ARIES
Antibiotic Resistance in Eye Surgeries

version 1.5

Antibiotic Resistance in Eye Surgeries (ARIES Trial)

Manual of Operations and Procedures

University of California, San Francisco
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Study Coordinator

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Abbreviations

DCC: Data Coordinating Center
IRB: Institutional Review Board
NP swabs: nasopharyngeal swabs
PCR: polymerase chain reaction
MR: Medical Record
UCSF: University of California San Francisco

Chapter 1: Overview

1.1. Executive Summary

Antibiotic use has saved many lives, but also comes with the issue of selecting for antibiotic-resistant organisms.

In this study, we hope to determine the effect of antibiotic use post-surgery on bacterial resistance and gain a better understanding of how antibiotic use during the perioperative period influences local and systemic antibiotic resistance in the individual.

1.2. Objectives

1: Determine if the use of topical ocular antibiotics for eye surgeries will lead to local (ocular surface) antibiotic resistance. *We hypothesize that topical ocular antibiotics for eye surgeries lead to ocular surface antibiotic resistance.*

2: Determine if the use of topical ocular antibiotics for eye surgeries will lead to systemic antibiotic resistance. *We hypothesize that topical ocular antibiotic use for eye surgeries leads to systemic antibiotic resistance.*

3: Determine if the frequency of topical ocular antibiotic usage for eye surgeries affects local antibiotic resistance. *We hypothesize greater frequency of topical ocular antibiotic usage for eye surgeries will increase local antibiotic resistance.*

1.3. Study Partners

This study was designed by investigators at UCSF. Funding is supported by internal grants.

1.4. Study Site

The study visits will be conducted at Mount Zion and Mission Bay campus at UCSF.

The study samples will be stored and processed at the Heintz Lab at 490 Illinois Street Floor 2, San Francisco, CA 94158.

Chapter 2: Context

Antibiotic use has saved millions of lives globally. However, this comes at the cost of selecting for antibiotic-resistant organisms at the individual and community level. It is estimated that every year, approximately 700,000 deaths are associated with drug resistance globally. This places a significant burden on the public health system and the judicious use of antibiotics is more important than ever before.

There exists little consensus on the use of antibiotics in ophthalmology, whether it's frequency, type of antibiotics, or when to use antibiotics. In the US, when or how the patients are instructed to take antibiotics for eye procedures is generally dependent on the individual ophthalmologist, which leads to a wide range of practice patterns. Furthermore, there are almost no randomized controlled trials evaluating the effects of commonly used topical antibiotics on antibiotic resistance at the local or systemic level in the host.

The proposed masked, randomized controlled trial evaluates the effects of topical antibiotic use on the selection for antibiotic resistance genes at the local and systemic levels. The results will provide guidance for antibiotic usage in ophthalmology and have the potential to inform public health policies.

Chapter 3: Study Design

The research team will assess antibiotic resistance over four weeks, comparing frequency of antibiotic use among adult patients undergoing ocular surgeries. All eligible participants will be randomized. A random sample of 108 (36/arm) participants from UCSF will be selected to participate in the "ARIES" study, which will entail biospecimen collection via nasopharyngeal, conjunctival, buccal, and rectal swabs 1-week post-op. Baseline will entail of conjunctival swab collection. 4-week post-op sample collection will entail of conjunctival, nasopharyngeal, and buccal swabs. All biologic specimens collected will be stored and made available to Dr. Thuy Doan for laboratory testing of antibiotic resistance.

