary Objectives

1. To evaluate adverse outcomes related to study medications in each group
2. To evaluate medication compliance

BACKGROUND

Urinary tract infections (UTI) are the most common hospital-acquired infections, accounting for nearly 30% of cases of nosocomial infections and affecting nearly 1 million people per year.[1-3] They account for nearly 8.1 million visits to health care providers and cost an estimated $1.6 billion a year in the United States alone.[3,4]

Following pelvic reconstructive and urinary incontinence surgery, UTIs are one of the most common complications.[4,5] The baseline risk of UTI associated with pelvic floor surgery ranges between 5-35%, increasing greatly with catheterization.[3] In women who are undergoing surgery for urinary incontinence, the risk of UTI ranges between 8.9% to 34%.[4,6,7] Risk factors for urinary tract infections in women undergoing pelvic floor and urinary incontinence surgery include: history of recurrent UTI, longer operative times, and increased duration of postoperative catheterization.[6]

Postoperative voiding dysfunction and incomplete bladder emptying is common following pelvic reconstructive and incontinence surgeries, with incidence ranging from 2.5 % to 31%.[6] As a result, these women may have additional catheterization for a short period of time, which increases the risk of UTI.[1,2,4,5] There is a 15-20% risk of developing a postoperative UTI with short-term catheterization, even if the catheter remains in place for merely 24 hours.[8] The risk of UTI increases 5-10% each day the catheter is left in place.[1] In the SISTEr trial, which was a multicenter, prospective, randomized trial comparing Burch colposuspension versus autologous fascial slings for the treatment of stress urinary incontinence, catheter usage postoperatively for incomplete bladder emptying resulted in an increased rate of UTIs. Participants who underwent the fascial sling (48%) had more UTI events (305) compared with the 32% of women in the Burch colposuspension group (203) ($p<0.001$).[9]

This was concluded to be secondary to the prolonged need for catheterization due to postoperative voiding dysfunction.[5,9,10]

Complications of catheter-associated UTI can include pyelonephritis, renal disease, and bacteremia.[2,5] These complications increase the morbidity of the patients undergoing these surgeries, especially in those who are elderly. The number of pelvic floor and urinary incontinence surgeries is expected to increase by 40% in the coming years; thus, it is imperative to target efforts to reduce the risk of postoperative UTI and its complications in the elderly population.[3,5]

Numerous studies have been conducted to evaluate different prophylactic antibiotic regimens to help decrease the rate of postoperative catheter-associated UTIs.[11] Many of these studies have shown precedent for the use of antibiotic prophylaxis.[1,4,12] In a randomized, double-blind, placebo controlled trial by Van der Wall et al., they reported on the efficacy of ciprofloxacin in preventing UTI in short-term catheterization following surgery.[1] In their study, 20% of placebo patients had symptomatic UTIs, compared with 5% UTI rate in the ciprofloxacin treated group.[1] Ghezzi et al. also demonstrated favorable results using single dose prulifloxacin to reduce the rate of UTI in women with short-term postoperative catheterization after undergoing a transvaginal tape procedure.[2] In this prospective trial, no women in the prulifloxacin treatment group had a positive urine culture ($p<0.0001$), symptomatic UTI at catheter removal ($p = 0.0015$) or a positive urine culture at 1 week follow-up ($p =0.2$).[2]

In addition to fluoroquinolones, nitrofurantoin has also been evaluated as a prophylactic regimen for use with short-term catheterization. In her prospective, multicenter randomized controlled trial, Rogers et al. demonstrated that the daily use of nitrofurantoin crystals decreased risk of UTI in patients undergoing pelvic organ prolapse (POP) or urinary incontinence surgery when compared with placebo in those patients who had an indwelling suprapubic catheter postoperatively (46% versus 61%, $p=0.002$).[12] Jackson et al. echoed these findings and found that a short 3-day course of nitrofurantoin twice daily after outpatient mid urethral sling surgery also significantly reduced the incidence of UTI in the first 6 weeks postoperatively in patients who were discharged with short-term catheterization (placebo 32% versus 17.6% in the nitrofurantoin group, $p=0.04$).[4] Conversely, Dieter et al. found that prophylactic once daily nitrofurantoin during catheterization did not decrease the risk of urinary tract infection in patients receiving short-term catheterization following POP or urinary incontinence surgery.[3] This finding was thought to be secondary to differences in study design lending to a lower baseline prevalence of UTI.[3] Additionally, a Cochrane review of antibiotic prophylaxis for short-term catheter bladder drainage does find that there is some evidence, although limited, that the rate of bacteriuria is decreased with the administration of antimicrobials within the first postoperative days, or from postoperative day two until the catheter is removed.[15]

