Maximizing Trichiasis Surgery Success

Trial Protocol

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Version Number: 2.4

10 October 2021

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

This protocol is modeled in part based on NIDCR Clinical Trial (Interventional) Protocol Template v4.0 - 20140103

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 10 October 2021

Name: Emily W. Gower, PhD

Title: Associate Professor

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PROTOCOL SUMMARY

Title: *Evaluating the Role of Incision Height in Trichiasis Surgery Outcomes*

Précis: In this trial we will randomize 4,953 individuals with previously unoperated trichiasis on a 1:1:1 basis to bilamellar tarsal rotation trichiasis surgery with an incision height of 3mm, bilamellar tarsal rotation trichiasis surgery with an incision height of 5 mm, or Trabut surgery. Participants will receive trichiasis surgery and will be followed at 1 day, 2 weeks, 6 weeks,12 months and 3 years after surgery. The primary outcome is development of post-operative trachomatous trichiasis (PTT) within 12-18 months after surgery. Logistic regression analyses will be performed to compare the rates of PTT in the 3 versus 5 mm incision BLTR groups, in the 3 mm BLTR versus Trabut group, and in the 5 mm BLTR versus Trabut group, adjusting for demographic characteristics and pre-operative trichiasis severity.

Objectives:

Primary objectives:

1) Examine whether the rate of post-operative trichiasis differs significantly for incisions placed 3 mm from the eyelid margin compared to incisions place 5 mm from the eyelid margin.

2) Examine whether the rate of post-operative trichiasis differs significantly between surgery performed with the Trabut procedure versus bilamellar tarsal rotation with 3 mm incision height.

3) Examine whether the rate of post-operative trichiasis differs significantly between surgery performed with the Trabut procedure versus bilamellar tarsal rotation with 5 mm incision height.

Secondary objectives:

1) Determine whether the frequency of moderate/severe eyelid contour abnormalities differs following surgery performed with the bilamellar procedure when the target incision height is 3 mm versus 5 mm

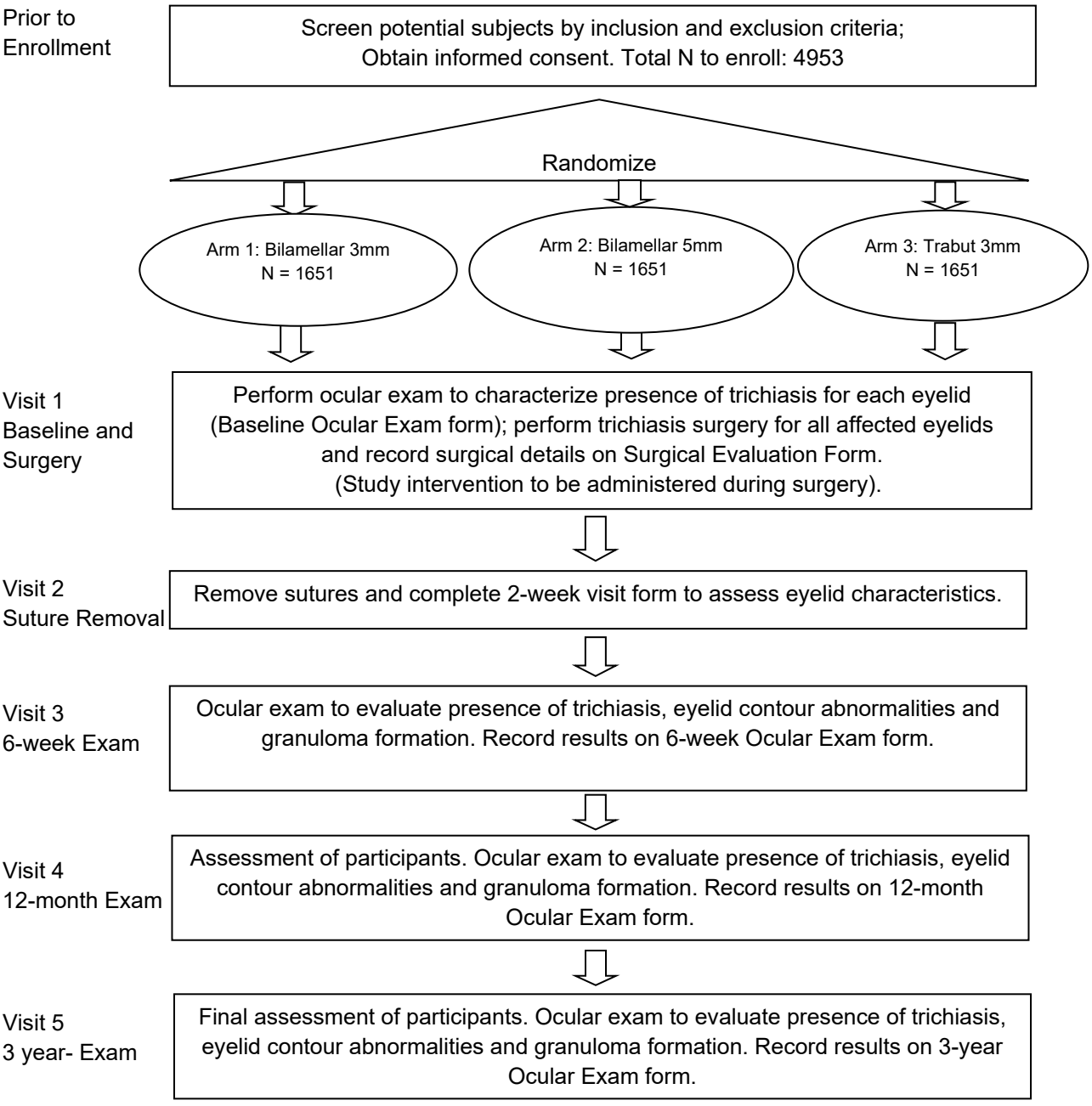
2) Compare the frequency of moderate/severe eyelid contour abnormalities at one year between surgeries

