PROPHY Study

Prophylactic Antibiotics or Placebo after Hypospadias Repair

Trimethoprim-sulfamethoxazole vs. placebo after hypospadias repair:
a multicenter, double-blind, randomized trial

ClinicalTrials.gov Identifier: NCT02096159

CLINICAL TRIAL PROTOCOL (v6.11.15)

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CONTENTS

1. Overview 5
    - 1.1. Title
    - 1.2. Study Summary
    - 1.3. Aim, Hypothesis, and Outcomes
    - 1.4. Study Centers and Principal Investigators
2. Background 6
    - 2.1. Prior Research and Relevant Knowledge
    - 2.2. Contemporary Importance
3. Methods 8
    - 3.1. Study Design
    - 3.2. Eligibility Criteria
        - 3.2.1. Inclusion Criteria
        - 3.2.2. Exclusion Criteria
    - 3.3. Study Medications (Antibiotic and Placebo)
        - 3.3.1. Suppliers
        - 3.3.2. Placebo Stability
        - 3.3.3. Shipping and Storage
        - 3.3.4. Inventory
    - 3.4. Randomization Tables
        - 3.4.1. Randomization Tables for On-site Study Participants
        - 3.4.2. Randomization Tables for Off-site Study Participants
    - 3.5. Study Recruitment and Initial Screening
    - 3.6. Pre-operative Procedures
    - 3.7. Peri-operative/Day of Surgery Procedures
        - 3.7.1. Verification of Eligibility
        - 3.7.2. Study Medication Prescription
        - 3.7.3. Intra-operative Procedures
        - 3.7.4. Intra-operative Data Collection
        - 3.7.5. Final Review of Eligibility
        - 3.7.6. Preparation and Dispensing of Study Medication for On-Site Cases
        - 3.7.7. Preparation and Dispensing of Study Medication for Off-Site Cases
        - 3.7.8. Other Post-operative Medications
        - 3.7.9. Discharge Instructions
        - 3.7.10. Initial Follow-up Appointments
    - 3.8. Post-operative Follow-up Procedures and Outcomes Assessment
        - 3.8.1. Study Participant Monitoring
        - 3.8.2. Reporting and Management of Study Participant Issues and Adverse Events
        - 3.8.3. Dressing and Stent Removal
        - 3.8.4. Month One Follow-up
        - 3.8.5. Assessment of Adherence to Study Medication
        - 3.8.6. Six-Month Follow-up
        - 3.8.7. Five-Year Follow-up
        - 3.8.8. PRN Encounters
    - 3.9. Early Discontinuation of Study Medication
    - 3.10. Subject Withdrawal
    - 3.11. Unblinding
    - 3.12. Site Initiation and Readiness
4. Definition of Study Outcomes 18
    - 4.1. Primary Outcome Measures

4.2. Secondary Outcome Measures
5. Data 20
5.1. REDCap Data Instruments/Electronic Case Report Forms (eCRFs)
5.2. Data Management and Security
5.3. Data Quality
5.4. Data Transfer and Data Sharing Contracts
6. Statistical Analysis and Data Monitoring 22
6.1. Data Analysis and Reporting
6.1.1. Intention-to-treat Analysis
6.1.2. Per-protocol Analysis
6.1.3. Descriptive Statistics
6.1.4. Analysis of Primary and Secondary Outcomes
6.1.5. Homogeneity and Exploratory Analyses
6.2. Power and Sample Size
6.3. Interim Analysis
6.4. Data and Safety Monitoring Committee
7. Rationale for Study Design 25
7.1. Superiority vs. Non-inferiority Trial
7.2. Utilization of Composite Primary Outcome
7.3. Use of TMP-SMX as the Antibiotic Agent
7.4. Study Medication Dosing
7.5. Limitation of Inclusion to Distal/Mid-shaft Hypospadias Repairs
7.6. Eligibility of Previously Circumcised Patients
7.7. Exclusion of Cases with Foreskin Reconstruction
7.8. Pre-operative Testosterone Use
7.9. Duration of Follow-up
8. Informed Consent, Ethical Review, and Regulations 30
8.1. Informed Consent
8.2. Ethical Review
8.3. Compliance with Regulations
8.4. Protocol Amendments
8.5. Protocol Deviations and Violations
8.6. Trial Postponement and Early Termination
8.7. Study Documentation
8.8. Clinical Trial Registration
9. Organization 32
9.1. Steering Committee and Protocol Development
9.2. Publication of Study Results
9.3. Publications Committee
9.4. Timetable
9.5. Financial Support
9.6. Participant Costs and Compensation
10. Appendices 34

1. Overview

1.1 Title

The official title of the study is Prophylactic Antibiotics or Placebo After Hypospadias Repair (PROPHY). In materials intended for laypersons, "Preventive" may be used instead of "Prophylactic."

1.2 Study Summary

The PROPHY Study is a multicenter, double-blind, randomized trial of prophylactic oral antibiotics vs. placebo after primary mid-to-distal hypospadias repair with open-drainage urethral stenting.

1.3 Aim, Hypothesis, and Outcomes

Aim: The principal aim of this study is to evaluate the impact of a 10-day post-operative course of prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) on the rate of infectious and wound healing-related complications following primary repair of mid-to-distal shaft hypospadias with open-drainage urethral stenting.

Hypothesis: The research hypothesis is that administration of prophylactic TMP-SMX reduces the aggregate risk of infectious and wound healing-related complications. At present, the investigators believe there is clinical equipoise with respect to whether antibiotic prophylaxis after repair of mid-to-distal hypospadias is beneficial.

Outcomes: The primary outcome is a composite variable of symptomatic urinary tract infection (UTI), cellulitis/wound infection, meatal stenosis, urethral stricture, urethrocutaneous fistula, glans/urethral dehiscence, and/or urethral diverticulum. Rationale for use of a composite outcome is provided in Section 7.2. Detailed definitions of each primary outcome measure are provided in Section 4.1.

Secondary outcomes include acute adverse drug reactions (ADRs), stratified by severity, and *C. difficile* colitis. Detailed definitions of each secondary outcome measure are provided in Section 4.2.

1.4 Study Centers and Principal Investigators

The initial study centers and respective principal investigators are:

- Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's; Chicago, IL, USA) – Primary Study Center
  Earl Y. Cheng, MD (Principal Investigator)
  Mark A. Faasse, MD MPH; Dennis B. Liu, MD (Co-Investigators)

- The Hospital for Sick Children (SickKids; Toronto, Canada)
  Walid A. Farhat, MD

Other centers may join the study with agreement and approval of principal investigators from the initial study centers. All participating centers and surgeons must confirm their intention to adhere to this protocol prior to initiating involvement in the study.

2. Background

2.1 Prior Research and Relevant Knowledge

Hypospadias is a congenital anomaly affecting approximately 1/150 males, in which the urethral meatus (urethral opening) is abnormally located along the ventral aspect (underside) of the penis, instead of in its normal position at the end of the penis.[1] The degree of abnormal positioning is variable, from near the glans (head) of the penis (distal) to the perineum (proximal). Surgical repair is the only form of treatment for hypospadias, and the rate of hypospadias surgery in boys under 3 years-old was 468 per 100,000 in 2002.[2] A urethral stent or catheter is commonly secured to remain *in situ* following hypospadias repair, with open drainage to a diaper in children who are not yet toilet-trained.

According to a survey conducted in 2009, 91% of pediatric urologists used antibiotic prophylaxis following hypospadias surgery with urethral stenting.[3] However, via personal communication, the study investigators have found that as few as 40-50% of attendings at leading academic institutions routinely use prophylactic antibiotics in this setting.

Evidence from a recent retrospective cohort study by Kanaroglou *et al.* supports the omission of antibiotic prophylaxis, as patients who received 2 mg/kg of trimethoprim daily until stent removal (n=78) had a similar incidence of complications as controls (n=71).[4] No UTIs occurred in the control group, and the only wound infection was diagnosed in the group that received prophylaxis. The overall complication rate was 18.2% in the prophylactic group vs. 15.3% in the non-prophylactic group (95% confidence interval [CI] for between-group difference [BGD], -11% to 16%).

The results of Kanaroglou *et al.* contrast with those of two randomized but non-placebo-controlled trials of prophylactic sulfamethoxazole (SMX, unspecified dosing; n=84)[5] and cephalexin TID (dose unspecified; n=101)[6] published in 1983 and 2004, respectively. The former study reported that prophylactic SMX reduced the incidence of fever from 10% to 0% (95% CI for BGD, 0-24%). The latter study reported a 19% absolute reduction in symptomatic UTI, from 25% to 6% (95% CI for BGD, 3-34%). Rates of urethrocutaneous fistulas and meatal stenosis were 6% vs. 18% and 2% vs. 8% in patients who did and did not receive antibiotic prophylaxis, respectively. Although this study was inadequately powered to find these differences statistically significant, it has been hypothesized that bacterial infection may contribute to wound healing-related complications of hypospadias repair.[7] Nevertheless, the findings of Kanaroglou *et al.* did not validate any benefit of prophylactic antibiotics in this regard.