Although there are a few studies showing favorable results for the use of prophylactic nitrofurantoin during catheterization after pelvic surgery, the optimal timing of antibiotic administration and length of dosing regimen is not well defined. The American Urological Association (AUA) recommends empiric antibiotic treatment at the time of external urinary catheter removal in patients with risk factors, such as tobacco use, advanced age, and anatomic abnormalities of the urinary tract.[13] The AUA Panel does cite that bacteriuria in the setting of noninfectious urinary tract disease is a risk factor for bacteremia, and, thus, prophylactic antibiotic treatment at time the of catheter removal may be indicated.[13] This recommendation is based on a few studies providing evidence for antibiotic treatment at the time of catheter removal. One of these studies, a randomized controlled trial by Harding et al., studied women with asymptomatic catheter-acquired bacteriuria after short-term catheterization and randomly assigned them to receive antibiotic therapy or no therapy at the time of Foley catheter removal. All women had urine cultures collected for up to 14 to 28 days following catheter removal. Those with antibiotic therapy demonstrated a significant increase in elimination of bacteriuria (81%) with oral antibiotics compared to the untreated population (36%).[14] Based on these studies, the AUA does recommend empiric antibiotic treatment at the removal of an external urinary catheter in patients with risk factors.[13] However, there is no standardization concerning the type of antibiotic to be used or treatment duration.

Although there are a few studies showing favorable results for use of nitrofurantoin doing catheterization after pelvic surgery, there are no clearly defined recommendations regarding its use for urinary tract infection prevention after catheter removal. Therefore, the objective of our study is to examine the effects of administration of nitrofurantoin therapy at the time of Foley catheter removal for the prevention of catheter-associated UTI in patients undergoing POP and/or urinary incontinence surgery.

STUDY DESIGN AND METHODS

This is a randomized, double-blind, placebo-controlled trial offered to patients who receive postoperative short-term transurethral catheterization after undergoing surgery for pelvic organ prolapse (POP), urinary incontinence, or both. The study will be conducted at two clinical sites:

1. Women's Center for Pelvic Health (Mercy), Atrium Health, Charlotte, NC
2. Women's Center for Pelvic Health (NorthEast) Atrium Health, Concord, NC

Human Subject Research and Informed Consent

Each participant will be required to sign an Internal Review Board (IRB) approved consent at the time of enrollment prior to any study-related interventions or

assessments. The informed consent form will describe the study in detail. Additionally, the study consent form will disclose the planned uses of study data, as well as potential risks to the participants. Each prospective subject will have the objectives of the study explained to them prior to enrollment. The subject will be given an opportunity to ask questions and decide whether or not to participate. Copies of the informed consent will be provided to the participants on request, and the originals will be stored at the primary study center (#1).

Subjects have the right to:

- Voluntarily participate in the study
- Withdraw or refuse participation in the study at any point without questioning
- Understand the objectives of the study
- Understand the risks and benefits of the study
- Have their confidentiality maintained

Participant Screening and Point of Enrollment

Participants scheduled to undergo surgery for pelvic organ prolapse (POP) or urinary incontinence will be identified and will be screened against inclusion and exclusion criteria. If confirmed to meet the requirements for the study, they will be eligible to be invited to participate in the study. Participants will be enrolled in the study once informed consent is obtained.

Participants will be enrolled by physicians, fellows, nurse practitioners, physician's assistants, and/or a research nurse prior to surgery. Each practitioner will receive education and training regarding the study enrollment.

STUDY POPULATION

Inclusion Criteria

The study will include women who are seeking surgical management for POP or urinary incontinence.

1. Age greater than 18
2. Creatinine clearance greater than 30 ml/min
3. Failed postoperative hospital voiding trial

Exclusion Criteria

1. Pregnant
2. History of glucose-6-phosphate dehydrogenase deficiency
3. History of renal insufficiency, renal transplant, or nephropathy
4. Allergy to nitrofurantoin