performed with bilamellar 5 mm incision height and Trabut.

3) Compare the frequency of moderate/severe eyelid contour abnormalities at one year between surgeries performed with bilamellar 5 mm incision height and Trabut.

Population:	Participants will be recruited from the Hadiya Zone of the SNNPR Region in Ethiopia. All individuals with previously unoperated trichiasis in at least one eye, aged >18 years, and living in the area will be eligible to participate. We aim to enroll 1,500 individuals during the 2016/2017 surgical campaigns being supervised by Orbis International (we will recruit from January to April), an additional 2,500 individuals during the 2017/2018 campaign (October to April), and approximately 1,000 in the Fall/Winter 2018/2019 campaign.
Description of Intervention:	Trabut surgery involves a partial-thickness incision through the upper eyelid parallel to the eyelid margin. Bilamellar tarsal rotation involves a full-thickness incision through the upper eyelid. For bilamellar surgery, the height of the incision will be assigned at 3 mm or 5 mm from the eyelid margin. For Trabut, it will be assigned at 3 mm.
Study Duration:	6 years
Subject Participation Duration:	3 years
Estimated Time to Complete Enrollment:	Recruitment is scheduled for mid-January 2017 - April 2017 and mid-October 2017 through March 2018 to account for the rainy season.

STUDY DESIGN SCHEMATIC:



1 KEY ROLES AND CONTACT INFORMATION

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Shannath L. Merbs, MD PhD (JHU SoM site PI)
Beatriz Munoz, MS (senior statistician)

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background and Rationale

Trichiasis is an important cause of blindness in developing countries with limited access to water and sanitation measures. The disease primarily affects adult women, although in areas where trachoma is highly-endemic, trichiasis is occasionally diagnosed in young children. Surgery is available to correct trichiasis, but long-term success rates are suboptimal in many settings. Two primary surgical procedures are used, bilamellar tarsal rotation (BLTR; bilamellar) and posterior lamellar tarsal rotation (PLTR), also known as Trabut.