Differences in published results such as these may occur for a variety of reasons. Although Kanaroglou *et al.* reported on consecutive patients, reducing the risk of selection bias, the results of their study may

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[1] Gallentine ML, Morey AF, Thompson IM. Hypospadias: A contemporary epidemiologic assessment. Urol 2001; 57:788-790.
[2] Pohl HG, Joyce GF, Wise M, Cilento BG. Pediatric urologic disorders. In: Litwin MS, Saigal CS, eds. Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office, 2007; NIH Publication No. 07-5512:461-481.
[3] Hsieh MH, Wildenfels P, Gonzales ET. Surgical antibiotic practices among pediatric urologists in the United States. J Ped Urol 2011; 7:192-197.
[4] Kanaroglou N, Wehbi EJ, Alotay A *et al*. Is there a role for prophylactic antibiotics after stented hypospadias repair? J Urol 2013; 190:1535-1539.
[5] Shohet I, Alagam M, Shafir R *et al*. Post-operative catheterization and prophylactic antimicrobials in children with hypospadias. Urol 1983; 22:391-393.
[6] Ben Meir D and Livne PM. Is prophylactic antimicrobial treatment necessary after hypospadias repair? J Urol 2004; 171:2621-2622.
[7] Bayne AP and Jones EA. Complications of hypospadias repair. In: Taneja SS (ed.), *Complications of urologic surgery: prevention and management*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2010. p. 713-722.

reflect unmeasured variables that changed over time, such as surgeon experience, refinements in surgical technique, or other aspects of patient care. Differences in follow-up and failure to capture relevant outcomes may have also biased the results. Potential compromises of the aforementioned randomized trials' validity include their relatively small size and therefore vulnerability to chance bias from imbalance in baseline variables. As neither was placebo-controlled and blinded, ascertainment bias may have also occurred. In addition, improvements in surgical technique, development of antimicrobial resistance, and other changes in the decade since Ben Meir and Livne's study may have reduced the marginal benefit of prophylactic antibiotics after hypospadias repair.

Medication dosing may have also contributed to variable outcomes, as the dose of TMP utilized in the study reported by Kanaroglou *et al.* was a standard "prophylactic" dose (2 mg/kg once daily). By comparison, Ben Meir *et al.* utilized a therapeutic dosing schedule for administration of cephalexin (TID), although the amount was not reported.

2.2 Contemporary Importance

During recent years, antimicrobial agents have received increasing attention from public health experts. More judicious use of antibiotics is imperative to prevent further escalation of antimicrobial resistance, which poses a grave threat to human health[8] and has contributed substantially to rising healthcare costs.[9] Adverse drug reactions and alteration of native flora, which may cause antibiotic-associated diarrhea, *C. difficile* colitis, and other consequences, represent additional disadvantages of antibiotic use.[10]

On the other hand, health-care providers and organizations are under pressure to do whatever possible to prevent catheter-associated UTIs (CAUTI), which are now being used as a quality metric.[11] In certain circumstances, such as when removing urinary catheters, prophylactic antibiotics may be beneficial.[12] Of note, a 2012 Cochrane Review did not support routine use of prophylactic antibiotics during urethral catheterization.[13]

In light of these issues, as well as the discrepancy in results of previously published trials (see Section 2.1), a well-powered, placebo-controlled randomized trial that aims to provide evidence supporting either the rational use or avoidance of prophylactic antibiotics after hypospadias repair is timely. If the results of this study indicate that prophylactic antibiotics are beneficial, additional research may be necessary to identify the optimal dose and duration of prophylaxis.

[8] Howell L, ed. Global risks 2013, 8th edition: an initiative of the Risk Response Network. World Economic Forum, 2013.
[9] Smith R and Coast J. The true cost of antimicrobial resistance. BMJ 2013; 346:f1493.
[10] Sammons JS and Toltzis P. Recent trends in the epidemiology and treatment of *C. difficile* infection in children. Curr Opin Pediatr 2013; 25:116-121.
[11] http://www.cdc.gov/HAI/ca_uti/uti.html (accessed 9/3/2013)
[12] Marschall J, Carpenter CR, Fowler S *et al.* Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis. BMJ 2013; 346:f3147.
[13] Niël-Weise BS, van den Broek PJ, da Silva EMK *et al.* Urinary catheter policies for long-term bladder drainage. Cochrane Database Syst Rev 2012; 8:CD004201.

3. Methods

3.1 Study Design

The study is a 1:1 parallel-group, double-blind, randomized trial, with targeted enrollment of 630 boys who undergo primary hypospadias repair with open-drainage urethral stenting for 5-10 days. Study participants will receive 0.5 mL/kg of TMP-SMX (4 mg/kg TMP) or placebo by mouth (PO) twice daily (BID) for 10 days post-operatively.

Physician follow-up visits are planned for 1 and 6 months post-operatively. A chart review and survey of all study participants will be conducted 5 years post-operatively to capture late-presenting complications.

3.2 Eligibility Criteria

3.2.1 Inclusion Criteria

a) age < 6 years
b) mid-to-distal shaft hypospadias (subjectively assessed by attending surgeon)
c) single-stage hypospadias repair
d) length of urethral repair (urethroplasty) ≤ 2.0 cm
e) open-drainage urethral stent, with the proximal end positioned in the urinary bladder and intended duration of stenting of 5-10 days post-operatively

3.2.2 Exclusion Criteria

a) previous hypospadias repair
b) contraindication or elevated risk of adverse reactions to TMP-SMX, including:
    a. prior allergic or adverse reaction
    b. cross-reactivity with an existing medication
    c. human immunodeficiency virus (HIV)
c) poorly controlled diabetes mellitus or other immune-compromising conditions
d) any patient condition deemed by the attending surgeon to present an elevated risk of infection or of adverse outcome(s) from potential infection (e.g., endocarditis related to congenital heart disease)
e) receipt of oral or intravenous (IV) antibiotics within 7 days prior to hypospadias surgery
f) foreskin reconstruction
g) prescription of post-operative oral antibiotic prophylaxis (other than study medication)

3.3 Study Medications (Antibiotic and Placebo)

3.3.1 Suppliers

The antibiotic used for this study will be TMP-SMX 40-200 mg/5 mL (see Appendix A). Placebo will be formulated to approximate the appearance, odor, taste, texture, and pH of the active medication as closely as possible and prepared by a certified compounding pharmacy.

Necessary arrangements will be made for participating study centers to obtain the antibiotic and placebo. If necessary, study medications will be distributed from Lurie Children's.

3.3.2 Placebo Stability

The stability of placebo formulation(s) will be evaluated and documented by the laboratory of Gagan Kaushal, PhD (Pharmaceutical Sciences, Thomas Jefferson University).

3.3.3 Shipping and Storage

Both study medications should be shipped and stored according to manufacturer/producer specifications. All pertinent regulatory guidelines should also be observed (e.g., inclusion of a No-Objection Letter from Health Canada when importing medications to Canada).

3.3.4 Inventory

Based on the weight of prior patients undergoing hypospadias repair, we anticipate that each study participant will require an average of 100-150 mL of study medication. At the time of study initiation, each participating center will stock an agreed-upon quantity (e.g., 1.0-3.0 L) of both antibiotic and placebo. For the duration of the study, pharmacy staff at each study center will monitor inventory of study medications and order additional supplies as necessary, taking necessary lead-time into consideration.

3.4 Randomization Tables

Study participants will be randomized 1:1 to antibiotic or placebo treatment in blocks of 10, stratified by study center.

3.4.1 Randomization Tables for On-site Study Participants

For allocation of patients undergoing surgery at facilities with on-site preparation of study medication bottles, randomization tables will be generated and uploaded into the REDCap randomization module prior to the beginning of the study. Please reference Section 3.7.6 for directions regarding patient assignment and medication preparation.

3.4.2 Randomization Tables for Off-site Study Participants

Separate randomization tables will be created by the statistician (or other designee not involved in patient care during the study) to be used for patients undergoing surgery at locations where day-of-surgery preparation of study medication is unavailable. The tables will allow preparation of study medication prior to surgery without recording the allocation in REDCap until final confirmation of eligibility to participate in the study. Each table will have one block of 10 allocations (5 TMP-SMX, 5 placebo).

At the time of study initiation, pharmacies at each study center with potential off-site participants will receive at least two randomization tables for off-site participants. When use of the first off-site randomization table has been completed (i.e., all 10 study medication bottles prepared and dispensed), pharmacy staff should proceed to use the next randomization table, while notifying the statistician or designee to generate the subsequent table.

At their discretion, pharmacy staff may utilize the off-site randomization tables either electronically or on paper. Creating multiple copies of the randomization tables should be avoided, as this may lead to errors in record-keeping and dispensing of study medication bottles.

3.5 Study Recruitment and Initial Screening

At each study center, Institutional Review Board (IRB)-approved methods should be followed in recruiting patients with mid-to-distal shaft hypospadias and obtaining consent for study participation prior

to or on the day of surgery. Patients with proximal hypospadias defects or any condition that presents an elevated risk of infection or of adverse outcome from potential infection (e.g., endocarditis related to congenital heart disease) should not be invited to participate. Recruitment materials may include an educational brochure regarding the study (Appendix B), referral to prophystudy.info, and/or a copy of the consent form.

An electronic case report form (eCRF) will be created in the study's REDCap database (Appendix C) for patients whose parent(s)/legally authorized representative(s) (LAR) indicate a desire to enroll in the study. Depending on IRB regulations, Protected Health Information (PHI) will be entered either into the eCRF or an off-line registry by which the REDCap Study ID corresponding to each patient can be identified.