5. History of recurrent UTI (defined as greater than two culture-proven infections in six months or three infections in one year)
6. Urinary Tract Infection (UTI) within one month of surgery
7. Non-English speaking
8. Urinary tract infection while Foley catheter is in place
9. On antibiotic therapy for other non-urological reasons
10. Sustained intraoperative bladder injury requiring prolonged catheterization greater than 5 days
11. Undergoing mesh excision from within the bladder, fistula repair, cystotomy repair, urethral diverticulectomy, sacral neuromodulation, urethral surgery, or any other procedure requiring prolonged catheterization and bladder decompression
12. Placement of a suprapubic catheter
13. Participants that request intermittent self-catheterization
14. Neurologic conditions affecting urinary tract system and normal voiding mechanisms
15. History of hepatic impairment due to prior nitrofurantoin use
16. Inability to provide consent/decisionally impaired
17. More than two in-office voiding trials

Rationale for Nitrofurantoin and Regimen Chosen for This Protocol

Nitrofurantoin was chosen as the interventional medication for this study due to its efficacy in reducing urinary tract infections in women that required short-term postoperative catheterization.[4,12] Both prophylactic dosing (once daily) and therapeutic dosing (twice a day) have been studied. There are conflicting outcomes with once daily dosing, as one studied showed a decrease in UTI rates, while another did not when given during the catheterization time period.[3,12] There is one study that showed a significant reduction in rate of UTI with twice daily dosing.[4] Therefore, we have decided to proceed with twice daily dosing to ensure maximum coverage for UTI.

Additionally, *Escherichia coli*, the most common uropathogen, displays low resistance patterns to nitrofurantoin in our geographical region.[16] Trimethoprim-sulfamethoxazole (TMP-SMX), another first line therapy for treatment of UTI, which was the agent studied in a prior randomized controlled trial[15], displays only a 75% sensitivity for treating *Escherichia coli* in our hospital system.[16] Conversely, nitrofurantoin has a 98% sensitivity for treating Escherichia coli in our hospital system.[16]

In this study, not all of the participants will be receiving antibiotic treatment during the study course. Per the 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America (IDSA), prophylactic antimicrobials should not be routinely used in patients with indwelling catheterization due to the concern about selection of antimicrobial resistance. However, they cite that additional studies must be undertaken, given the findings of previous research that does illustrate fewer UTIs in patients who

receive antimicrobial prophylaxis at the time of catheter removal.[17] The data is still evolving regarding prophylactic antimicrobials. We are also limiting the exposure to the antibiotic treatment to only 5 days; recommended treatment courses for nitrofurantoin range from 5-7 days.[21,22]

Study Withdrawal

Participants may withdraw from the study at any point in time. Documentation of the reason for withdrawal will be captured in the data collection forms. There will be no risk to participants that choose to withdraw from the study.

Preoperative Period

All consecutive participants undergoing a scheduled surgery for POP and/or urinary incontinence will be identified, screened, and approached for enrollment. All will be screened for UTI. To be eligible to participate, the participant is not to have a UTI from 1 day to 1 month prior to surgery. Participants will be asked if they have any dysuria, frequency, or bladder irritation in the absence of vaginal discharge. A "YES" to all three of these symptoms indicates a positive screen, and therefore, the participant will be excluded. Additionally, the participant with be asked if they have been treated for a UTI within the past month with antibiotics. A "YES" indicates a positive screen, and therefore, the participant will be excluded.

Participants who do not meet the inclusion and exclusion criteria will be considered screen failures. Screen failures will be captured and the cause for screen failure will be documented.

Perioperative and Surgery Period

All participants will receive routine preoperative intravenous antibiotic prophylaxis based on standard hospital protocols. This will either be 2 or 3 grams of cefazolin based on patient weight. In the event of an allergy, an appropriate alternative, such as clindamycin 900 milligrams plus aztreonam 2 grams, will be given. All participants will have a 16 French latex Foley catheter placed intraoperatively using sterile technique. Any patient with a latex allergy will receive a non-latex 16 French Foley catheter.

Postoperative Period

All participants will undergo a postoperative retrograde fill voiding trial per our division's standard protocol on postoperative day zero prior to discharge (for outpatient procedures) or on the morning of postoperative day 1 for hospitalized participants.

Participants will pass the voiding trial if they void more than 200 mL with less than one-third post-void residual. If they fail, a 16 French Foley catheter will be reinserted.

All participants that fail the voiding trial will be discharged home with an indwelling Foley catheter. These participants will receive Foley maintenance education prior to discharge. They will be scheduled for a follow up voiding trial in the office in 1-7 days. The names of all participants that fail the voiding trial will be communicated to the principal investigator and/or the research nurse for continued follow up.

In Office Voiding Trial

Participants who are discharged with an indwelling Foley catheter will be scheduled to return to the office in 1-7 days for an in-office retrograde voiding trial. All office personnel (nurses, medical assistants, physicians, physician's assistants, and nurse practitioners) will receive education regarding voiding trial technique as outlined below prior to study commencement.