Surgical Procedure Comparison

A recent trial conducted in the Amhara region of Ethiopia compared BLTR and Trabut and found a significant reduction in post-operative trichiasis following Trabut as compared to BLTR (22% vs. 13%; Adjusted Odds Ratio 1.96; 95% CI: 1.40-2.75). The trial employed Trabut-trained surgeons who received conversion training to perform BLTR. Each surgeon performed both procedures as part of the trial. The trial was exceptionally well run, and some programs are now strictly training surgeons with Trabut. However, there is much debate over whether the trial results are broadly applicable for experienced surgeons who were first trained in BLTR and for newly trained surgeons. Specifically, since the release of the trial results, two meetings of the global trichiasis community have been held (one a WHO-sponsored meeting of trichiasis experts and the other the annual program review of the organization performing the largest volume of trichiasis surgeries worldwide, which included global experts from most trachoma-endemic countries). At both meetings, experts strongly recommended that another trial should be conducted which utilizes BLTR surgeons who receive conversion training to Trabut. Additionally, Dr. Wondu Alemayehu is a member of the planned trials and has indicated strong in-country support for the need for an additional study to examine this question. In the planned trial, we will compare post-operative trichiasis rates for surgeries performed with each of these procedures. Surgeons will be either newly trained in both procedures or will be BLTR surgeons who have received conversion training in Trabut and have performed at least 100 Trabut surgeries.

Incision Height Comparison

In both the BLTR and Trabut procedures an incision is made in the eyelid, parallel to the eyelid margin, such that inturned eyelashes can be corrected to their normal position. Currently, the recommended height for making the incision is 3 mm above the eyelid margin. However, preliminary evidence from bilamellar surgery trials suggests that this height may not be the best height for achieving optimal outcomes. Data from both the PRET trial and the recent Trabut versus BLTR trial show reduced post-operative trichiasis among eyelids operated with the BLTR procedure with an incision scar height

of 5 mm at 1 year versus a lower incision scar height. Specifically, the PRET trial examined the role of a surgical clamp (the TT Clamp) in improving bilamellar trichiasis surgery outcomes. Use of the TT clamp improved eyelid contour abnormalities and granuloma formation, but it did not improve risk of trichiasis returning (post-operative trichiasis). Evaluation of incision height scars for a subset of this population suggests that incisions that are made closer to the eyelid margin are more likely to develop post-operative trichiasis than eyelids with an incision further away from the eyelid margin. When surgeons perform TT surgery with the clamp, they are guided on where to place the incision, and by design of the clamp, the height of the incision is limited; hence, it is possible that the TT clamp did not improve post-operative trichiasis rates because the incisions in the TT clamp arm were closer to the eyelid margin than eyelids operated with standard instrumentation (without a TT clamp). We have conducted a similar analysis of incision scar heights for the Amhara based BLTR vs. Trabut trial and found similar results for the BLTR surgeries in that study. Incision scar height and post-operative trichiasis were not correlated in Trabut surgeries; however, rates of post-operative trichiasis in the higher scar height BLTR surgeries were similar to rates in the Trabut arm.

One goal of the planned trial is to determine whether altering the incision height to 5 mm can improve surgical outcomes. We will compare target incision heights of 3 mm and 5 mm among BLTR surgeries. We selected this comparison since 2 studies have provided a suggestion that increasing the incision height in BLTR surgeries could positively affect post-operative trichiasis rates.

The follow up period for this trial is one year after surgery. Historical evidence suggests that the majority of post-operative trichiasis occurs within the first year after surgery, and that most recurrence that happens after one year is more related to disease severity than to the manner in which the procedure was performed.

2.2 Potential Risks and Benefits

Potential Risks

The risks associated with this study are minimal. Trichiasis surgery is a standard procedure commonly performed in many countries, and all subjects enrolled in this study would receive trichiasis surgery regardless of whether they participate in the clinical trial. Theoretically, increasing the incision height could result in an increased risk of eyelid contour abnormalities since a larger portion of the tarsus must be everted. Preliminary data suggest that higher incision heights are not associated with an increased risk of eyelid contour abnormalities. However, it is important to be aware of this possible risk.

Potential Benefits

Participants enrolled in this study will not benefit directly from this study. Most trichiasis surgery programs do not follow their patients after sutures are removed. In this study,

we will evaluate patients 6 weeks,12 months and 3 years after surgery. Participants may view this as a benefit.

3 OBJECTIVES

3.1 Study Objectives

This study has three primary objectives:

1) Examine whether the rate of post-operative trichiasis differs significantly for incisions placed 3 mm from the eyelid margin compared to incisions place 5 mm from the eyelid margin.

2) Examine whether the rate of post-operative trichiasis differs significantly between surgery performed with the Trabut procedure versus bilamellar tarsal rotation with 3 mm incision height.