3.1. Randomization

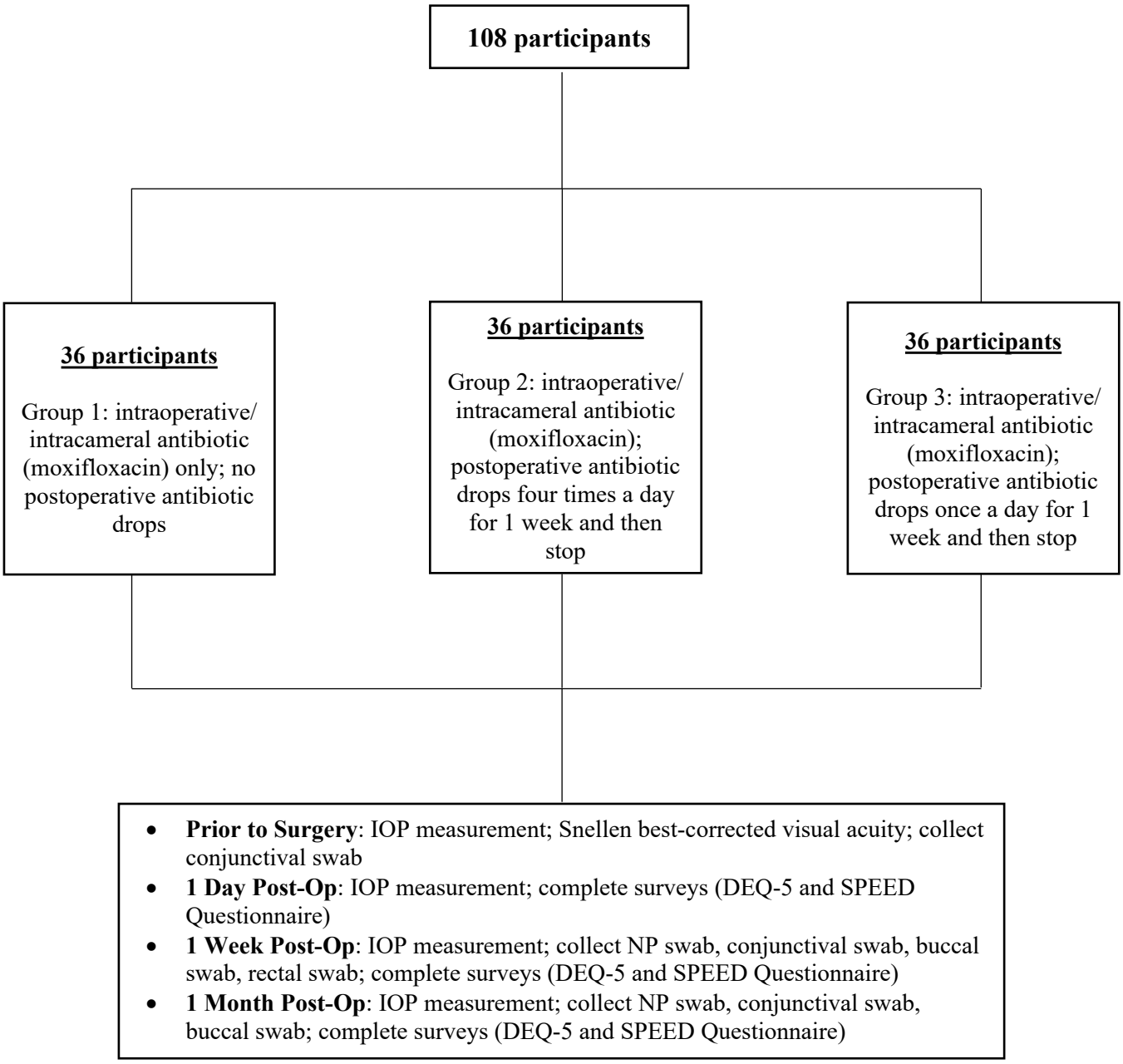
Randomization of Treatment Allocation. All eligible UCSF adult patients undergoing ocular surgery will be randomized in a 1:1:1 fashion to three groups:

- **Group 1**: intraoperative/intracameral antibiotic (moxifloxacin) only; no postoperative antibiotic drops
- **Group 2**: intraoperative/intracameral antibiotic (moxifloxacin); postoperative antibiotic drops four times a day for 1 week and then stop
- **Group 3:** intraoperative/intracameral antibiotic (moxifloxacin); postoperative antibiotic drops once a day for 1 week and then stop

Refer to SAP for randomization details.

Study Participants: UCSF adult patients undergoing ocular surgeries will be recruited if they consent and the study doctor deems the participant meets all study criteria.