Enrollment information will include screening questions pertinent to eligibility criteria (see Section 3.2). For patients with a potentially immune-compromising comorbidity, their pediatrician or other relevant specialist(s) should be contacted to assess its current status of control (i.e., well vs. poorly controlled). Cross-reactivity of medications with TMP-SMX should be assessed using Epocrates, Lexicomp, or other clinical pharmaceutical software.

3.6 Pre-operative Procedures

For study purposes, pre-operative use of topical or intramuscular (IM) testosterone is left to surgeons' discretion. When a decision to administer testosterone is made, physicians should document measurements of glans width and stretched penile length at the initial clinic visit. These data may facilitate *post hoc* analysis of the relationship between testosterone use, change in penile size, and surgical outcomes. As described by Aaronson (1994), stretched penile length should be measured by gripping the glans gently but firmly enough to stretch the penis to its full length and recording the distance along the dorsal aspect from the symphysis pubis to the tip of the glans, disregarding the prepuce.[14]

For (potential) study participants who may undergo hypospadias repair at an off-site facility, a weight should be obtained within 30 days prior to surgery and documented in the eCRF. This will facilitate preparation of study medication in advance of the day of surgery.

3.7 Peri-operative/Day of Surgery Procedures

3.7.1 Verification of Eligibility

On the day of surgery, study personnel should verify that the patient has not received oral or IV antibiotics within 7 days prior to surgery. Contact information, medical conditions, current medications, allergy history, and information regarding pre-operative testosterone use should also be confirmed and documented in the REDCap Preop Verification data instrument.

3.7.2 Study Medication Prescription

For patients undergoing surgery at a location with on-site pharmacists, the prescription for study medication may be completed when the patient arrives and is weighed pre-operatively, however, randomization and preparation of the medication should be deferred until final, intra-operative confirmation of patient eligibility (see Section 3.7.6). For off-site surgeries, the prescription must be provided further in advance to allow earlier preparation of study medication (see Section 3.7.7).

3.7.3 Intra-operative Procedures

[14] Aaronson IA. Micropenis: medical and surgical implications. J Urol 1994; 152:4-14.

Use of peri-operative IV antibiotics is recommended but not required. Generally speaking, cefazolin or an alternate agent such as clindamycin or vancomycin (for patients with penicillin allergies) should be administered. The initial dose should ideally be administered within 1 hour *prior* to incision (2 hours for vancomycin). Redosing guidelines should be followed (http://www.medscape.com/viewarticle/742992_11). Surgical scrub technique will not be standardized but should be documented in the REDCap Surgery data instrument.

A catheterized urine culture may optionally be collected as part of routine care at the outset of the procedure, with documentation of whether the culture was collected prior to or following IV administration of prophylactic antibiotics. The results will be used to assess baseline levels of bacteriuria and its possible relationship to post-operative complications. Patient management should not be affected by intra-operative cultures unless there are symptoms/signs of infection post-operatively.

No standardization of surgical technique is required, but various technical aspects should be documented in the Surgery data instrument. At the conclusion of the case, either absorbable or non-absorbable suture(s) may be used to secure the urethral stent in place. Follow-up should be arranged per Section 3.8.3, according to the suture type.

3.7.4 Intra-operative Data Collection

The meatal location should be assessed with the patient under anesthesia. If the hypospadias defect is subjectively regarded as "proximal," the patient should be excluded from the study, regardless of the eventual length of the urethral repair.

Penile measurements (glans width and stretched penile length) should be taken after sterile preparation of the surgical field. Stretched penile length should be measured by lifting the glans via traction suture to stretch the penis to its full length and recording the distance along the dorsal aspect from the symphysis pubis to the tip of the glans, disregarding the prepuce.[15] Incision time should be regarded as the time of skin incision, not placement of the glans traction suture.

A skeletonized portion of the REDCap Surgery data instrument is available to facilitate intra-operative recording of data, such as the time of peri-operative antibiotic administration and incision, intra-operative measurements, and case duration (Appendix D). This "Cheat Sheet" also includes a guide for final verification of criteria for study eligibility (Section 3.7.5).

Point-of-care data entry to the Surgery data instrument by the attending surgeon or designee is encouraged. Paper CRFs may also be utilized. Study coordinators should verify documentation of necessary data.

3.7.5 Final Review of Eligibility

The final review of eligibility for study participation will occur after completion of the urethroplasty. The surgeon must confirm (a) his/her subjective impression that the hypospadias defect was distal or midshaft, (b) the urethroplasty length was no greater than 2.0 cm, (c) the surgical repair will be completed in a single stage (with circumcision, if the patient was not previously circumcised), and (d) an open-drainage urethral stent will be used, with the proximal end positioned in the urinary bladder and intended duration of stenting of 5-10 days post-operatively. When a patient's final eligibility for participation has been

[15] Aaronson, 1994.

determined, a study coordinator/investigator or other personnel should notify pharmacy staff to fill the previously provided prescription (for on-site cases).

3.7.6 Preparation and Dispensing of Study Medication for On-Site Cases

For on-site cases, pharmacy staff should await notification of participants' final eligibility before preparing study medication. When confirmed, the REDCap Study Medication Dispensing data instrument will be used to assess each study subject's eligibility and allow one-click randomization to antibiotic or placebo using the REDCap randomization module. Once randomization is performed in REDCap, a study subject's allocation cannot be changed.

Pharmacists will calculate the total amount (mL) of study medication to be dispensed for each participant by multiplying the child's weight (kg) by 10 and adding 10 mL for minor spillage or inaccuracies in dose administration. Bottles will be labeled with "PROPHY Study Medication," as well as the patient's name, Study ID number, instructions for weight-based dosing ("__ mL PO BID x 10 days"), contact information for a study coordinator, expiration date, and any other study center-specific requirements, such as Canadian Qualified Investigator labeling and translation. Provision of syringes marked with the desired volume for each dose is encouraged.

Study medication should be dispensed in a double-blind fashion. Other than pharmacy staff, all individuals involved in the care of study participants and/or conduct of the study must remain unaware of participants' allocation until completion or termination of the study, except in circumstances described by Section 3.10.

3.7.7 Preparation and Dispensing of Study Medication for Off-Site Cases

When a study medication prescription is received for off-site cases, the pharmacy staff should identify the next assignment in the off-site randomization table. Study medication bottles should be prepared and labeled as described in Section 3.7.6. The pharmacy staff should record the patient's Study ID, name, and an "X" in the "Prepared" column of the randomization table. No record of the allocation should be entered into REDCap at this time.

Study medication will be dispensed to personnel who will transport the medication to the off-site location on the day of surgery. Following surgery, this individual (or designee) should notify the pharmacy of whether the patient was eligible for the study and received study medication. If so, pharmacy staff will record an "X" in the "Dispensed" column of the randomization table and enter the participant's allocation into the eCRF (REDCap Study Medication Dispensing data instrument). Blinding of both patients and study personnel (other than pharmacy staff) to the allocation should be maintained in this process.

If an off-site patient is ineligible for the study, the study medication should be returned to the pharmacy. Pharmacy staff will record an "X" in the "Not Dispensed/Reassigned" column, and this study medication assignment will be given to the next off-site study participant, regardless of whether one or more subsequent off-site assignments were prepared in the interim.

3.7.8 Other Post-operative Medications

At the discretion of each attending surgeon, any medications other than oral antibiotics may be prescribed for patients post-operatively; topical preparations containing antibiotics are also permissible. All post-operative medications should be recorded in the REDCap Surgery data instrument.

3.7.9 Discharge Instructions

Discharge instructions may be adapted according to center/attending-specific preferences. Caregivers should be instructed to administer study medication twice daily for 10 days post-operatively, retain possession of the medication bottle(s) with any leftover contents, and report any concerns to a study coordinator/investigator as soon as possible, including symptoms/signs of UTI, cellulitis/wound infection, medication intolerance, diarrhea, rash, or other ADRs.

3.7.10 Initial Follow-up Appointments

Initial follow-up may include an appointment for dressing removal. When the urethral stent is secured by non-absorbable suture(s), a visit should be scheduled for stent removal 5-10 days post-operatively. Patients whose stent is secured with absorbable suture(s) may receive an appointment on or as close as possible to (but not later than) post-operative day 10. If the stent falls out prior to this date, a study coordinator should be informed, and this appointment may be cancelled. All patients should have a physician visit scheduled for approximately 1 month post-operatively.

3.8 Post-operative Follow-up Procedures and Outcomes Assessment

3.8.1 Study Participant Monitoring

Periodic emails or telephone calls should be used to monitor study participants, encourage adherence to BID administration of study medication, and remind caregivers to report any symptoms/signs of infection or ADR as well as if/when the urethral stent falls out. Participants should be reminded to discontinue study medication on post-operative day 10 and to retain possession of their study medication bottle(s) with any residual medication, which should be returned at the time of their next follow-up visit. Reminders of follow-up appointments may also be provided.

A study coordinator should also contact participants on or shortly after post-operative day 15 specifically to assess for occurrence of medication intolerance, diarrhea, rash, and other ADRs, which are secondary study outcomes when occurring within 14 days post-operatively. This opportunity should also be used to confirm medications and topical agents used since surgery. Another contact should occur on or shortly after post-operative day 31 to assess for primary outcomes, unless a follow-up appointment is scheduled to occur in the same time frame. Data from these contacts should be recorded in the REDCap Month One Followup data instrument.