The bladder will be retrograde filled with normal saline up to a maximum of 300mL, and the catheter will then be removed. The participant will attempt to void immediately, but the participant will have up to 60 minutes to attempt voiding. After voiding, the participant will be asked to complete a Force of Stream questionnaire.[17] The urine will be measured and a post-void residual will be obtained with a bladder scan. If urine voided is 200 mL or greater, and the post-void residual is less than one-third of the total amount (voided volume plus residual volume), the catheter will be left out and the participant will be considered a voiding trial pass. If the volume is less than 200 mL, and the post-void residual is greater than one third of the total amount, the participant will be deemed a voiding trial failure; these patients will be sent home with a Foley catheter. After completing a bladder scan immediately after voiding attempt, the provider will be notified of the voided volume and post-void residual (to be obtained by bladder scan).

Once a participant has successfully passed the voiding trial, they will be eligible for randomization.

Randomization

Randomization will be controlled by the Carolinas HealthCare System Investigational Drug Services pharmacy through random permuted blocks and stratified per site. The biostatistician will generate the randomization sequence and provide this information to the pharmacist.

The study will be double-blinded such that both study participants and investigators will be masked to treatment allocation and block size randomization, except for the pharmacist and statistician, who will have no contact with the patients.

The Investigational Drug Services (IDS) pharmacy will provided blinded medication bottles containing either nitrofurantoin or placebo 100mg capsules. Each bottle will

contain 10 capsules. These bottles will be labeled by the IDS pharmacy with a randomization number. The study medications will be released by the pharmacy to the research nurse, who is also blinded. The medication bottles will be stored in a locked cabinet in a climate-controlled room until dispensed.

Eligible participants that have successfully passed the in-office voiding trial will be randomized into one of two groups upon completion of the voiding trial data collection sheet. There will be no indication which group the participant was randomized to. These sheets will be fluorescent colored and a part of each participant's chart. This sheet will need to be completed by the nurse administering the voiding trial.

The participants randomized to Group A will receive 100 mg nitrofurantoin every 12 hours by mouth starting on the day the Foley catheter is removed and complete a five-day course. Conversely, participants randomized into Group B will receive a matched placebo every 12 hours each day starting on the date of Foley catheter removal, for five days. Again, there will be no indication which group the participant was randomized to.

At the time of randomization, the participant will be assigned a randomization number. The bottle of medication with the same corresponding randomization ID will be dispensed. This will be a bottle of 10 capsules of nitrofurantoin or matching placebo with instructions to take every 12 hours for five days. The first dose will be given in the office. Participants will be asked to complete a one-week medication diary. Participants will be asked to return this bottle of medication, any unused medication, and a medication compliance diary at the first postoperative visit following surgery.

Any participant that fails the in-office voiding trial will be treated per standard clinical practice. That participant will be scheduled to return for an additional in-office voiding trial in 1-7 days. They will still be eligible to participate in the study after a passed voiding trial in the office. Data will still be collected on these participants. If the participant elects to intermittent self-catheterize, they will then be excluded from the study. Any participant that required any more than two in-office voiding trials postoperatively will be excluded.

Week 2 Postoperative Visit (+/- 1 week)

Participants will be scheduled for a 2-week postoperative follow up visit. They will be instructed to return their bottle of study medication and a medication compliance diary at this visit.

Treatment of UTIs

Urinary tract infection will be defined as:

- Any treatment received (outside of study drug) for clinically suspected UTI and/or a culture-proven UTI with a uropathogen within the first 30 days following surgery.
    - A urine culture is deemed positive if there are greater than 100,000 colony-forming units of a single organism. Urine cultures with mixed bacterial flora will **NOT** be classified as a positive culture.
    - Clinically suspected UTIs will be defined as dysuria, frequency, and irritation in the absence of vaginal discharge.

Study participants will not be eligible to take phenazopyridine while on study medications.

If a participant has clinical symptoms of a UTI during the study period, a urine specimen will be sent for culture and treatment will be based on appropriate antibiotics regarding specific susceptibilities. Per the IDSA guidelines, the following duration of treatment guidelines will be followed[18]:

- 7-14 days duration of antimicrobial treatment for patients with a catheter-associated UTI, regardless of whether the catheter is in place or not
- A 3-day antimicrobial regimen may be considered for women aged 65 years old or less who develop a catheter-associated UTI after the catheter has been removed

The investigator will maintain discretion to deviate from these guidelines pending clinical reasons.