3) Examine whether the rate of post-operative trichiasis differs significantly between surgery performed with the Trabut procedure versus bilamellar tarsal rotation with 5 mm incision height.

Secondary objectives:

1) Determine whether the frequency of moderate/severe eyelid contour abnormalities differs following surgery performed with the bilamellar procedure when the target incision height is 3 mm versus 5 mm
2) Compare the frequency of moderate/severe eyelid contour abnormalities at one year between surgeries performed with bilamellar 5 mm incision height and Trabut.
3) Compare the frequency of moderate/severe eyelid contour abnormalities at one year between surgeries performed with bilamellar 5 mm incision height and Trabut.

3.2 Study Outcome Measures

Post-operative Trichiasis

We will evaluate post-operative trichiasis at 4 time points after surgery: 2 weeks, 6 weeks,12 months and 3 years. Patient examiners standardized against Dr. Shannath Merbs or Dr. Alemayehu Sisay will perform the assessments. The assessment is made by looking at the eyelid with the eye in primary gaze. Any eyelashes touching the eye with the eye in primary gaze are considered to be trichiatic. Presence of post-operative trichiasis (primary outcome) is defined as 1+ trichiatic eyelashes or evidence of recent epilation. If an eyelid has trichiasis at 2 weeks but not at a later point, the eyelid will be considered not to have post-operative trichiasis.

Eyelid Contour Abnormalities

We will evaluate eyelid contour abnormalities at each post-operative visit. The examiner will grade the presence of abnormality using the definition provided below in the statistical considerations chapter. Both field and photographic grades will be utilized. The field grade will serve as the primary grade for the primary study analyses; secondary analyses will utilize the photograph grade. Examiners will be standardized at the start of the 6-week visits.

Pyogenic Granuloma

Pyogenic granulomas occasionally develop after trichiasis surgery, and it is thought that these are a response to a foreign body, such as suture material or a jagged incision edge. The patient examiners will evaluate presence of granulomas at 6 weeks, 12 months, and 3 years (with primary outcome being granuloma formation by the 12-18 month visit). All granulomas will be noted, regardless of size.

4 STUDY ENROLLMENT AND WITHDRAWAL

Study participants will be recruited from patients presenting for trichiasis surgery in the Hadiya Zone, in southern Ethiopia. We will not exclude subjects based on race or gender; however, participants must be aged 18 or older.

4.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Aged 18 or older
- At least one eyelid with previously unoperated upper eyelid trichiasis
- Willing to comply with all study procedures and be available for the duration of the study

4.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Inability to provide independent, informed consent
- All eyes with previously unoperated trichiasis are phthisical

4.3 Strategies for Recruitment and Retention

Subjects will be recruited on the day that they present for trichiasis surgery. We will collaborate with an ongoing surgical program in the area (Orbis International) and will assist them with identifying patients with trichiasis. Advance screening will be conducted by the Orbis team. All individuals with trichiasis who would like to have surgery will be scheduled for surgery within 2-4 weeks after screening. On the day of surgery, they will be told about the study and anyone interested in learning more will meet with a consent specialist to hear a full description of the study and to complete the consent process if eligible and interested. All trichiasis patients will receive surgery free of charge, regardless of participation in the trial.

Subjects will not receive compensation for participation. Participant retention is maintained through contact with a local community health worker, who lives in the village with the participants and has a long-term relationship with them. The project director will call community health workers approximately 2 weeks before upcoming study visits to remind them that they need to contact the subjects living in their village to bring them for the follow up visit. Also, during the surgery day and at each follow up, patients will receive reminder cards stating the date and location of the next follow up

visit. This approach has been extremely successful in our previous trials, with retention rates of over 95% of eligible subjects.

4.4 Treatment Assignment Procedures

4.4.1 Randomization Procedures

Participants will be randomized at the participant level to one of three arms: 1) BLTR with target incision height of 3 mm 2) BLTR with target incision height of 5 mm and 3) Trabut with target incision height of 3 mm. Both eyes will be operated with the same surgical procedure and incision height if both eyes need surgery. Randomization assignments will be prepared in individual opaque envelopes with the patient ID number on both the outside of the envelope and on the internal papers indicating the arm assigned. The envelope will be opened during enrollment by the Program Manager. The surgeon and surgical assistant will both confirm the assigned surgical procedure and incision height at the start of the procedure. They will be required to indicate the assigned procedure and height on the surgical evaluation form and to measure and record the actual height of the incision made. Incision heights will be measured for patients in all three randomization arms.