3.8.2 Reporting and Management of Study Participant Issues and Adverse Events

Issues with study participants, including study outcomes, that are recognized during routinely scheduled follow-up visits should be documented in the corresponding REDCap data instrument. Issues that are evaluated or diagnosed by healthcare encounters/visits outside of routine follow-up visits should be documented in the PRN Encounters data instrument, including if those encounters/visits occur at other medical facilities. If no healthcare encounter occurs to evaluate an issue that is reported or discovered outside of routine follow-up visits, it should be recorded in the Patient Contacts, Adverse Events & Protocol Deviations data instrument.

Any unfavorable change in a study participant's medical condition should be considered an adverse event, including but not limited to changes related to occurrence of any primary or secondary study outcomes (infections, post-operative complications, and/or ADRs). Study coordinators should be made aware of all possible adverse events, and these cases should be reviewed immediately with the patient's attending physician. In addition to relevant documentation described in the preceding paragraph, adverse events should also be recorded in the Patient Contacts, Adverse Events & Protocol Deviations data instrument.

Study coordinators and PIs are responsible for adhering to local IRB guidelines on reporting of adverse events. The Lurie Children's IRB requires adverse events to be classified as serious, unexpected, and/or related or possibly related to the patient's participation in the PROPHY Study, with these designations being defined as follows:

- a serious adverse event involves hospitalization or prolongation thereof, life-threatening injury, persistent or significant disability, death, or development of a condition that would (have) likely jeopardize(-d) the patient's life or ability to conduct normal life functions if it remains(-ed) untreated;
- an unexpected event is unanticipated, including in terms of severity or frequency of occurrence to a particular research subject, given the nature of the research procedures and population being studied;
- an event is related or possibly related to study participation if it is related or possibly related to the patient's receipt of prophylactic antibiotics (or lack thereof) post-operatively.

All serious or unexpected adverse events that are related or possibly related to study participation must be reported to the primary study center (Lurie Children's) within 10 days of their recognition.

Study participants' attending and/or treating physician(s) are responsible for deciding on appropriate management of reported issues. This may include arrangements for a clinic visit to the patient's primary care physician/pediatrician or urologist, Emergency Room (ER) visit, hospital admission, urine culture, wound culture, *C. difficile* testing, temporary or permanent discontinuation of study medication, initiation of an alternative (known) antibiotic, or other management.

In the event of nonspecific symptoms/signs that may be referable to an infection (e.g., fever, hypothermia, apnea, bradycardia, lethargy, and vomiting) or symptoms/signs of UTI (dysuria or suprapubic/costovertebral pain or tenderness), patients will be instructed to be seen as soon as possible for evaluation, whether in the ER, primary care physician/pediatrician's clinic, or urology clinic. Evaluation for alternate (non-UTI) causes of nonspecific symptoms/signs should be performed. If clinically indicated, a urine specimen should be collected for both urinalysis and culture via the urethral stent (prior to its removal), suprapubic aspirate, urethral catheterization, or urine bag ± Credé maneuver. Because of poor specificity, use of bagged specimens is discouraged unless other alternatives are deemed unacceptable. A study coordinator should follow-up on the results of any cultures collected.

If symptoms/signs of infection are present, the decision to initiate treatment with known antibiotics will be made by the treating physician. If the patient's condition does not allow deferral of treatment until culture results are available, empiric antibiotics should be initiated. If the patient is still taking study medication at this time, it should be discontinued. Selection of the antibiotic agent(s) to be used empirically is at the physician's discretion, keeping in mind that the patient may or may not have been receiving TMP-SMX. The patient's clinical record should subsequently be reviewed for relevant data to be documented in both the PRN Encounters and Patient Contacts, Adverse Events & Protocol Deviations data instruments.

If medication intolerance occurs (i.e., isolated vomiting or spitting up on at least 2 consecutive occasions after taking study medication), routine advice regarding administration of the medication with food or milk, etc., will be provided. If medication intolerance persists, study medication may be discontinued – temporarily or permanently – at the discretion of the attending physician.

If symptoms/signs of other mild ADRs, including diarrhea, occur while the patient is on study medication, the participant will be instructed to temporarily discontinue it. Testing for *C. difficile* is advised for evaluation of diarrhea unless it has already resolved by the time study personnel become aware of it. For symptoms/signs of a mild hypersensitivity reaction (i.e., generalized

erythema/rash, urticaria, periorbital edema, or angioedema), caregivers will be instructed to administer diphenhydramine until symptom resolution. Study medication should be restarted at the attending's discretion when symptoms improve/resolve or when 48 hours have elapsed since discontinuation of the medication. If symptoms recur or worsen with resumption of study medication, it should be permanently discontinued.

If symptoms/signs of a moderate-to-severe ADR (as defined in Section 4.2) occur, the study medication should be permanently discontinued, with further management as directed by the patient's treating physician(s). Unblinding may be necessary to direct patient care (see Section 3.10). If study medication is permanently discontinued because of an ADR, an alternative prophylactic antibiotic may be initiated at the discretion of the attending physician, with documentation in the Patient Contacts, Adverse Events & Protocol Deviations data instrument.

If a study participant requires emergent assessment by a physician for any reason and is unable to come to the study center, a study coordinator will invite treating physicians at outside institutions to contact him/her to discuss collection and reporting of culture results, study criteria for infection, etc. Medical records from outside institutions may be obtained with the participant's permission.

3.8.3 Dressing and Stent Removal

At surgeons' discretion, a clinic visit may be scheduled for dressing removal. All patients whose stent is secured with a non-absorbable suture should be scheduled to have a clinic visit with a nurse or physician 5-10 days post-operatively for stent removal. Patients whose stent is secured with an absorbable suture should receive an appointment on or as close as possible to (but not later than) post-operative day 10, which can be cancelled if the stent falls out prior to this date.

If it is part of routine care, a urine culture may optionally be collected at one or both of these clinic visits, with documentation of whether it was collected and its eventual results in the appropriate REDCap data instrument (Dressing Removal or Stent Removal). As in the case of urine cultures collected intra-operatively, patients with positive post-operative cultures should not be managed differently unless they manifest symptoms/signs of infection.

Routine assessment should be performed at the time of dressing and stent removal. If symptoms/signs of infection, wound healing-related complications, medication intolerance, diarrhea, rash, or other ADR are evident, a study coordinator should be notified, and the case should be reviewed with the patient's attending physician to determine subsequent management. Patients with possible cellulitis/wound infection should be examined by a physician for diagnostic confirmation. A study coordinator should be notified if any cultures are collected, in order to follow-up on results.

Nurses with research certification may enter data relevant to dressing and/or stent removal directly into REDCap. Otherwise, they should utilize paper CRFs and submit these to a study coordinator for data entry. Occurrence of primary and secondary outcomes should only be documented in REDCap by study coordinators or physicians.

3.8.4 Month One Follow-up

Early post-operative monitoring of study participants by telephone calls or emails is described in Section 3.8.1. All patients should have a physician visit scheduled for approximately 1 month post-operatively. The primary purpose of this visit is to confirm the occurrence or absence of symptoms/signs of infection, as UTI and cellulitis/wound infection are primary study outcomes when occurring within 30 days post-operatively. If the 1-month clinic visit occurs prior to post-operative day 30, it should be supplemented by

a telephone call or email on or shortly after post-operative day 31 to confirm absence of symptoms/signs of infection. Data from the 1-month clinic visit and/or other routine contacts occurring at this time should be recorded in the REDCap Month One Followup data instrument. Any receipt of antibiotics (other than study medication) during the first 30 days after surgery should also be documented.

The 1-month clinic visit should also include assessment of other primary outcomes by reviewing voiding symptoms (strength and singularity of the urinary stream) and physical examination, noting the adequacy of meatal caliber, dehiscence, and/or evidence of urethrocutaneous fistulae or urethral diverticulae. If any symptoms/signs of meatal stenosis or urethral stricture are identified, urethral calibration with an 8 Fr catheter/sound/dilator should be attempted. Inability to introduce the catheter/sound/dilator through the urethral meatus is considered diagnostic of meatal stenosis, whereas ability to pass the 8 Fr instrument beyond the meatus but not into the urinary bladder should prompt further evaluation (e.g., cystoscopy) for urethral stricture (see Section 4.1). A study coordinator should be notified if any cultures are collected, in order to follow-up on results.

3.8.5 Assessment of Adherence to Study Medication

Each patient's study medication bottle(s) should be collected after post-operative day 10. This may occur at the 1-month clinic visit. The volume of residual medication should be measured either by pharmacy staff or other personnel and recorded in the REDCap eCRF.

3.8.6 Six-Month Follow-up

The final scheduled follow-up appointment for the PROPHY Study should be approximately 6 months post-operatively. At that time, participants will be advised of symptoms/signs relevant to primary outcomes that may present at a later date. If any occur, the parent(s)/ caregiver(s) will be requested to contact a study coordinator to arrange a PRN follow-up appointment.

3.8.7 Five-Year Follow-up

Five years post-operatively, a chart review and brief survey of parent(s)/caregiver(s) will be conducted to assess if late-presenting complications have occurred, using the REDCap Five-Year Followup data instrument. If applicable, permission to obtain relevant medical records from other facilities may also be requested at this time. Periodic contacts should occur approximately annually between the 6-month visit and 5-year follow-up survey in order to verify and maintain accurate contact information for study participants.

