Clinical Research Protocol

A Randomized Controlled Trial of Preoperative Prophylactic Antibiotics for Ureteroscopy in Moderate to High Infectious Risk Population

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Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 22-37824

Protocol Title: A Randomized Controlled Trial of Preoperative Prophylactic Antibiotics for Ureteroscopy in Moderate to High Infectious Risk Population

Protocol Date: 11/21/2023

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	adverse event
AUA	American Urological Association
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	serious adverse experience

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PROTOCOL SYNOPSIS

TITLE	A Randomized Controlled Trial of Preoperative Prophylactic Antibiotics for Ureteroscopy in Moderate to High Infectious Risk Population.
FUNDING ORGANIZATION	American Urological Association (AUA)
NUMBER OF SITES	1 (UCSF)
RATIONALE	As there is no standardized pre-operative antibiotic protocol endorsed by the major urological associations (American Urological Association or European Association of Urology), the standard of care regarding antibiotic duration in moderate to high-risk patients undergoing ureteroscopy is left to provider discretion which has led to a wide variation in clinical practice. Notably, the Infectious Disease Society of America (IDSA) guidelines on asymptomatic bacteriuria in 2019 for patients undergoing endourological procedures recommends only 1 or 2 doses of antibiotics within 30 to 60 minutes of the procedures (statement XIII). At our institution, depending on the provider performing the preoperative evaluation, patients will often be prescribed 2 to 7 days of antibiotics. A review of our own data showed no differences in clinical outcomes regardless of antibiotic duration. The hypothesis of this non-inferiority randomized controlled trial is that there is no additional benefit from a longer course (7 days) versus a shorter course (2 days) of pre-operative antibiotics in patients with moderate to high risk of infection undergoing ureteroscopy.
STUDY DESIGN	This will be a prospective, non-blinded, non-inferiority randomized clinical trial
PRIMARY OBJECTIVE	Determine the safety and efficacy of a short course (2 days) as compared to a long course (7 days) of pre-operative prophylactic antibiotics in patients at moderate or high risk of postoperative infectious complications
SECONDARY OBJECTIVES	Identify secondary predictors of post-operative infectious complications such as intra-renal pressure and measures of inflammation
NUMBER OF SUBJECTS	72
SUBJECT SELECTION CRITERIA	<u>Inclusion Criteria</u>: 1. Adults (age >18 years) scheduled for ureteroscopy for any indication 2. Asymptomatic bacteriuria on preoperative evaluation 3. Symptomatic urinary tract infection with treatment course

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	completed >7 days from surgery 4. History of recurrent UTIs or pyelonephritis 5. Ureteral stent or nephrostomy tube in place 6. Performs clean intermittent catheterization 7. Indwelling foley catheter or suprapubic catheter 8. Bowel interposition (ileal conduit, neobladder) 9. Immunosuppressant use (ex: chronic steroid or immunomodulatory therapy, chemotherapy within last 30 days) Exclusion Criteria: 1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study. 2. Receipt of antibiotics within 7 days preceding surgery that were not prescribed for the study.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The total duration of the study is expected to be **30 minutes**. This will include recruitment, consent and survey activity after subject is randomized. Study activities will take place during standard of care procedures. **The total duration of the study is expected to be part of standard of care. Study consent and postoperative check is the only added time commitment.**
PRIMARY ENDPOINT	Rate of infectious complications defined as post-operative urinary tract infection, pyelonephritis or sepsis.
SECONDARY ENDPOINTS	1) Non-infectious complications including readmission 2) Adverse reaction to antibiotic regimen 3) Identification of secondary markers of post-operative infection
SAFETY EVALUATIONS	Risks to patients are expected to be minimal. Both study arms are considered acceptable standards of care and are both performed at UCSF currently.
STATISTICS **Primary Analysis Plan**	A two-sided Student's t test will be used for normally distributed continuous data and a Wilcoxon rank sum test for non-normally distributed continuous variables. A Fischer's exact test will be used for categorical data. For all statistical methods a two-sided p-value of <0.05 will be considered statistically significant.

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Rationale for Number of Subjects	Based on our preliminary data and other cohort studies we anticipate a total infectious complication rate of approximately 10%. With a non-inferiority limit set to 1.2, a sample size of 56 would be required to have 80% power and alpha at level of 0.05. We anticipate a 20% drop-out rate and therefore plan to enroll 72 patients (36 patients randomized to each arm).