The randomization assignments will be developed at UNC. Each week reported assigned surgical procedures and incision heights will be compared against the master table to ensure the assigned procedure and heights are consistently being reported for each participant. Details on monitoring are available in the quality assurance section.

4.4.2 Masking Procedures

The study subject and the outcomes assessment team will be masked to treatment assignment. However, the surgeon will not be masked to the treatment assignment since s/he must know what procedure to perform and what height to make the incision at. In order to ensure the outcomes assessors remain masked, they will not be present at the surgical site, and they will not have access to data from the baseline and surgical visit.

4.5 Subject Withdrawal

Subjects may withdraw voluntarily from the study at any time. Because the intervention is a one-time intervention, the investigators should not have reason to withdraw a study subject for non-compliance.

5 STUDY INTERVENTION

In this trial, all subjects will receive trichiasis surgery using the BLTR or Trabut procedure. The primary study intervention is surgical procedure, with either Trabut or BLTR with 3 mm or 5 mm from the eyelid margin.

5.1 Study Procedural Intervention Description

Surgeons will receive the surgical procedure and incision height assignment just prior to surgery for that participant. Immediately before beginning surgery, the surgeon will confirm with the surgical assistant what the procedure is (BLTR or Trabut) and if BLTR, what the assigned target incision height is.

5.2 Procedures for Training of Clinicians on Procedural Intervention

Prior to recruitment, each study surgeon must be certified using the World Health Organization's checklist for final assessment of surgeons by an external evaluator (Dr. Amir Bedri Kello, Alemayehu Sisay or Dr. Demissie Tadesse) to ensure s/he consistently performs high-quality surgery following the World Health Organization's recommended procedure. Then the surgeon will be trained by the study oculoplastic surgeon, Dr. Shannath Merbs, on how to appropriately indicate where to make the incision and then to measure the incision after making it.

Target incision heights will be indicated using a sterile surgical marker. Each study surgeon will receive extensive practice in measuring the distance from the eyelid margin with calipers and marking the location of the incision across the length of the eyelid. We will utilize our surgical simulation device, HEAD START, to practice measuring and marking the incision height. Once surgeons are comfortable with the approach, we will prepare a series of incised eyelids (on HEAD START) and will ask the surgeons to measure the height of each incision nasally, centrally, and temporally. Once they reach a kappa of >0.7 for measuring the heights compared to Dr. Merbs measurements, we will proceed to similar practice with live patients. Again, kappas of >0.7 for measuring the height of the incision will be required before the surgeon is able to work independently.

Monthly throughout the enrollment and surgery phase of the trial, one of the study ophthalmologists (Dr. Bedri, Dr. Alemayehu and Dr. Demissie) will visit the surgery team and will assess surgical measurements.

5.3 Assessment of Clinician and/or Subject Compliance with Study Procedural Intervention

The Project Director will regularly monitor surgical activities in-person to ensure that the surgeons are following the study procedures, performing the correct procedure, and accurately measuring and recording the incision height. Each week the Coordinating Center (CC) will compare the assignment reported on the Surgical Evaluation form against the actual assignment. The CC will issue a query for each instance where there is any disagreement between the recorded assignment and actual assignment. The CC will also compare the reported assigned height on the Surgical Evaluation against the actual height measurements. Frequency of differences greater than 0.5mm will be reported at the surgeon level on a cumulative basis. Whenever more than 5% of the actual measurements are more than 0.5 mm different than the assigned measurements, the surgeon will be reevaluated by one of the study ophthalmologists to determine what corrective measures need to be made.