Figure 1: Trial Profile



Chapter 4: Study Eligibility

4.1. Eligible Participants

To be eligible for the trial, participants must meet the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Over 18 years of age
2. Undergoing cataract surgeries that would benefit from intracameral antibiotics
3. Able to provide swabs
4. Able to provide consent
5. Surgery of the second eye occurs at least 8 weeks after surgery of the first eye

Exclusion Criteria:

1. Same-day bilateral cataract surgeries
2. On immunosuppression medication such as Prednisone, Methotrexate, Cellcept, or anti-TNF inhibitors within past 3 months
3. On systemic antibiotic within past 3 months
4. On topical antibiotics within past 8 weeks
5. Allergies to fluoroquinolone
6. Patients needing glaucoma drainage device or trabeculectomy
7. Inability to consent

4.2. Study Schedule

The schedule for examination and treatment is shown below in Table 1:

	Pre-Op	1-Day Post-Op	1-Week Post-Op	4-Week Post-Op
Consent	**X**			
Randomization	**X**			
Specimen Collection	**X**		**X**	**X**
Survey		**X**	**X**	**X**

Chapter 5: Core Study Elements

An overview of core elements for the ARIES study is provided here but will be described in more detail in the following chapters.

We will conduct the following study activities for the ARIES study:

Recruitment
UCSF adult patients undergoing cataract surgeries will be recruited if they meet the criteria as written above.

Enrollment
The study will be explained by the study doctors or study coordinators. The patient will be enrolled in the study after obtaining written consent from the patient (and witness if needed).

The participant will be randomly assigned to one of three groups only after obtaining consent.

Survey
An ocular symptom/quality of life survey (DEQ-5 and SPEED questionnaires) will be given to the patient to be filled at 1-Day post-op, 1-Week post-op, and 4-Week post-op.

Specimen Collection
All participants will have NP swabs, conjunctival swabs, and buccal swabs collected by the study doctors or study coordinator. Rectal swabs will be collected by the patient themselves by following instruction guide (see Appendix).

All specimens will immediately be placed in a Zymo preservative after collection and labeled with the participant's study number. Samples will then be transported to the Heintz laboratory at 490 Illinois Street Floor 2, San Francisco, CA 94158 for long-term storage at -80C and processing.

Conjunctival swabs will be collected prior to surgery. Conjunctival, NP, buccal, and rectal swabs will be collected 1-Week post-op. Conjunctival, NP, and buccal swabs will be collected 4-Week post-op.

Specimen Processing
Metagenomics deep sequencing (MDS) and or directed PCRs will be conducted on all collected samples. Trained laboratory technicians in the Ralph & Sophie Heintz laboratory will be responsible for processing all samples.

Chapter 6: Registering Participants for Specimen Collection

Samples will be collected with reference to age, surgical history, and history of ocular disease, but participant names will not be included in laboratory records to ensure privacy. Samples will thus not be associated with an individual's name, but with a random identification number, masking laboratory personnel and preventing identification of individuals.

At each time point, each participant selected for specimen collection will be assigned an identification number for database anonymity.

Chapter 7: Specimen Collection for Resistance and Microbiome Testing

7.1 Participants

We will collect nasopharyngeal, conjunctival, buccal, and rectal swab samples from all 108 participants. The swabbing will occur prior to surgery (conjunctival), 1-week post-op (conjunctival, NP, buccal, rectal), and 4-Week post-op (conjunctival, NP, buccal). The enrolled participants will be given instructions on when and where to go for swabbing visits after surgery.

7.2 Conjunctival, Nasopharyngeal, Buccal, and Rectal Swabs

All swabs will be stored in DNA/RNA shield media by Zymo and MDS and/or directed PCRs will be performed on all samples to evaluate for changes in antibiotic resistance and microbiome.

7.2.1 Conjunctival Swabs:

The examiner will:

1. Have the patient sit or lay on a chair with their head well supported. The chair will be adjusted to the appropriate height to ensure the patient's safety.
2. Each individual will use new bottle of proparacaine eyedrop for local anesthesia before taking conjunctival sample. Instruct the patient to look up and expose the conjunctiva by gently pulling down the lower lid of the surgical eye. Gently sweep the conjunctival swab along the lower fornix from inner to outer canthus without touching the eyelids.
3. Place each swab in a separate tube containing 2.0 mL DNA/RNA shield media by Zymo, break it off at its natural break-off point, and close the cap of the tube with the swab immersed.
4. Place study number label on the collection tube and then store at -80C until processing.