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1 BACKGROUND

The prevalence of nephrolithiasis continues to rise, with 1 in 11 people expected to experience a stone event in their lifetime.[1] At present, ureteroscopy is not only the most frequently utilized operation for treating stone disease but also one of the most commonly performed procedures in urology.[2,3] This procedure boasts an excellent safety profile with complication rates reported to be 9-25%, comprised mostly of minor complications.[4] Infectious complications have been reported after 2%-22.8% of cases.[5-8] Presentations range from relatively minor urinary symptoms manageable with oral antibiosis (fevers, urinary tract infection) to potentially catastrophic (pyelonephritis, SIRS and sepsis) leading to significant morbidity, mortality and cost.[9,10] Efforts to reduce these infections center around single dose, perioperative antibiotics which are supported by both the American Urological Association (AUA) and European Association of Urology (EAU)[11-13] however these guidelines do not take into account patient infection risk which has been demonstrated to impact pre-operative antibiotic prophylaxis duration.[14,15] Patients with colonized urinary tracts are frequently encountered in practice and are more susceptible to infectious complications after ureteroscopy. Mitigating the risk of post-operative infections however is clinically challenging in these patients as they often have multiple comorbidities and harbor MDR organisms. No randomized data exists regarding the optimal pre-operative antibiotic choice, timing or duration to reduce the risk of post-operative infections in this vulnerable population of patients.

1.1 Overview of Clinical Studies

There is no consensus regarding pre-operative prophylactic antibiotic administration for patients undergoing stone surgery at high risk for postoperative infectious complications, even amongst members of the endourological society. While the AUA and EAU have both released a Best Practice Statement and clinical guidelines citing the need to balance the risk of infectious complications with the risk of unnecessary antibiotics, both have stopped short of outlining standardized regimen or protocols.[11,12] Single dose peri-operative antibiotics seem to be sufficient for most cases of ureteroscopy given a negative urine culture[21] however there are no guidelines for patients with asymptomatic bacteriuria or otherwise at high risk of urinary tract colonization. As a result, there is a wide range of practice patterns for managing these patients pre-operatively, which is demonstrated by a survey of the endourological society where participants were posed with various clinical vignettes and asked to report their antibiotic prescribing pattern. For an asymptomatic patient with a positive urine culture planned for ureteroscopy, the breadth of pre-operative antibiotic regimens reported included ~25% prescribing 1-3 days, 45% prescribing 4-7 days and ~15% prescribing >7 days or peri-operative antibiotics only.[22] These data highlight the need for randomized data to address this disparity in our understanding of peri-procedural antibiotic therapy.

There is a critical gap in the randomized data evaluating pre-operative antibiotics regimens for high-risk patients. Prior randomized trials for perioperative antibiotics before ureteroscopy have included only patients with negative preoperative urine cultures and have shown that a single dose or perhaps even no antibiotics is appropriate in uncomplicated cases especially if there have been no breaks in the urothelium.[21,23,24] There

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is however a critical gap in randomized studies including patients at high risk of urinary tract colonization. The need for such studies is demonstrated by a recent pair of randomized trials from the Endourological Disease Group for Excellence (EDGE) consortium. The group investigated antibiotic duration prior to PCNL in low risk[15] and moderate to high risk populations.[14] They found no benefit for a week of preoperative prophylactic antibiotics compared to no antibiotics in the low risk group however did find a benefit to a week of antibiotics compared to 2 days in the high risk group.[14] These results highlight the importance of stratifying patient risk of infection pre-operatively and the need for well designed clinical trials to evaluate each patient population.

Limiting antibiotic exposure has the potential to combat the growing rates of multi-drug resistance urinary tract pathogens, especially in vulnerable populations. Uncontrolled antibiotic use has already led to high rates of MDR bacteria leading to reported prevalence as high as 70% in certain countries.[25] In endourology, MDR organisms have been reported in up to 30-33% of pre-operative urine cultures and is an independent predictor of post-operative infectious complications even after appropriate preoperative treatment.[26,27] The most important measure to help prevent MDR infections is the creation and implementation of a culture of antimicrobial stewardship[28] however in order to accomplish such a feat, high quality data is required to lay the groundwork for standardized protocols and guidelines.