6 STUDY SCHEDULE

Visit Type	Timing	Window
Eligibility Screening	Day 0	N/a (potential subjects to be screened for eligibility when they present for surgery)
Enrollment and Baseline Exam	Day 0	N/a (subjects to be enrolled right after screening)
Surgery	Day 0	0-14 days after enrollment. If surgery must be delayed more than 2 weeks, a new baseline exam should be completed.
1-day post-operative visit	Day 1	Day 1-2
Suture Removal	2 weeks after surgery	10 – 18 days after surgery
6 week follow up	6 weeks after surgery	5 to 9 weeks post-surgery
12 month follow up	12 months after surgery	11 to 18 months post-surgery
3 year follow up	3 years after surgery	30 to 42 months post-surgery

6.1 Eligibility Screening and Enrollment (Day 0)

Eligibility screening will take place at trichiasis surgery camps. Prior to this, local eye care workers will have identified all individuals with trichiasis and scheduled them for surgery. When patients present for trichiasis surgery, a trichiasis surgeon or screener will screen them for the presence of trichiasis and will note whether prior surgery has been performed on any eye that has trichiasis that day. Then the consent specialists will make a general announcement about the study and invite those who would like to learn more and possibly participate to meet individually with one of them.

The consent specialists will meet with trichiasis surgery patients in small groups to tell them about the study and then individually will assess eligibility using the Eligibility Review form. If they are eligible and interested in participating, the consent specialist will proceed to obtain informed consent with one patient at a time. The full process for

obtaining informed consent is provided in the Manual of Procedures. Those who provide consent will then meet with the project manager to be enrolled in the study.

Required Procedures/Data Collection:

- Complete Eligibility Screening form (Form 1)
- Obtain informed consent
- Collect Demographic and Tracking Information

6.2 Baseline Ocular Exam and Surgery (Day 0)

The baseline exam occurs immediately after enrollment and just prior to surgery (all happen on the same day). The goal of this exam is to characterize trichiasis severity and visual acuity prior to surgery. Baseline trichiasis severity is an important predictor of post-operative trichiasis; hence, these data will be included in all models evaluating the outcome.

After the ocular exam, the patient receives trichiasis surgery.

Required Data Collection:

- Baseline Ocular Exam Form
- Surgical Evaluation Form

6.3 Follow up Visits

Follow up visits occur 1 day, 2 weeks, 6 weeks,12 months and 3 years following surgery. At the 2 week visit, sutures are removed. At each follow up visit the patient examiner evaluates each eyelid for the presence of trichiasis, eyelid contour abnormality and granuloma. At the one-day post-operative visit, the examiner checks the status of the surgery. If eyelashes are touching the eye or if the eyelid is completely flipped (gross over-correction) then the surgeon should adjust the surgery to correct the eyelid.

Required Procedures/Data Collection:

- Follow up visit form (2 week, 6 week, 12 month or 3 year form)
- Adverse Event Form (if applicable)

6.4 Unscheduled Visit

Between visits, the primary point of contact between subjects and the study team typically will be the community health worker (CHW) living in their community. Subjects

who experience problems between study visits will meet with the CHW who will assess the issue and determine whether a study team member should come to the village for an unscheduled study visit or whether the CHW can resolve the issue himself. If such a visit is necessary, the study team member will visit the subject and will complete an Unscheduled Visit form to document the purpose of the visit and what procedures, if any, were performed. If the CHW and study team member determine that a study visit is not required, the study team member simply needs to complete the CHW/Participant Call Log, indicating the date of the call, participant ID, reason for call and actions taken.

Required Procedures/Data Collection:

- CHW Participant Call Record
- Unscheduled Visit Form

6.5 Timeline and Feasibility of Adhering to Study Schedule

The study recruitment and follow up schedule is outlined in the table below.

	Year 1 (Mar 2016 – Feb 2017)				**Year 2 (Mar 2017 – Feb 2018)**				**Year 3 (Mar 2018 – Feb 2019)**				**Year 4 (Mar 2019 – Feb 2020)**			
Activity	Q1 (Mar-May)	Q2 (Jun-Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)	Q1 (Mar-May)	Q2 (Jun-Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)	Q1 (Mar-May)	Q2 (Jun-Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)	Q1 (Mar-May)	Q2 (Jun-Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)
Ethics Applications	X	X	X													
Recruitment/Enrollment				Start Jan					End Mar or Apr*		Start Oct	X	End Mar			
2 and 6-week follow up				X					X	X	X	X	End May			
1 year follow up					X							Start Jan	X		Start Oct	X
Data cleaning				X	X	X			X	X	X	X	X	X	X	X
Dissemination of Study Findings (manuscripts and presentations)						X	X	X								

*Depends on when the rains start.