The participant will be treated empirically for seven days with one of the following antibiotics while awaiting urine culture results, based on personal treatment history, contraindications, and allergies[17]:

- Cephalexin (500mg every 12 hours for 7-14 days) by mouth OR
- Fosfomycin (3 grams once) by mouth OR
- Ciprofloxacin (250 mg every 12 hours for 3 days OR 250-500mg every 12 hours for 7-14 days) by mouth

Fosfomycin is a single dose regimen. Although the IDSA recommends a 3-day or 7-14 day treatment course, recent in-vitro studies indicate that a single dose of fosfomycin is also effective and cost effective.[19,20] Fosfomycin was demonstrated to have high bactericidal activity against biofilms on siliconized latex catheters.[19] Therefore, it will also be offered as a treatment option for UTI to our participants.

Urine cultures will be obtained with susceptibilities, and antibiotic treatment may be changed depending on resistance. Once the uropathogen is known, the appropriate antibiotic regimen to treat the known uropathogen will employed.

If a participant is being empirically treated for a UTI, and the urine culture returns negative, the participant will be notified and instructed to stop taking the antibiotics.

The triage nursing staff, both in office and through the nursing phone triage service will receive study training prior to study commencement. Any participant that contacts our office outside of normal business hours with concerns of a UTI will be triaged and empirically treated with one of the appropriate antibiotics listed above. If they receive treatment from another provider outside our hospital system, authorization for release of records will be need to be signed by the participant.

Any participant that has a positive urine culture from an outside provider, or is treated based on clinical symptoms without evidence of a positive urine culture will be deemed a treatment failure. These participants will be included in the study analysis as treatment failures.

DATA COLLECTION AND MANAGEMENT

All study data will be recorded by research staff and securely maintained at primary site.

Data will be entered by study staff into REDCap database that will be stored on a secure server.

Each patient will have a unique identification number to which only the principal and co-investigators will have access. The data collection spreadsheet will not contain any patient identifiers and will be password protected. The master list that links the patients and their study identification number will be stored separately from the database. All collected information will be stored separately on a password protected hard drive. A back up copy of the file will be stored on a password protected hospital network drive. All hard copies of study data will be stored in a locked cabinet in the office of the research nurse, which will also be locked.

OUTCOME MEASURES

Primary Hypothesis

The primary hypothesis is that the administration of nitrofurantoin will reduce the UTI rate compared to the UTI rate in the placebo arm upon discontinuation of catheterization. The null hypothesis is that the administration of nitrofurantoin will not reduce the rate of UTI.

Primary Outcome Measure

The primary outcome of the study will be the treatment of symptomatic urinary tract infection and rate of urinary tract infection in the first 30 days following pelvic reconstructive surgery.

Secondary Outcome Measures

1. Adverse Events
    a. Any adverse event related to drug administration will be reported. Adverse events not related to medication administration will not be collected. Please refer to section on Adverse Events for details of reportable criteria.
2. Medication compliance
    a. All participants will need to complete a medication diary during the study drug treatment period. They will be asked to return this diary at their follow up. Medication compliance will be assessed and analyzed by way of these medication diaries.

STATISTICAL CONSIDERATIONS

Calculations of sample size were based on comparisons of UTI rates in the nitrofurantoin and placebo arms. According to published results, the UTI rate in the placebo arm was 32% and approximately a 14-15% reduction was observed in the treatment arm.[4,12] Using this information, we designed our study to mimic these findings, and assumed a UTI reduction rate of 18% in the nitrofurantoin arm could be observed in our clinical setting. Based on this assumption, total sample size of 164 patients was projected to achieve 80% power with a two-sided α error of 0.05. We increased the total sample size to 180 to allow for a 10% dropout rate. However, due to primary investigator timeline and lack of attrition, recruitment ceased once the sample size of 164 was reached. The power was calculated by using the PASS 15 (2017, NCSS, LLC. Kaysville, Utah, USA). All analyses were conducted using an intent-to-treat principle, which included all women

randomized and not withdrawn from the study. A per-protocol analysis was also performed, and only included patients that completed the study.

Categorical data were compared using X2 or Fisher's Exact test where appropriate. Continuous variables were compared using Student's t-test or Wilcoxon rank sum where appropriate, and are presented as mean±standard deviation or median (interquartile range). We estimated risks for UTI with odds ratio (OR) and corresponding 95% confidence intervals (95% CI) calculated using logistic regression. A P value <0.05 defined statistical significance. All analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC). No interim analysis was performed.