2 STUDY RATIONALE

As there is no standardized pre-operative antibiotic protocol endorsed by the major urological associations (American Urological Association or European Association of Urology), the standard of care regarding antibiotic duration in this population is left to provider discretion by these governing bodies. At our institution, depending on the provider performing the preoperative evaluation, patients will often be prescribed 2 to 7 days of antibiotics. Notably, the Infectious Disease Society of America (IDSA) guidelines on asymptomatic bacteriuria in 2019 for patients undergoing endourological procedures recommends only 1 or 2 doses of antibiotics within 30 to 60 minutes of the procedures (statement XIII). Most urologists however prefer to provide preoperative prophylactic antibiotics leading up to the time of surgery.

2.1 Risk / Benefit Assessment

Standard risks associated with surgery and anesthesia. These risks do not differ from those
associated with routine care. In addition, since this study involves randomizing patients to two different forms of routine care, this study does not create any additional risks. We will minimize risks associated with participating in research by monitoring outcomes in real time.

The anticipated benefit of the study is to show a short duration of pre-operative prophylactic antibiotics leads to similar outcomes to a longer duration. Benefits to minimizing antibiotic use is better antibiotic stewardship, decreased risk of adverse reaction from antibiotics and decreased development of multi-drug resistant bacteria. Without this information, there is no evidence to support recommending one treatment

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algorithm over the other, and management decisions would continue to be made based on factors that create disparities.

3 STUDY OBJECTIVES

3.1 Primary Objective

Determine the safety and efficacy of a short course (2 days) as compared to a long course (7 days) of pre-operative prophylactic antibiotics in a single-center, non-inferiority, randomized clinical trial.

3.2 Secondary Objectives

Identify secondary predictors of post-operative infectious complications such as intra-renal pressure and measures of inflammation

4 STUDY DESIGN

4.1 Study Overview

This will be a prospective, non-blinded, non-inferiority randomized controlled trial comparing a short (2 days) versus long (7 days) of preoperative prophylactic antibiotics in patients who are at moderate to high risk of infectious complications. Patients will be recruited, consented, and randomized into either **Group A** or **Group B.**

Group A: 2 days of preoperative prophylactic antibiotics
Group B: 7 days of preoperative prophylactic antibiotics

Once the subject is randomized a provider will provide a prescription of the necessary duration. The choice of antibiotic will be left to the provider to determine based on pre-operative evaluation and local sensitivities as per standard of care. Total duration of subject participation will be 1-2 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Rate of infectious complications within 30 days postoperatively as defined by:

1) Occurrence of post-operative sepsis (meeting at least two of the following criteria: temperature above 38.3^{o}C or below 36^{o}C, heart rate above 90/min, respiratory rate above 20/minute, altered mental status, systolic blood pressure < 90mmHg, mean arterial pressure < 70mmHg or systolic blood pressure decrease more than 40mmHg or white blood cell count greater than 12,000 or less than 4,000.

2) Post-operative febrile urinary tract infection defined as temperature ≥ 38.3^{o}C with significant pyuria (≥ 10 white blood cells per high powered field on urinalysis with microscopy) or bacteriuria (≥ 100,000 colony forming units of uropathogens/mL on urine culture)

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5.2 Secondary Efficacy Endpoints

1) Non-infectious complications including readmission

All patients will be contacted within 3-14 days after surgery to assess for occurrence of non-infectious post-operative complications including unplanned presentations to care or readmissions.

2) Adverse reaction to antibiotic regimen

At any point during their antibiotic regimen if a patient develops an adverse reaction, we will follow the standard of care and continue the antibiotic if the adverse reaction is minimal or transition to an antibiotic of a difference class.

3) Identification of secondary markers of post-operative sepsis

Other described markers of infectious complications including ESR and CRP will be drawn pre-operatively. Endotoxin titers and intra-operative urine cultures will be obtained by collecting urine from the bladder and renal pelvis intra-operatively and sending this for analysis.