	Year 5 (Mar 2020 – Feb 2021)				**Year 6 (Mar 2021 – Feb 2022)**				**Year 7 (partial) (Mar 2022 – July 2022)**	
Activity	Q1 (Mar-May)	Q2 (Jun-Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)	Q1 (Mar-May)	Q2 (Jun - Aug)	Q3 (Sep-Nov)	Q4 (Dec-Feb)	Q1 (Mar-May)	Q2 (Jun - Aug)
1 year follow up	Planned but didn't happen									
3 year follow up				X	X		X	X	X	
Data cleaning				X	X	X	X	X	X	X
Dissemination of Study Findings (manuscripts and presentations)								X	X	X

7 STUDY PROCEDURES / EVALUATIONS

Detailed methods for data collection for each of the study procedures are provided in the Manual of Procedures. This section lists the procedures and describes the general approach for data collection.

Ocular Examination: At baseline, the ocular exam will consist of an evaluation of each eyelid for the presence of trichiasis and presence of corneal opacity. At each follow up study visit, both eyelids will be assessed for the presence of trichiasis, eyelid contour abnormality and granuloma.

Visual Acuity: Visual acuity will be assessed monocularly at baseline (pre-operatively) and 12 months postoperatively using an Early Treatment of Diabetic Retinopathy (ETDRS) tumbling “E” chart on a smartphone.

Trichiasis Surgery: All participants will receive trichiasis surgery with either the BLTR or Trabut procedure outlined in the World Health Organization’s Trichiasis Surgery Manual, with exception of the incision placement for ½ of the BLTR surgeries. In the trial, BLTR incisions will be placed 3 mm or 5 mm away from the eyelid margin, depending on randomization assignment. Detailed methods for how to measure and mark where to make the incision are provided in the Manual of Procedures.

Photographs: Photographs will be taken of each eyelid preoperatively, during surgery after incision is made, immediately postoperatively, and at each follow up visit.

8 PROVISIONS FOR MONITORING STUDY PROGRESS

Multiple levels of oversight have been built into the trial to ensure patient safety and data integrity. These include:

Internal Monitoring:

- Weekly monitoring of accumulating data to ensure complete data collection
- Weekly assessment of compliance with assignment of surgical procedure and incision height
- Regular field monitoring by local and international team members
- Active collection of adverse events during surgery and at each follow up visit.

In addition, we will follow UNCs guidelines for reporting all safety events.

External Monitoring:

- An NEI-designated Data and Safety Monitoring Board
- Annual reports to the Institutional Review Boards at each institution and to the Ethiopian ethics board (National Health Research Ethics Review Committee, Ministry of Science and Technology).

Detailed information on the managing guidelines and approaches for each of these is provided in the Manual of Procedures.

9 STATISTICAL CONSIDERATIONS

9.1 Study Hypotheses

Primary Aims:

Primary study null hypotheses:

1) Among BLTR surgeries, increasing the target incision height from 3 mm to 5 mm will not affect the rate of post-operative trichiasis (PTT).

2) BLTR surgery with a target incision height of 3 mm will have the same rate of post-operative trichiasis as Trabut surgery.

3) BLTR surgery with a target incision height of 5 mm will have the same rate of post-operative trichiasis as Trabut surgery.

Alternative hypotheses:

1) Among BLTR surgeries, increasing the target incision height from 3 mm to 5 mm will result in a 25% reduction in the rate of post-operative trichiasis (PTT).

2) Trabut surgery will result in a 25% reduction in the rate of post-operative trichiasis compared to BLTR surgery with a 3 mm target incision height.

3) Trabut surgery will result in a 25% reduction in the rate of post-operative trichiasis compared to BLTR surgery with a 5 mm target incision height.

Secondary Aims:

Null hypothesis:

1) Among BLTR surgeries, increasing the target incision height from 3 mm to 5 mm will not affect the rate of eyelid contour abnormalities.

2) Eyelids operated with Trabut will have the same rate of moderate/severe eyelid contour abnormalities rate as eyes operated with BLTR with a target incision height of 3 mm.

3) Eyelids operated with Trabut will have the same rate of moderate/severe eyelid contour abnormalities rate as eyes operated with BLTR with a target incision height of 5 mm.

4) Eyelids operated with Trabut will have the same rate of granuloma formation as eyelids operated with BLTR.