7.2.2 Nasopharyngeal Swabs:

The examiner will:

1. Place an adult flocked swab with a nylon tip through the right nostril and down the nasopharynx of each participant. Note that if the swab is not perpendicular to the frontal plane of the face, it is likely not in the inferior turbinate.
2. Once you reach the nasopharynx, rotate the swab 180° as you remove the swab from the nose.
3. Place the swab in a tube containing 1.0 mL DNA/RNA shield media by Zymo media, cut the handle off using sterile scissors, and close the cap of the tube with the swab immersed.
4. Place study number label on the collection tube and then store at -80C until processing.

Do not attempt to collect the NP swab if you are not successful after **three** attempts.

7.2.3 Buccal Swabs:

The examiner will:

1. Have the patient rinse mouth with water prior to sample collection
2. Instruct the patient to open their mouth and insert the buccal swab into one side of their mouth, between the cheek and upper gum. Press firmly and twirl swab against the inside of their inner cheek and over the gums for at least 30 seconds using an up/down and front/back motion on each side (1 minute total for both sides). Hold the swab as close to its head as is

comfortable for the patient. While you rub the cotton swab, turn the plastic shaft. This will ensure the entire tip is covered with cells from the cheek. This sampling technique should collect buccal cells without drawing blood.

3. Place the swab in a tube containing 2.0 mL DNA/RNA shield media by Zymo, break the swab at its break-off point, and close the cap of the tube with the swab immersed.
4. Place study number label on the collection tube and then store at -80C until processing.

7.2.4 Rectal Swabs:

The test will require that the participant themselves to obtain a good sample. It is important to describe the test to the participant thoroughly to ensure a good sample is taken. The rectal swabs include an instruction guide (see Appendix) with the following instructions:

1. Put on a clean pair of gloves.
2. Partially open the fecal swab package and remove the top section of the collection vial (this can be discarded).
3. Remove the swab from the package. Take care that the cotton tip is not touched. If it is touched, throw the swab away and begin with a new one.
4. Insert the tip of the swab into your anus only as far as needed to contact fecal material (1-3cm) and rotate 180 degrees. The tip should be a brownish color when removed.
5. Place swab into the preservative in the collection tube. Make sure the swab is fully submerged in the liquid preservative and then break the swab off using the pre-scored breaking point.
6. Screw the cap back on the tube and make sure that it's tightened. Wrap the area where the cap meets the tube with Parafilm to ensure that the sample will not leak, and then place the tube into the appropriate sample box.
7. If the swab cannot be broken off while the tip is fully submerged in the liquid, try twirling the swab in the liquid first (to release the contents of the sample into the preservative) before breaking it off. Avoid rubbing the

sample on the tip of the swab off on the side of the tube where there is no liquid.

8. Hand the tube with the sample to the investigator/study coordinator.
9. The investigator/study coordinator places the number label on the collection tube.
10. Tube will be stored at -80C until sample processing.

7.2.5 Materials for Swab Collection for Molecular Testing

Swabs

Conjunctival, NP, and buccal specimens will be collected using sterile, individually wrapped adult flocked swabs with a plastic swab shaft (manufactured by Copan or similar manufacturer). Rectal swab specimen will be collected using sterile individually wrapped swab (Zymo Research).

Sample Tubes

Conjunctival, NP, and buccal samples for molecular testing will be collected into sterile 2.0ml microcentrifuge tubes, manufactured by Sarstedt®. (DNA-free tubes will be used for collection in DNA/RNA shield (Zymo).) Rectal swab specimens will be stored in 2 mL sterile tube with DNA/RNA Shield solution provided as part of the DNA/RNA Shield Collection Tube with Swab (Cat # R1108).

-80°C Freezer

A dedicated -80°C freezer located at the Heintz laboratory will be available for storage of study samples, including nasopharyngeal, conjunctival, buccal, and rectal swabs.

7.2.6 Protocol for Tubing and Handling of Samples

The tubing and handling protocol must be carefully followed in order to prevent contamination and ensure the safe transport of the samples back to the Heintz laboratory and/or to other institutions for processing. The person in charge of labeling, tubing, arranging, and handling the samples needs to perform this task in the most orderly and attentive manner.