If the patient is not yet toilet-trained at the time of 5-year follow-up and/or his parent(s)/caregiver(s) have not had an opportunity to observe him voiding, a subsequent contact will be arranged to occur after toilet-training and observance of voiding. If concerns for potential complications are identified and have not yet been addressed, the participants will be asked to schedule a PRN follow-up appointment.

Longer-term follow-up assessments will require separate IRB authorization. Outcomes that may be relevant to longer-term follow-up include voiding symptoms, patient satisfaction with penile appearance, and sexual function.

3.8.8 PRN Encounters

Data should be recorded in the REDCap PRN Encounters data instrument for all PRN (unscheduled) visits that occur for evaluation of concerns related to the patient's hypospadias surgery. This should include visits to the study site ER, primary care physician/pediatrician, and outside hospital ERs. A study

coordinator should be notified or investigate if any cultures were collected, in order to follow-up on results. Permission to obtain relevant records from other medical facilities will be requested from study participants.

3.9 Early Discontinuation of Study Medication

Study medication should be temporarily discontinued if a mild ADR occurs (see Section 3.8.2). It should be permanently discontinued under the following circumstances:

- initiation of treatment with known antibiotics for a symptomatic UTI or cellulitis/wound infection less than 10 days post-operatively;
- initiation of treatment with trimethoprim and/or sulfamethoxazole for any other reason less than 10 days post-operatively;
- symptoms/signs of a moderate-to-severe ADR;
- recurrent symptoms/signs of a mild ADR;
- subject withdrawal from the study; or
- any other reason deemed appropriate by a treating physician.

A study coordinator and the patient's attending physician should be notified if study medication is discontinued. Follow-up should continue per protocol, and all data will be analyzed on an intention-to-treat basis.

3.10 Subject Withdrawal

Study participants may opt to withdraw from the study at any time. Subjects will also be withdrawn if they do not have surgery after enrollment, eligibility criteria are not satisfied, or the study is discontinued. The reason(s) for withdrawal should be recorded in the REDCap Subject Withdrawal data instrument. Data collected to date will be included in the study analysis unless the parent(s)/LAR indicate a preference otherwise.

3.11 Unblinding

In the event that a patient's clinical management depends critically on knowledge of whether the patient received TMP-SMX or placebo, a study coordinator will contact a pharmacist, data manager, or statistician to provide emergency unblinding. Data of patients for whom unblinding is required will still be analyzed according to an intention-to-treat principle.

3.12 Site Initiation and Readiness

A dry run/dummy test may be used to confirm readiness at each study center. The dry run may include simulated recruitment of potential study participants, collection of study-related data prior to and on the "day of surgery," alerting of the pharmacy to perform randomization and dispense study medication, and post-operative follow-up, with data entry into REDCap eCRFs. Management of atypical scenarios, such as a participant's development of symptoms/signs of UTI, should be considered.

4. Definition of Study Outcomes

4.1 Primary Outcome Measures

The components of the primary outcome are defined as follows:

- symptomatic UTI within 30 days post-operatively – both of the following criteria must be satisfied (modeled after the CDC and AAP definitions[16,17]):
  1. one or more of the following symptoms/signs: fever > 38°C, hypothermia < 36°C, or apnea/bradycardia/lethargy/vomiting with no other likely alternate cause(s); dysuria; suprapubic or costovertebral pain or tenderness; AND
  2. positive urine culture, as defined by ≥ 50,000 cfu/mL of no more than 2 species of microorganisms AND (dipstick positive for leukocyte esterase at trace or greater levels OR pyuria > 5 wbc/hpf, unless urinalysis was not obtained)
- cellulitis/wound infection within 30 days post-operatively: (erythema OR warmth) AND tenderness to gentle palpation, OR purulent drainage with positive wound culture;
- meatal stenosis: urethral meatus unable to accommodate an 8Fr catheter or sound/dilator
- urethral stricture: < 8Fr stenosis, proximal to the urethral meatus
- urethrocutaneous fistula: multiple urinary streams, including urine leakage from a location proximal to the urethral meatus, or a visible fistula
- dehiscence: ventral separation of the reconstructed glans penis/urethra
- urethral diverticulum: "ballooning" of the urethra evident on physical examination, during voiding, or by cystoscopic evaluation

When urine or wound cultures are positive, study coordinators should ensure documentation of relevant symptoms/signs before recording a diagnosis of symptomatic UTI or wound infection.

4.2 Secondary Outcome Measures

Secondary outcome measures include acute ADRs (within 14 days post-operatively), stratified by severity, and diagnosis of *C. difficile* colitis within 6 months post-operatively. Stratification of ADRs is modeled after the Brown scale of hypersensitivity reactions.[18,19]

a) Acute adverse drug reactions (ADRs)

1) Mild
   - medication intolerance: isolated vomiting/spitting up on at least 2 consecutive occasions after administration of study medication
   - isolated diarrhea: loose or watery stools, with increase in frequency to twice the usual number per day in infants, or 3 or more per day in older children; *C. difficile* assay negative or not obtained (with duration, if applicable)
   - mild hypersensitivity reactions (HR): generalized erythema/rash, urticaria, periorbital edema, angioedema

2) Moderate-to-Severe
   - blistering

[16] http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (accessed 11/1/2014)
[17] Roberts KB, Downs SM, Finnell SM *et al.* Urinary tract infection: clinical practice guidelines for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011; 128:595-610.
[18] Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371-376.
[19] Brown AFT. Current management of anaphylaxis. Emerg 2009; 21:213-223.

- Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hepatic necrosis, blood dyscrasia, or other severe reaction
- moderate-severe HR:
    - one or more symptoms/signs of mild HR; AND
    - cough, dyspnea, stridor, wheezing, cyanosis/hypoxia, drooling, vomiting, diaphoresis, abdominal pain, hypotension, or altered mental status

b) Diagnosis of *C. difficile* colitis within 6 months post-operatively

If occurring within 14 days post-operatively, diarrhea and *C. difficile* colitis will be regarded as mutually exclusive outcome measures (i.e., if a patient is documented to have *C. difficile* colitis, he will not be reported as also having had diarrhea).

5. Data

5.1 REDCap Data Instruments/Electronic Case Report Forms (eCRFs)

REDCap is a mature, freely available, and secure Clinical Research Information System developed at Vanderbilt University and utilized by over 1400 institutions worldwide (http://www.project-redcap.org). Study data will be recorded using data instruments/electronic Case Report Forms (eCRFs) programmed in REDCap (Appendix C). Data instruments may also be available on paper, however, any data collected on paper should be transferred into REDCap as soon as possible. Training on data entry and use of REDCap should be provided to all users prior to study initiation and on a PRN basis thereafter.

Protected Health Information (PHI) should not be included in the database for patients enrolled at study centers where inclusion of such information is not permitted. Instead, study coordinators should maintain a secure registry off-line of which Study ID corresponds to each patient. All data from each study center will be de-identified for analysis.

5.2 Data Management and Security

Records containing subject medical information must be handled in accordance with the requirements of the HIPPA Privacy Rule. Such records must not be shared with or accessed by any person or for any purpose not contemplated by the informed consent. Furthermore, case report forms and other documents to be transferred to the investigator should be completed in strict accordance with the instructions provided by the investigator, including the instructions regarding the coding of subject identities.

REDCap has application-level security that restricts access to study data based on user roles and permissions. User roles and permissions within REDCap should be restricted to the minimum number of data instruments that each individual needs to access. In addition to application-level security, all access to REDCap at Lurie Children's/Northwestern Univerity is over SSL (https). This prevents any third party from deciphering data sent between a user of REDCap and the system itself. This is the same level of encryption used on online banking, e-commerce, and other sensitive websites.

Each participating study center is responsible for ensuring that sufficient mechanisms are in place for secure data entry and storage. At Lurie Children's/Northwestern University, REDCap is HIPAA-compliant. A network firewall controls access to the REDCap application servers by only allowing traffic from known subnets, minimal set of data ports and minimal protocols. Thus, access is denied or closed by default. Behind this firewall is a two-tiered system design. One server hosts the web server and application specific code. A second server hosts the database. Traffic between these two servers is again restricted by IP, port, and shared access key, and never leaves the private network. This ensures that only the trusted application server can talk to the database server and prevents unauthorized access to the database server from direct external attacks. To protect data in the case of corruption or system error, all data are backed up on a nightly basis with full redundancy.

5.3 Data Quality

Whenever feasible, database programming will be put in place to identify outliers and prompt verification of data entry. An audit log will identify variables that are changed after initial data entry. Study coordinators and/or data manager(s) will regularly review data to ensure completeness.

If any study personnel develop concerns regarding the integrity or quality of study data, these should be reported to a study coordinator and/or PI as soon as possible. The concerns and results of subsequent

investigation should be documented. Any protocol deviations/violations should be reported to the relevant IRB, as per Section 8.5.

5.4 Data Transfer and Data Sharing Contracts

Deidentified data from all study centers will periodically be transferred to the primary study center for review by the Data and Safety Monitoring Committee and statistical analysis. Data will be analyzed and reported on a pooled, aggregate basis, without stratification or comparison of outcomes by study center. Relevant data sharing contracts will be established.

6. Statistical Analysis and Data Monitoring

6.1 Data Analysis and Reporting

6.1.1 Intention-to-treat Analysis

The primary analysis will be based on the intention-to-treat (ITT) principle. All randomized patients will be analyzed in the group to which they were allocated, regardless of whether they actually received the intended treatment or whether a protocol deviation/violation occurred. No adjustments for multiple comparisons will be used since a single primary endpoint has been defined and thresholds adjusting for interim analyses will be applied.