STUDY MONITORING AND DOCUMENTATION

The Principal Investigator will monitor the study and assess the need for amendments as the study progresses. A protocol revision may be necessary for reasons including but not limited to rights, safety of participants, welfare of participants, and thus, and amendment will be required. Appropriate approvals (i.e., IRB) of the revised protocol must be obtained prior to implementation at each site.

Site Documentation

All study documents included in this protocol that will be presented to subjects will be submitted to the IRB for approval. The primary site will maintain a study binder for all sites that will include the following:

- Enrollment log of patients that have consented to be in the study (electronic version)
- Protocol deviation log (electronic version)
- Adverse event log (electronic version)
- Investigator protocol and amendments
- IRB submissions, modifications, and renewals
- Data safety monitoring committee reports
- IRB approved consent form
- Data collection forms

Monitoring

Monitoring will be conducted by the data safety monitoring board (DSMB) throughout the study to ensure that the study is conducted in accordance with the study protocol. By verifying compliance, monitoring helps to safeguard the subject safety, ensure data quality, and provide ongoing training and support to ensure compliance.

Data verification will occur at 6-month intervals to verify data, assess continued compliance with protocol.

An interim analysis will be completed at 6 months from the study commencement date. The purpose of the interim analysis is to discern whether the trial can be stopped for early benefit, as well as evaluate for safety and efficacy. Interim data analyses will be presented to the Data Safety and Monitoring Board for their review and recommendation.

Study Drug Information

- **Drug:** Nitrofurantoin 100 mg capsules, with matched placebo, will be provided by Central Compounding Center South
- **Storage:** all study medications will be in a secure, locked, climate controlled location accessible only to authorized study personnel. All study medications will be maintained at controlled room temperature between 20-25°C with excursions permitted from 15-30°C.
- The principal investigator and/or her designee(s) will be responsible for ensuring accountability of study medications is maintained throughout the study for all study medications that is received, dispensed, and disposed of per institutional standards of procedures. This log will be maintained on the electronic application, Vestigo.
- Only participants enrolled and randomized in this study may receive study medications
- All unused study medications will be destroyed per the institution's destruction policy

Protocol Deviations

Protocol deviations will be documented and logged on the Protocol Deviations log (electronic version). This will be done for every protocol related deviation related to any portion of the study timeline. Deviations will be reviewed and evaluated on an ongoing basis, and, as necessary, appropriate corrective and preventive actions (including notification, re-training, or discontinuation) will be put in place.

Data Safety Monitoring Board (DSMB)

A data safety monitoring board (DSMB) will be comprised of an external physician and research nurse. They will be tasked to review all adverse events that occur across both study sites. A semi-annual report of all adverse events will be generated and sent to the Data Safety Monitoring Committee every 6 months.

All Serious Adverse Events (SAEs) will be reported to the DSMB via email within 2 days of site staff being informed of its occurrence. The PI and research nurse will be cc'd on all communications with the DSMB. Copies of de-identified source documentation regarding the SAE will be included, as well as other clinically meaningful documentation.

The PI will be responsible for ensuring that all sites comply with the DSMB requests.

Reporting Adverse Events

Adverse events (AE) will be recorded and reported per the criteria and timeline below.

All AEs must be recorded and entered into the AE log and REDCap. An event number will be assigned by each site and recorded.

SAEs must be reported to the DSMB within two business days as outlined above in the Data Safety Monitoring Committee section.

Reportable AEs include those determined to be related to the study medication. AEs not related to the study medications will not be collected. Please note that underlying diseases are not reportable AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but as an outcome of a specific SAE.

Any participant that suffers an allergic reaction to the study medications will be unblinded. This will be a reported adverse event that will also be reported to the DSMB, as outlined above.

Adverse Event Definitions

<u>Adverse Event:</u> any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory finding) in subjects, whether or not related to study medications

<u>Serious Adverse Event:</u> an adverse event that led to:

- Death
- Serious deterioration in the health of the subject that either resulted in
    - A life-threatening illness or injury

- A permanent impairment of a body structure or a body function
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function

Unrelated: No evidence that the timing of the AE has a relationship to the time study medications were taken

Possibly Related: The AE has a timely relationship to the study medications, however a potential alternative etiology may be responsible for the AE

Probably Related: The AE has a timely relationship to the study medications and the causative relationship can clearly be established. No potential alternative etiology is apparent.

Severity Definitions

Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

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Figure 1. Study Trial Flow