1. Both hands of the tuber should be gloved at all times. The tuber's gloves only need to be changed when any potential contamination of the gloves

occurs. The tuber opens the capped, hinged lid of a microcentrifuge tube, which has been labeled with the participant's random identification number.

2. The investigator/study coordinator should screw the cap of the microcentrifuge tube tightly, flick the tube to mix the sample with the media (for tubes with DNA/RNA shield media), and place it in the sample collection box until transfer to a -80C for storage in the Heintz lab.

All samples will be in sample boxes, labeled with the participant's study number for easy future identification.

Chapter 8: Training

8.1 Standardization

The research team will work together prior to the baseline visit to standardize all study procedures. We will review the format, general logistics, and procedures for all participants. Training and standardization of sample processing will be under the guidance of Dr. Thuy Doan.

Chapter 9: Sample Organization, Transport, and Storage

9.1 De-identification

All specimens will be labeled in the outpatient clinic with a random identification number linked to their name, MR number, and surgical/ocular disease history, but to facilitate masking, only the designated Study Coordinator and the Biostatician will have access to the key linking the ID with patient information. Age, gender, and surgical/ocular disease history will be available for each specimen, but names will be kept confidential. Therefore, all specimens will be de-identified. Please note that the Study Coordinator who is unmasked to the study arms will not be collecting samples at 1-week post-op (primary endpoint) to prevent potential biases.

9.2 Specimen Transport

After sample collection, samples from the clinic will be transported to the Heintz laboratory for storage and processing.

9.3 Specimen Storage

Sample storage will occur in two stages: short-term and long-term.

9.3.1 Short-term Sample Storage

Samples will be labeled with study ID only and are unidentifiable without access to the study database. All samples will be transported to the Heintz laboratory for storage and processing.

9.3.2 Long-term Sample Storage

All samples processed by the Heintz laboratory will be stored in the -80°C freezer for at least 5 years.

9.4 Catalog Specimens

We will create a list of study data and specimens, including the age, gender, surgical history, ocular disease history, group participant was in, and symptom questionnaire. We will also list the date of collection and transport, and the storage conditions while in the field and while banked at UCSF. This will facilitate identification of specimens for future analyses.

Chapter 10: Study Medication

All adult participants over 18 years of age will be given moxifloxacin intracamerally during surgery. Depending on which group the participant is assigned to, the participants may also be instructed to take topical moxifloxacin at home.

We will monitor as described in the adverse events section. The treatment and monitoring schedule for all study arms is shown in Table 1.

10.1 Study Medication Description

Moxifloxacin

Will be purchased by the subjects

10.2 Dosage Information

Moxifloxacin will be administered intracamerally during surgery for all participants. The study doctor will use a different moxifloxacin vial for each participant.

All participants in Group 2 and Group 3 will also be taking topical moxifloxacin eye drops at home.

- Group 2: 4 times a day
- Group 3: once a day

Individuals who are allergic to fluoroquinolones will not be in the study.

10.3 Medication Procurement/Donation

None.

10.4 Medication Quality Control

Intracameral moxifloxacin will be obtained through UCSF pharmacy in compliance with UCSF policy. Topical antibiotics will be dispensed as prescribed. All topical medications are FDA approved.

10.5 Adverse Reactions/Side Effects

Moxifloxacin is generally well-tolerated. The most common side effects of moxifloxacin are diarrhea, nausea, dizziness, and headache, each of which may occur as likely as 4% when taking orally and 8% while taking intravenously. Rarer side effects include dysphagia and stomatitis. Diarrhea due to *Clostridium difficile* has been reported in rare cases.

During the consent process, the common adverse reactions that may occur will be explained to the participant and they will be advised to communicate adverse events to UCSF study staff immediately. If, for any reason, the participant needs further care, they will be referred to the nearest health center for examination and treatment.

The trial sites will be masked to molecular outcomes. There will be no interim analysis given that this is a small study. Statistical monitoring is discussed in the Statistical Analysis Plan. The Data Safety and Monitoring Committee (DSMC)

will be given authority to discontinue treatments at any time if there is evidence of unexpected harm.