6.1.2 Per-protocol Analysis

Inclusion in the per-protocol analysis will require the following:
- completion of the 10-day course of assigned study medication with at least 80% adherence, as assessed by the volume of residual study medication, unless study medication was discontinued either temporarily or permanently (see Section 3.9.1); and
- completion of the 6-month physician follow-up visit or 5-year follow-up survey.

6.1.3 Descriptive Statistics

Descriptive statistics will be prepared for all variables at all assessments and reviewed for data quality. The number of patients with missing data for each assessment and/or variable will be analyzed. There will be no imputation of missing data in the primary analyses; however, sensitivity analyses may be conducted using multiple imputation to ensure that final conclusions are consistent across different assumptions for the missing data mechanism.

Baseline demographic and clinical characteristics will be compared between the treatment arms using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. In a randomized trial such as this, baseline differences can generally be attributed to chance, but if differences are found, the primary analyses may also be performed with uni- or multi-variate adjustment. A similar approach will be taken for any other baseline variables identified *a priori* by the study investigators as being of potential prognostic value, such as pre-operative testosterone use, glans size, asymptomatic bacteriuria, perioperative IV antibiotic use, administration of locoregional anesthesia, length of urethral repair, ratio of length of repair to penile shaft length, neourethral coverage, and case duration.[20]

6.1.4 Analysis of Primary and Secondary Outcomes

The primary outcome measure is a binary (i.e., "any or none") variable as defined in Section 4.1, where 0 indicates no complications and 1 indicates occurrence of at least one complication (symptomatic UTI, cellulitis, etc.). Fisher's exact test will be used to test the unadjusted difference in primary outcome between the two groups.

The secondary endpoints are also binary variables and will be analyzed using the same methods. Secondary endpoints include all individual components of the primary outcome (symptomatic UTI, cellulitis/wound infection, meatal stenosis, urethral stricture, urethrocutaneous fistula, dehiscence, and urethral diverticulum) and secondary outcomes (acute ADR or *C. difficile* colitis).

[20] Roberts C and Torgerson DJ. Baseline imbalance in randomized controlled trials. BMJ 1999; 319:185.

Ninety-five percent confidence intervals will be calculated for all estimated differences between groups.

6.1.5 Homogeneity and Exploratory Analyses

Breslow-Day testing for homogeneity will be performed to determine consistency of results between study centers. Logistic regression may be used to test for a difference between groups adjusted for study center, surgeon, and various baseline characteristics and risk factors as described in Section 6.2.3. Kaplan-Meier estimates may be used to analyze time-to-complications. The frequency of specific organisms being isolated in urine and wound cultures from patients with symptomatic UTI and wound infections will be compared between treatment groups using Fisher's exact test.

6.2 Power and Sample Size

We made the following assumptions in calculating the desired sample size of 630 study subjects:

(1) rate of the primary outcome in patients receiving prophylactic antibiotics: 10%
(2) statistical power: 90%
(3) absolute difference in primary outcome rate to be detected: 10% (NNTT 10)
(4) dropout rate: 10%

Symptomatic UTI occurs in 0-6% of patients receiving antibiotic prophylaxis following hypospadias repair,[21,22] with a 2-5% incidence of urethrocutaneous fistula, 3-5% risk of meatal stenosis/stricture, and 1-2% risk of dehiscence following distal/mid-shaft repairs.[23] Urethral diverticulae seldom if ever occur after mid-distal hypospadias repair but are included in the primary outcome for the sake of thoroughness. The sum of the aforementioned complication rates is 6-18%, however, it is likely that some patients experience more than one complication. For purposes of our binary primary outcome (i.e., "any or no complications"), such patients will be counted only once. Therefore, calculation of sample size for this study will be based on an assumed 10% aggregate risk of complications. This assumption is also consistent with the overall 11% complication rate of primary hypospadias repairs reported by Kanaroglou *et al.*, keeping in mind that some proximal repairs were also included in this series.[24]

We desire a power of 90% to detect a 10% absolute difference in complication rate as statistically significant (NNTT 10). We consider 10% to be a reasonable threshold given that complications of hypospadias repair are almost unequivocally not life-threatening, and the outcome of medical or surgical intervention for these complications is generally positive. Presently available data are insufficient to quantify the full extent of potential costs related to antibiotic prophylaxis (treatment of multi-drug resistant infections, etc.).

Utilizing these parameters, the necessary sample size is 286 patients per group (http://www.cct.cuhk.edu.hk/stat/proportion/Casagrande.htm). With allowance for a 10% dropout rate, a total of 630 study subjects is required.

6.3 Interim Analysis

Unless prompted earlier by safety concerns or poor accrual, a formal interim analysis of primary outcomes will be conducted when 300 patients have completed 6 months of follow-up. Descriptive reports will be prepared on the data quality and occurrence of adverse events. For analysis, a group

[21] Kanaroglou *et al.*, 2013.
[22] Ben Meir and Livne, 2004.
[23] Bayne AP and Jones EA, 2010.
[24] Kanaroglou *et al.*, 2013.

sequential design will be used. Group sequential testing cut-offs are designed to maintain the overall type I error rate for the study. According to O'Brien-Fleming boundaries, in order to maintain an overall alpha/type I error rate of 0.05, an alpha of 0.0054 should be used for one interim analysis and an alpha of 0.0492 for the final analysis.[25]

Assuming a 10% complication rate in one group comprised of 150 patients at the time of interim analysis, with an alpha of 0.0054, a complication rate of ≥ 22% in the other group of 150 patients would be identified as statistically significant (p=0.0046) and warrant early termination of the study (http://www.vassarstats.net/propdiff_ind.html). If interim review reveals the baseline rate of complications to be substantially different than the 10% assumed for sample size calculations, consideration will be given to amending the requisite sample size in order to achieve the desired statistical power. Analysis of secondary outcomes will not factor into study termination, as the study medication is a widely utilized antimicrobial agent with a well-established safety profile.[26]

If accrual of subjects has been less than anticipated prior to the interim analysis, the Steering Committee may consider making an *a priori* decision to close the study and proceed with the final analysis instead. An alpha of 0.05 would be used in this circumstance.

6.4 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) will consist of a pediatric urologist from a non-participating institution, a pediatric infectious disease specialist, an independent statistician, and the study statistician (non-voting member). The frequency of DSMC meetings will be self-determined but not less than annual. A letter summarizing DSMC activity and recommendations will be filed with the IRB at each participating institution after each meeting. Concerns should be reviewed with the Steering Committee.

DSMC meetings will include a report from the Steering Committee regarding recruitment progress, completeness of participant follow-up, protocol deviations/violations, episodes requiring unblinding, and availability of resources for study continuation and completion. The DSMC will monitor study and data quality (e.g., confirmation of patient eligibility, accurate recording of study medication assignments, etc.), adverse events, and study outcomes. The DSMC may also evaluate the integrity of procedures relevant to randomization, blinding, and documentation of outcome measures.

[25] O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.
[26] May DB. Trimethoprim-sulfamethoxazole: an overview. In: UpToDate, Basow DS (ed); UpToDate, Waltham, MA; 2013.

7. Rationale for Study Design

7.1 Superiority vs. Non-inferiority Trial

In Section 2.1 (Prior Research and Relevant Knowledge), we noted that prior studies have suggested that prophylactic antibiotics may reduce the risk of post-operative UTI and wound healing-related complications. However, this benefit was not identified by Kanaroglou *et al.* and has not been demonstrated by a placebo-controlled trial. Therefore, we elected to design this study as a well-powered superiority trial, specifically to answer the question of whether administration of prophylactic TMP-SMX reduces the aggregate risk of infectious and wound healing-related complications following mid-to-distal hypospadias repairs.

The study has been designed with parameters by which antibiotics may be proven superior to placebo on interim or final analysis. Our goal is to recruit a sample size large enough to achieve sufficient (90%) power to detect a clinically meaningful difference in primary outcomes, so that if no such difference is found (i.e., the study is "negative"), it will be regarded as convincing evidence that antibiotics do not affect the outcomes of mid-to-distal hypospadias repairs relative to placebo.

A non-inferiority trial design would generally be considered appropriate in circumstances where the outcome of a particular intervention (e.g., prophylactic TMP-SMX) has already been established as superior to placebo and is now being compared with a "new" intervention.[27] The results of such a trial would be interpreted as demonstrating that the new treatment is superior, non-inferior, or inferior to the old treatment, with the possibility that the data may be inconclusive.[28] This complexity is unnecessary for purposes of addressing the research question relevant to this study.

7.2 Utilization of Composite Primary Outcome

The clinical question relevant to selection of outcome measures in this study was: "What complications might administration of prophylactic antibiotics be expected to prevent following hypospadias repair?" Broadly speaking, there are three possibilities:

1) symptomatic UTI;
2) cellulitis/wound infection; and
3) infection-related impairment of wound healing (whether the infection was recognized or not), which may contribute to meatal stenosis, urethral stricture, urethrocutaneous fistula, dehiscence, and/or urethral diverticulum).