5.3 Safety Evaluations

Adverse reactions to antibiotics will be assessed as per standard of care. Postoperatively, our typical pathway is to assess patient symptoms 4-6 weeks after surgery at their routine postoperative appointment. As this protocol calls for a postoperative check within 3-14 days after surgery, the study team will keep patients under closer observation for postoperative symptoms than per standard of care.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of XX who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

10. Adults (age >18 years) scheduled for ureteroscopy for any indication
11. Asymptomatic bacteriuria on preoperative evaluation
12. Symptomatic urinary tract infection with treatment course completed >7 days from surgery
13. History of recurrent UTIs or pyelonephritis
14. Ureteral stent or nephrostomy tube in place
15. Performs clean intermittent catheterization
16. Indwelling foley catheter or suprapubic catheter
17. Bowel interposition (ileal conduit, neobladder)

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18. Immunosuppressant use (ex: chronic steroid or immunomodulatory therapy, chemotherapy within last 30 days)

6.3 Exclusion Criteria

3. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
4. Receipt of antibiotics within 7 days preceding surgery that were not prescribed for the study.

7 CONCURRENT MEDICATIONS

All subjects will be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies as per standard of care.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

We will use concealed block randomization (1:1)

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at initial clinic visit as per standard of care.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at initial clinic visit as per standard of care.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at initial clinic visit as per standard of care.

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9.1.4 Physical Examination

A complete physical examination will be performed either in person or via telehealth by either the investigator or a subinvestigator who is a physician at the initial clinic visit as per standard of care. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Measurement of body temperature, blood pressure, pulse and respirations will be performed as per standard of care at the initial clinic visit (if an in-person visit). Otherwise all patients will have their vitals assessed and documented during the day of surgery (pre-, intra- and postoperatively) as per standard of care.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study.

9.2 Clinical Laboratory Measurements

9.2.1 Hematology, Blood Chemistry Profile, Pregnancy Test, Urinalysis, Urine culture

Preoperative laboratory testing to include blood and urine tests will be performed as per standard of care.

10 EVALUATIONS BY VISIT

10.1 Visit 1: Patient presenting to initial clinic visit with attending urologist

1) Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2) Assign the subject a unique screening number.
3) Review demographics data, medical history, comorbidities, pregnancy, medication,
4) imaging, labs etc. as part of standard of care
5) Randomize the subject to a treatment group
6) Schedule patient for surgery per standard of care

10.2 Visit 2: Ureteroscopy procedure

1) Surgery done according to standard of care

10.3 Visit 3: Postoperative check

1) Research team member will call patient within 3-14 days of surgery to assess postoperative symptoms

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10.4 Visit 4: Postoperative visit

1) Postoperative follow-up to be arranged as per standard of care usually within 4-6 weeks after surgery.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

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The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

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11.3 Medical Monitoring

Dr. Wilson Sui should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone : (267) 799-3126
Pager : (415) 443-8617

12 WITHDRAWAL OF SUBJECTS FROM THE STUDY

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator, fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study will be included in an intention to treat analysis of primary and secondary endpoints.

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14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by randomization arm: race, gender, age, BMI

14.3 Analysis of Primary and Secondary Endpoints

A two-sided Student's t test will be used for normally distributed continuous data and a Wilcoxon rank sum test for non-normally distributed continuous variables. A Fischer's exact test will be used for categorical data. For all statistical methods a two-sided p-value of <0.05 will be considered statistically significant.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to antibiotic duration.

14.4 Sample Size and Randomization

Based on our preliminary data and other cohort studies we anticipate a total infectious complication rate of approximately 10%. With a non-inferiority limit set to 1.2, a sample size of 56 would be required to have 80% power and alpha at level of 0.05. We anticipate a 20% drop-out rate and therefore plan to enroll 72 patients (36 patients randomized to each arm).

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific the information corresponding to that visit is available.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

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15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to

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eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

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A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX 1. STUDY CHART

	VISIT 1 (Initial clinic visit)[a]	VISIT 2 (Surgery)	VISIT 3 (postoperative check)	VISIT 4 (routine postoperative visit)
Screening	**X**			
Medical and surgical history	**X**			
Physical Exam	**X** [a]			
Vital signs	**X** [a]	**X**		**X** [a]
Informed consent	**X**			
Randomization	**X**			
Assessment of postoperative complications			**X**	**X**
Adverse experiences	**X**	**X**	**X**	**X**

[a]**Not applicable if telehealth visit**

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