10.6 Adverse Events Systems

Both active and passive monitoring systems for adverse events are in place for this study. We will monitor adverse events at 1-Day post-op, 1-Week post-op, and 4-Week post-op.

10.6.1 Passive Adverse Events Monitoring

We will implement a passive monitoring system during the study, by instructing patients to report any adverse events during the study period. Patients will be referred for follow-up care on a case-by-case basis.

10.6.2 Active Adverse Events Monitoring

Ocular Symptoms/Quality Survey

To identify any adverse events during the study, the research team will administer the survey (DEQ-5 and SPEED questionnaires) to each participant at 1-day, 1-week, and 4-weeks after surgery. This survey will be completed by the participants themselves before specimen collection.

10.6.3 Adverse Events Data

We will keep records and report all potential adverse events to the DSMC. Reporting of non-serious and serious adverse events will follow UCSF IRB procedures.

Chapter 11: Protection of Human Subjects

Study staff will proceed only if participants consent to participate. To be able to collect specimens, we will obtain written informed consent from the participant. This written consent will contain information regarding all study activities with patient contact. We will collect one written consent form for each patient the first time we enroll them. The subsequent visits we will explain the study to the participant, but we will only obtain verbal consent. If, at any time, the participant elects to withdraw themself from the study, they will be free to do so. Individuals who withdraw will be offered the same medical treatment outside the study.

11.1 Institutional Review Board Approval

UCSF Committee on Human Research

UCSF's Committee on Human Research will annually review study protocol for ethical approval.

11.2 Written Consent

Each participant will be asked to sign the written consent form if they agree to be included in the study.

11.3 Risks and Benefits of Study Procedures

11.3.1 Swabbing Procedures

There are minimal risks to the participant who receives nasopharyngeal, conjunctival, and buccal swabbing. Participants may experience some temporary discomfort, but the swabbing involves minimal risk. Any adverse effects, such as nosebleeds, will be treated immediately by the examiners. Other health care will be provided at no cost to the study participant if necessary to address a study-related adverse health event.

11.3.2 Antibiotic Frequency

There are minimal risk of antibiotic resistance developing within the participant depending on how frequent they are instructed to take antibiotics. This will be rare, however, as all moxifloxacin regimens are commonly used in current practice.

Chapter 12: Study Monitoring

The project will be continuously monitored by the study team.

Chapter 13: Data and Safety Monitoring Committee Charter

This Charter is for the Data Safety and Monitoring Committee (DSMC). The Charter will define the primary responsibilities of the DSMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and communication, statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the Open and Closed Reports that will be provided to the DSMC.

13.1 Primary Responsibilities of the DSMC

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the trial. The DSMC will provide recommendations about stopping or continuing the trial. To contribute to the integrity of the trial, the DSMC may also formulate recommendations relating to the selection/recruitment/retention of participants, protocol-specified regimens, and the procedures for data management and quality control.

The DSMC will be advisory to the trial leadership group, hereafter referred to as the Steering Committee (SC). The SC will be responsible for promptly reviewing the DSMC recommendations and determining, whether to continue or terminate the trial, and to determine whether amendments to the protocol are required. If needed, the DSMC may seek the advice of a content expert outside of the committee.

13.2 DSMC Membership

The DSMC is an independent multidisciplinary group consisting of epidemiologists, biostatisticians, and clinicians that collectively has experience in the conduct and monitoring of randomized clinical trial.

13.3 Conflicts of Interest

The DSMC membership has been restricted to individuals free of apparent conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory. Thus, neither study investigators nor individuals employed by the

sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DSMC.

The DSMC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organizations (CRO), or with other sponsors having products that are being evaluated or that are competitive with those in the trial. The DSMC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DSMC members will be responsible for advising fellow members of any changes in any of the membership requirements that occur during the course of the trial. It may be appropriate for DSMC members who develop significant conflicts of interest resign from the DSMC.

DSMC membership is to be for the full duration of the trial. If any members leave the DSMC, the SC, in consultation with the DSMC, will promptly appoint a replacement.

13.4 Timing and Purpose of the DSMC Meetings

Organizational Meeting
The initial meeting of the DSMC will be an Organizational Meeting. This is during the final stages of protocol development and the purpose is to provide advisory review of scientific and ethical issues relating to study design to discuss the standard operating procedures and to discuss the format and content of the Open and Closed Reports that will be used to present trial results.