While the first two possibilities may appear obvious, hypothesis-generating evidence of the third is found in the previously discussed data published by Ben Meir and Livne (see Section 2.1). Congruent with this hypothesis, a contemporary chapter on hypospadias complications includes bacterial infection (recognized or unrecognized) as a potential factor in wound healing-related complications.[29]

It should be noted that each of these complications (UTI, wound infection, stenosis/stricture, fistula, dehiscence, and urethral diverticulum) is generally cause for substantial, though not life-threatening, clinical concern, requiring pharmacologic or elective surgical intervention. Because of this similarity, we

[27] Motulsky H. Testing for equivalence or noninferiority. In: *Intuitive biostatistics: a nonmathematical guide to statistical thinking*. 2nd ed. New York, NY: Oxford University Press; 2010. p. 150-155.
[28] Piaggio G, Elbourne DR, Altman DG *et al*. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152-1160.
[29] Bayne AP and Jones EA, 2010.

believe it is reasonable to utilize the composite rate as the primary measure of the impact that antibiotic prophylaxis has on the outcome of hypospadias repair.

During the early post-operative period following hypospadias repair, the surgical site is usually characterized by substantial edema and erythema, making it difficult to diagnose cellulitis/wound infection with confidence. This provides additional rationale for intermediate-term assessment of wound healing-related complications to which wound infection may contribute.

We recognize that numerous variables may contribute to the development of wound healing-related complications of hypospadias repair, including patient-specific factors, surgical technique, and post-operative hygiene. By achieving randomized assignment to which patients and providers remain blinded, the influence of these confounding variables on the outcomes of interest should be mitigated.

7.3 Use of TMP-SMX as the Antibiotic Agent

Anecdotally, TMP-SMX is the most commonly utilized antibiotic in the United States for prophylaxis following hypospadias repair. It is currently used by a majority of pediatric urologists at Lurie Children's, and it is mentioned as the author's preference for post-operative prophylaxis in the current chapter on hypospadias in Campbell-Walsh Urology.[30]

At Lurie Children's, 2012 bacterial susceptibility reports indicated the following percentages of urinary isolates to be sensitive to TMP-SMX:

- gram-negative rods (GNR): Acinetobacter 100%, Citrobacter freundii 61%, C. koseri 100%, Enterobacter aerogenes 100%, E. cloacae 77%, Escherichia coli 61%, Klebsiella oxytoca 91%, K. pneumoniae 81%, Morganella morganii 86%, Proteus mirabilis 80%, Serratia marcescens 100%
- gram-positive cocci (GPC): Staphylococus aureus 100%, S. epidermidis 69%, other Staph. spp. 81%

Of note, the Lurie Children's antibiogram indicates that urinary and non-urinary GPC are 26-40% more likely to be susceptible to TMP-SMX than to cefazolin. Susceptibility of urinary GNR to cefazolin is not reported, but sensitivity of non-urinary GNR to cefazolin is generally similar to lower.

7.4 Study Medication Dosing

Dosing of antibiotic prophylaxis following hypospadias repair is variable among pediatric urologists, both within the group at Lurie Children's and throughout the published literature. Several surgeons in the Lurie Children's group use a therapeutic dose of TMP-SMX (i.e., 0.5 mL/kg, or 4 mg/kg TMP, BID). Another uses 0.5 mL/kg TMP-SMX once daily, while another uses a sub-therapeutic dose of cephalexin (10 mg/kg BID).

In the study by Kanaroglou *et al.*, which *did not* find a difference in outcomes between patients who did and did not receive antibiotic prophylaxis, TMP alone was administered at a sub-therapeutic dose of 2 mg/kg once daily. By contrast, Ben Meir and Livne, who *did* identify a lower incidence of UTI in patients who received antibiotics, used cephalexin on a therapeutic dosing schedule (TID; the amount was not indicated).

Because the primary aim of this study is to address the controversy of whether administration of antibiotics provides any benefit following hypospadias repair, a full therapeutic dose of TMP-SMX (i.e., 4 mg/kg TMP BID) will be utilized. In the event that no difference in outcomes is seen between the study

[30] Snodgrass WT. Hypospadias. In: Wein AJ, Kavoussi LR *et al.*, editors. Campbell-Walsh Urology. 10th ed. Philadelphia, PA: Saunders Elsevier; 2012. p. 3503-3536.

groups, we wish to avoid criticism that the antibiotic dose may have been insufficient. We recognize that cost and the risk of antibiotic side effects may be somewhat increased on account of this decision, and if antibiotics are found to have beneficial effects, subsequent research may be necessary to identify the optimal dose to balance risks and benefits.

7.5 Limitation of Inclusion to Distal/Mid-shaft Hypospadias Repairs

The complication rates associated with repair of proximal hypospadias are substantially higher than for distal/mid-shaft hypospadias.[31] To increase homogeneity and reduce the sample size required to achieve desired statistical power, patients with proximal hypospadias (as defined by subjective intra-operative assessment or length of urethral repair > 2.0 cm) will be excluded from the study.

7.6 Eligibility of Previously Circumcised Patients

Patients who have had previous circumcision are eligible for the PROPHY Study. Recently published reports have consistently indicated low rates of post-operative complications (0-5%) in patients who undergo hypospadias repair following previous circumcision.[32,33,34,35] The rarity of urethroplasty complications in these series likely reflects the fact that contemporary techniques of mid-to-distal hypospadias repair do not commonly rely on use of preputial tissue.

7.7 Exclusion of Cases with Foreskin Reconstruction

Foreskin reconstruction (preputioplasty) is an alternative to circumcision with hypospadias repair. At present, it remains uncertain whether foreskin reconstruction increases the likelihood of urethroplasty complications, such as urethrocutaneous fistulae.[36,37,38] There are no published data on the risk of infectious complications. However, the additive risk of foreskin dehiscence is 2.5-10%.[39,40,41,42,43,44]

Based on these data, inclusion of cases with foreskin reconstruction would increase the heterogeneity of the study population with respect to the likelihood of dehiscence. A higher baseline risk of complications would also increase the sample size required to achieve desired statistical power. Because cases with foreskin reconstruction are relatively uncommon, their inclusion would also increase the risk of chance

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[31] Marrocco G, Vallasciani S, Fiocca G *et al*. Hypospadias surgery: a 10-year review. Pediatr Surg Int 2004; 20:200-203.
[32] Snodgrass WT, Khavari R. Prior circumcision does not complicate repair of hypospadias with an intact prepuce. J Urol 2006; 176:296-298.
[33] Pieretti RV, Pieretti A, Pieretti-Vanmarcke R. Circumcised hypospadias. Pediatr Surg Int 2009; 25:53-55.
[34] Rashed FK, Gholizade R. Comparison of distal hypospadias repair in circumcised patients and uncircumcised patients. ISRN Urol 2013; doi:10.1155/2013/957581.
[35] Chalmers D, Wiedel CA, Siparsky GL *et al*. Discovery of hypospadias during newborn circumcision should not preclude completion of the procedure. J Pediatr 2014; 164:1171-1174.
[36] Snodgrass W, Dajusta D, Villanueva C *et al*. Foreskin reconstruction does not increase urethroplasty or skin complications after distal TIP hypospadias repair. J Ped Urol 2013; 9:401-408.
[37] Suoub M, Dave S, El-Hout Y *et al.* Distal hypospadias repair with or without foreskin reconstruction: a single-surgeon experience. J Ped Urol 2008; 4:377-380.
[38] Fasching G, Arneitz C, Gritsch-Olipp G. Foreskin reconstruction and preservation of a thin distal urethra: a challenge in tubularized incised plate urethroplasty. Pediatr Surg Int 2011; 27:755-760.
[39] Ibid.
[40] Papouis G, Kaselas C, Skoumis K et al. Repair of distal hypospadias and preputioplasty in one operation: risks and advantages. Urol Int. 2009; 82:183-186.
[41] Suoub M *et al.*, 2008.
[42] Leclair MD, Benyoucef N, Héloury Y. [Morbidity of foreskin reconstruction in distal hypospadias repair surgery] (French). Prog Urol 2008; 18:475-479.
[43] Snodgrass WT, Koyle MA, Baskin LS *et al*. Foreskin preservation in penile surgery. J Urol 2006; 176:711-714.
[44] Klijn AJ, Dik P, de Jong TP. Results of preputial reconstruction in 77 boys with distal hypospadias. J Urol 2001; 165:1255-1257.

bias, while not contributing substantially to recruitment. Therefore, patients for whom foreskin reconstruction is performed will be excluded from the study.

7.8 Pre-operative Testosterone Use

At the discretion of attending surgeons, testosterone (T) is sometimes administered as part of routine care prior to hypospadias repair, either topically or by IM injection. The goals of using T may include short-term penile growth, increased availability of tissue for reconstructive purposes, and improved tissue vascularity. For most pediatric urologists, use of T is less common prior to mid-to-distal hypospadias repairs than proximal repairs (which are excluded from this study).

To date, the only prospective study of pre-operative androgen stimulation for hypospadias repairs was a randomized trial of dihydrotestosterone (DHT) transdermal gel, in which DHT reduced rates of dehiscence (0% vs. 8%) and reoperation (3% vs. 24%) in patients undergoing primary hypospadias repair, the majority of whom had a mid-distal hypospadias defect.[45] This study was relatively small (n=75), lacked a placebo control, and did not provide stratification of complications by hypospadias severity. The results of this study have not been replicated. At Lurie Children's, DHT is costly and impractical to obtain on a routine basis.