The Organizational Meeting will be attended by all DSMC members, lead trial investigators, and the trial biostatistician. The DSMC will be given the drafts of the trial protocol, the Statistical Analysis Plan, the DSMC Charter, and the current version of the case report forms. At subsequent meetings, committee members will receive Open and Closed Data Reports.

Formal Interim Analysis Meetings
There will be no planned interim analysis given this is a small trial.

13.5 Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has access to all emerging information from the trial regarding comparative results of efficacy and safety, aggregated by treatment arm.

Closed Sessions

Sessions involving only DSMC members and, where appropriate, those unmasked trial investigators (on the Data Coordinating Committee) who generate the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the trial, including information about the relative efficacy and safety of interventions.

At a final Closed Session, the DSMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

Open Session

In order for the DSMC to have access to information provided, by study investigators, or members of regulatory authorities, a joint session between these individuals and DSMC members will be held between the Closed Sessions.

Open and Closed Reports

For each DSMC meeting, Open and Closed Reports will be provided. Open Reports will include data on recruitment and baseline characteristics, pooled data on eligibility violations, and completeness of follow-up and compliance. The study statistician (TCP) will prepare these Open Reports.

Closed reports, available only to those attending the Closed Sessions of the meeting, will include analyses of primary and secondary efficacy endpoints, including subgroup and adjusted analyses, AEs and symptom severity, and Open Report analyses that are displayed by intervention group. These Closed Reports will be prepared by the study biostatistician.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within two months of the date of the DSMC meeting. The Reports should be provided to DSMC members approximately three days prior to the date of the meeting.

Minutes of the DSMC Meeting
The research team will prepare minutes for the open portion of the meeting, including the DSMC's recommendations.

Recommendations to the Steering Committee (SC)
At each meeting of the DSMC during the trial, the committee will make a recommendation to the Steering Committee to continue or terminate. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter.

Recommendations to amend the protocol or conduct of the study made by the DSMC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue or to stop the trial based on the DSMC recommendations.

The DSMC will be notified of all changes to the protocol or to study conduct. The DSMC concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to implementation.

The SC may communicate information in the Open Report to the sponsor and may inform them of the DSMC recommended alterations to study conduct or early trial termination in instances in which the SC has reached a final decision agreeing with the recommendation. The SC will maintain confidentiality of all information it receives other than that contained in the Open Reports until after the trial is completed or until a decision for early termination has been made.

13.6 Statistical Monitoring Guidelines

The SC will propose statistical rules for a futility stopping rule and an efficacy stopping rule at the first DSMC meeting.

13.7 DSMC Contact Information

Table 2: DSMC Contact Information

Julie Schallhorn	Julie.Schallhorn@ucsf.edu
Catherine Oldenburg	Catherin.Oldenburg@ucsf.edu
Gerami Seitzman	Gerami.Seitzman@ucsf.edu

Chapter 14: Data Collection, Management, and Security

14.1 Scope of Data

Genetic data will be collected in this trial from specimen collection.

14.2 Data Storage, Management, and Security

Data will be recorded electronically using an encrypted and secure Excel spreadsheet and REDCap, which can securely store confidential information. Only people on the study team will have access to the information.

14.3 Data Monitoring and Cleaning

Data monitoring and cleaning will be overseen by the data coordinating center (DCC) at the coordinating site. Data collection will be monitored on a weekly basis by the study coordinator using the dashboard function on REDCap.

Appendix

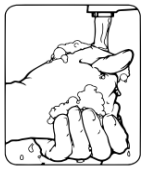
Appendix 1. SAP
Appendix 2. Instructions for self-sample collection
Appendix 3. DEQ-5 Questionnaire
Appendix 4. SPEED Questionnaire

Appendix 2. Instructions on Self-Collected Rectal Samples

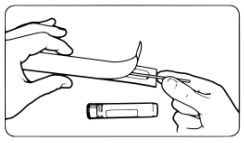
ARIES Instructions on Self-Collected Rectal Samples

Thank you for providing a rectal sample. Your sample will help the researchers at the University of California, San Francisco better understand how topical antibiotic use affects antibiotic resistance in the gut.