No prospective studies have addressed the impact of pre-operative T on the outcomes of hypospadias repairs. In 2011, Gorduza *et al.* reported that T administered less than 3 months prior to surgery was associated with a trend toward an increased risk of wound healing-related complications in *proximal* hypospadias repairs.[46] Snodgrass *et al.* also observed a trend toward increased risk of glans dehiscence in patients receiving pre-operative T.[47] As retrospective analyses, both of these studies are vulnerable to selection bias. A recent systematic review and meta-analysis of pre-operative hormonal stimulation concluded that the effect "remains unclear."[48]

Given the lack of consistent or prospective evidence indicating that pre-operative androgen stimulation affects the outcome of hypospadias repairs, the decision to utilize T will be left to the discretion of each surgeon on a patient-by-patient basis for purposes of this study. For patients who do receive pre-operative T, assessment of glans and penile size before and after administration is encouraged. This will facilitate multivariable analysis and improve the quality of hypothesis-generating comparison of outcomes in patients who did and did not receive T.

7.9 Duration of Follow-up

Considerations pertinent to the duration of follow-up include a desire to ensure adequate time for detection of the majority of primary and secondary outcomes, while minimizing attrition of study participants and costs. Several previous studies have contributed to an understanding of how long after hypospadias repair complications may present.

On one end of the spectrum, Ziada *et al*. indicated that "the majority" of complications in their contemporary series of mid-to-distal hypospadias repairs were evident prior to 6 weeks post-

[45] Kaya C, Bektic J, Radmayr C *et al.* The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. J Urol 2008; 179:684-688.
[46] Gorduza DB, Gay CL, de Mattos E Silva E *et al.* Does androgen stimulation prior to hypospadias surgery increase the rate of healing complications? - A preliminary report. J Ped Urol 2011; 7:158-161.
[47] Snodgrass W, Cost N, Nakonezny PA *et al.* Analysis of risk factors for glans dehiscence after tubularized incised plate hypospadias repair. J Urol 2011; 185:1845-1851.
[48] Wright I, Cole E, Farrokhyar F *et al.* Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. J Urol 2013; 190:652-660.

operatively.[49] 58% of urethrocutaneous fistulas presented less than 1 month after primary hypospadias repair in Wood *et al.*'s series.[50] Aulagne *et al.* reported that all complications in their series of proximal hypospadias repairs occurred within 6 months post-operatively.[51]

However, Wood *et al.*,[52] Powell *et al.*,[53] Nuininga *et al.*,[54] and Spinoit *et al.*[55] reported that many complications presented more than 1 year post-operatively. Importantly, in this group of studies, it is unclear whether patients adhered to prescribed follow-up intervals, and late-presenting complications may have been evident and detected earlier if follow-up had been more rigorous. Unpublished data from Lurie Children's support this hypothesis.

Weighing these and other practical considerations, we elected to standardize scheduling of two physician clinic visits at 1 and 6 months post-operatively. Standardization is intended to prevent follow-up bias. Five years post-operatively, a chart review and survey will be conducted to assess whether late-presenting complications have occurred. In the studies cited above, at least 90% of complications have consistently presented by 5 years post-operatively.

[49] Ziada A, Hamza A, Abdel-Rassoul M *et al.* Outcomes of hypospadias repair in older children: a prospective study. J Urol 2011; 185:2483-2486.

[50] Wood HM, Kay R, Angermeier KW *et al.* Timing of the presentation of urethrocutaneous fistulas after hypospadias repair in pediatric patients J Urol 2008; 180:1753-1756.

[51] Aulagne MB, Harper L, de Napoli-Cocci S *et al.* Long-term outcome of severe hypospadias. J Ped Urol 2010; 6:469-472.

[52] Wood *et al.*, 2008.

[53] Powell CR, McAleer I, Alagiri M *et al.* Comparison of flaps versus grafts in proximal hypospadias surgery. J Urol 2000; 163:1286-1289.

[54] Nuininga JE, DeGier RP, Verschuren R *et al.* Long-term outcome of different types of 1-stage hypospadias repair. J Urol 2005; 174:1544-1548.

[55] Spinoit AF, Poelaert F, Groen LA *et al.* Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. J Urol 2013; 189:2276-2281.

8. Informed Consent, Ethical Review, and Regulations

8.1 Informed Consent

Study investigators and study personnel are responsible for ensuring that all parent(s)/LAR of eligible patients understand the nature, risks, and benefits of study participation in plain language. Center-specific IRB-approved protocols regarding informed consent should be followed. Consent documentation should indicate that data collected during the PROPHY Study may also be used in future *post hoc* analyses and other research studies related to hypospadias.

8.2 Ethical Review

The principal investigator at each study center will obtain IRB approval of the protocol and center-specific supporting documents (e.g., the informed consent form) before initiating patient recruitment.

8.3 Compliance with Regulations

Every effort will be made to conduct this study in accordance with the protocol and ethical principles stated in the 2000 version of the Declaration of Helsinki, as well as all applicable federal, state, and local laws, rules, and regulations.

For participation of Canadian centers, a Clinical Trial Application (CTA) to Health Canada will be completed. No Objection Letters will be obtained from Health Canada and included with packages of medications shipped to Canada.

8.4 Protocol Amendments

Protocol amendments must be approved by the Principal Investigators and relevant IRB(s) prior to implementation.

8.5 Protocol Deviations and Violations

A protocol deviation is defined by the Lurie Children's IRB as "any aberration, whether accidental, unintentional or intentional, from the IRB-approved protocol/research plan." Major protocol deviations (i.e., violations) "are those that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, or compromise the human subject protection program." Study coordinators and PIs are responsible for following local IRB requirements on reporting protocol deviations and violations, as well as reporting protocol violations to the primary study center (Lurie Children's) within 10 days of their recognition.

8.6 Trial Postponement and Early Termination

The Steering Committee may elect to postpone or terminate the study early due to inadequate funding, poor accrual, or other concerns. Follow-up of previously enrolled participants should continue, if feasible. Trial postponement will be reported to the IRBs of all participating institutions, and resolution of outstanding issues (e.g., acquisition of additional funding) will be attempted. If this effort is successful, the trial will be resumed; if not, the trial will be concluded and results to date reported, if possible. The IRBs of all participating institutions will be advised of study completion or early termination.

8.7 Study Documentation

All documentation pertaining to the conduct of this study should be retained by the investigators. All eCRFs will be stored as original source documents. Any paper copies (consents, forms) should be managed in accordance with local IRB requirements. If requested, the principal investigators will provide regulatory agencies and IRBs with direct access to original source documents.

8.8 Clinical Trial Registration

The study is registered with ClinicalTrials.gov (Identifier NCT02096159).

9. Organization

9.1 Steering Committee and Protocol Development

The following individuals are members of the PROPHY Study Steering Committee and have contributed to and/or reviewed the protocol:

- Mark Faasse, MD MPH (Lurie Children's)
- Earl Cheng, MD (Lurie Children's)
- Dennis Liu, MD (Lurie Children's)
- Walid Farhat, MD (SickKids)

The Steering Committee will oversee all aspects of study design, execution, and publication.

9.2 Publication of Study Results

All efforts will be made to ensure that the results arising from the trial are published in established peer-reviewed journals. The trial protocol may also be published. Initial results will be analyzed and published when all participants have completed 6-month follow-up, with a subsequent publication of intermediate-term results after completion of 5-year follow-up.

CONSORT 2010 guidelines will be followed in manuscript preparation. Analysis of covariates, long-term follow-up data, and other considerations pertinent to the utility of prophylactic antibiotics following hypospadias repair may warrant additional publications.

Study data will only be presented and published in aggregate, without stratification or comparison of outcomes by study center. No characteristics that may correspond to the identity of participating surgeons will be reported.

9.3 Publications Committee

The Steering Committee will establish a Publications Committee consisting of at least one representative from each participating study center. The Committee will identify topics for publication and make writing group assignments for each. Investigators from participating study centers may submit ideas for consideration by the Committee.

All proposed abstracts and manuscripts that utilize study data must be reviewed and approved by the Committee. Committee members should make every effort to ensure that assignment of responsibilities for preparation of abstracts and manuscripts is equitable among participating study centers and commensurate with the investment and contributions each has made to the study.

9.4 Timetable

The sample size necessary to achieve desired power will be 630 patients. Assuming recruitment of 30-50% of eligible patients (50-75 patients per year at Lurie Children's and 100-150 patients per year at SickKids), the initially estimated timetable for all participants to be enrolled and complete 6 months of follow-up was 4-5 years. Final follow-up will be completed 5 years after study recruitment is complete.

9.5 Financial Support

The Children's Hospital of Chicago (CHOC) Faculty Practice Plan has provided an annually renewable Faculty Development Grant for this clinical trial. Pursuit of additional avenues of funding support will be ongoing.

9.6 Participant Costs and Compensation

Study medication will be provided free of charge, and there will be no research costs to study participants. Compensation/reimbursement may be provided with local IRB approval. The patient-physician encounters relevant to this study are part of routine care for patients who undergo hypospadias repair, therefore, financial payment for these services remains the responsibility of the patients' insurance or parent(s)/LAR.

10. Appendices

A. TMP-SMX package insert
B. Educational brochure
C. REDCap data instruments/eCRFs
D. Skeletonized Intra-operative Data Instrument (“Cheat Sheet” & Eligibility Criteria)
E. Assessment schedule