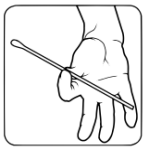
1. Wash hands with soap and water. Dry hands thoroughly and put on the provided gloves from the kit.



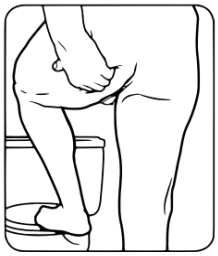
2. Loosen but do not remove the cap of the collection tube labeled "RECTAL".

3. 

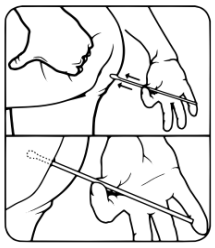
In a private location, open the Sterile Flocked Collection Device and remove the swab from its wrapper without touching the soft, cotton tip.

4. 

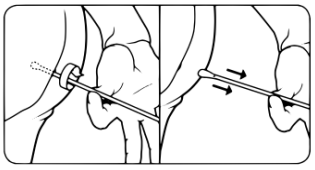
Hold the swab between your thumb and forefinger so that you have good control.

5. 

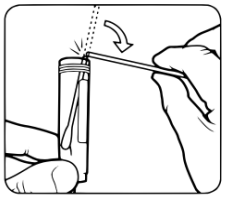
With one foot on the edge of the toilet bowl, pull back your left buttock with your left hand.

6. 

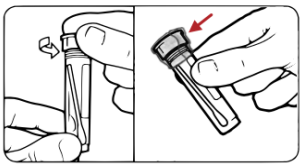
Gently insert the tip of the swab into your anus about 1 to 3 cm.

7. 

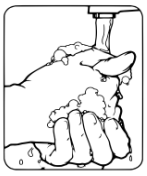
Rotate the swab 360 degrees at least twice. Gently remove the swab from your anus. It should be a brownish color.

8. 

Place the soft tip of the swab into the container and break off the swab using the pre-scored breaking point.

9. 

Close the specimen container carefully and ensure the lid is fully secured. Gently stretch the Parafilm (arrow) around the seal to prevent tube leakage.

10. 

Dispose of the gloves in the trash and thoroughly wash your hands.

Version 1 (November 24, 2020)

Appendix 3. DEQ-5 Questionnaire

DEQ 5

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, how often did your eyes feel discomfort?
      - 0 ☐ Never
      - 1 ☐ Rarely
      - 2 ☐ Sometimes
      - 3 ☐ Frequently
      - 4 ☐ Constantly

   b. When your eyes felt discomfort, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?

Never have it	Not at all intense				Very intense
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?
      - 0 ☐ Never
      - 1 ☐ Rarely
      - 2 ☐ Sometimes
      - 3 ☐ Frequently
      - 4 ☐ Constantly

   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at all intense				Very intense
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

3. Question about **WATERY EYES**:
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?
      - 0 ☐ Never
      - 1 ☐ Rarely
      - 2 ☐ Sometimes
      - 3 ☐ Frequently
      - 4 ☐ Constantly

Score:	1a	+	1b	+	2a	+	2b	+	3	=	Total
	____	+	____	+	____	+	____	+	____	=	_____

Appendix 4. SPEED Questionnaire

SPEED™ QUESTIONNAIRE

Name: _____ **Date:** ____/____/____ **Sex:** M F (Circle) **DOB:** ____/____/____

For the Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire, please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

	At this visit		Within past 72 hours		Within past 3 months	
Symptoms	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

2. Report the FREQUENCY of your symptoms using the rating list below:

Symptoms	**0**	**1**	**2**	**3**
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

0 = Never **1** = Sometimes **2** = Often **3** = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

Symptoms	**0**	**1**	**2**	**3**	**4**
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

0 = No Problems
1 = Tolerable - not perfect, but not uncomfortable
2 = Uncomfortable - irritating, but does not interfere with my day
3 = Bothersome - irritating and interferes with my day
4 = Intolerable - unable to perform my daily tasks

4. Do you use eye drops for lubrication? ☐ YES ☐ NO **If yes, how often?** _____

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Total SPEED score (Frequency + Severity) = ____/28