Alternative hypotheses:

1) Eyelids operated with the BLTR surgery and 3 mm will have fewer eyelid contour abnormalities than eyelids operated with Trabut.

2) Eyelids operated with Trabut will have a higher rate of moderate/severe eyelid contour abnormalities rate than eyes operated with BLTR with a target incision height of 3 mm.

3) Eyelids operated with Trabut will have a higher rate of moderate/severe eyelid contour abnormalities rate than eyes operated with BLTR with a target incision height of 5 mm.

4) Eyelids operated with Trabut will have a lower rate of granuloma formation than eyelids operated with BLTR.

9.2 Sample Size Considerations

The planned sample size for this trial is 4,953 participants. This sample size will give sufficient power to detect a 25% difference in post-operative trichiasis rates between 3 mm and 5 mm target incision heights for BLTR, a 25% difference in post-operative trichiasis rates for BLTR 3 mm versus Trabut and a difference of 25% between BLTR 5 mm and Trabut. This estimate is based on the following assumptions:

- 15% of eyelids in the BLTR 3 mm target height group will develop post-operative trichiasis during the 12 months following surgery
- Two-sided alpha error = 5%
- Power = 80%
- 40% of participants will have 2 eligible eyes
- The correlation between 2 eyes of an individual is 0.24
- 5% loss to follow up.

Based on these assumptions, the table below shows the total number of participants needed within the 3 arms combined.

Prevalence in control group	RR	Subjects per Arm	Total number of subjects In the 3 arms if 100% bilateral	Total number of surgeries needed	Only 40 % of surgeries will be bilateral # of surgeries	Additional Subjects (surgeries) to accrue the total number needed	Total number of subjects to be enrolled	Increase to account for 5% lost to follow-up
15%	0.70	743	2229	4458	3121	955 (1337)	3184	3351

16%	0.70	690	2070	4140	2898	887 (1242)	2957	3112
15%	0.75	1098	3294	6588	4612	1411 (1976)	4705	4953
16%	0.75	1019	3057	6114	4280	1310 (1834)	4367	4597

9.3 Analysis Plan

We will follow these general analysis principles:

- The primary analyses will be performed according to the participant's assigned intervention.
- All participants who complete randomization and have surgery performed will be included in analyses.
- All events following surgery will be counted.
- All analyses will be conducted at the eye level, using the generalized estimating equations approach to correct standard errors (to account for the correlation between two eyes of a subject).
- Unless otherwise indicated, three sets of analyses will be performed:1) BLTR 3 mm versus BLTR 5 mm and 2) BLTR 3 mm versus Trabut 3 mm 3) BLTR 5 mm versus Trabut 3 mm.

Post-operative Trichiasis Analyses:

*The **primary analyses** will be based on the dichotomous outcome: presence or absence of post-operative trichiasis at any time point within 12-18 months following surgery. Both unadjusted and adjusted analyses will be performed. Adjusted analyses will account for the severity of pre-operative trichiasis, with severity defined based on the table below.*

Trichiasis Severity Classification	**Description**
Mild	1-4 Eyelashes touching globe, no epilation OR 1-10 Eyelashes epilated, no eyelashes touching globe

Moderate	5-9 Eyelashes touching globe, no epilation OR 1-4 Eyelashes touching globe and 1-10 eyelashes epilated
Severe	5-9 Eyelashes touching globe and 1-10 eyelashes epilated OR 10+ Eyelashes touching globe, regardless of epilation status OR 11-20 Eyelashes epilated, regardless of eyelashes touching globe OR *Entire eyelid epilated*

(Gower et al. 2013. *JAMA Ophthalmol*.;131(3):294-301.)

Multiple secondary analyses of post-operative trichiasis will be performed. We will compare the severity of post-operative trichiasis between groups, with severity defined using the table above. First, we will compare the primary groups utilizing severity at first observation (6 weeks or 12 months for the primary outcome). Then we will compare groups using severity at final observation. This will allow us to determine whether one group has a higher 'surgical failure' rate and whether recurrent trichiasis progression varies across interventions. We will conduct both unadjusted and adjusted analyses.

Eyelid Contour Abnormalities:

Primary analyses of eyelid contour abnormalities will be based on a dichotomous variable: presence or absence of moderate/severe contour abnormality at the last study visit where the participant was seen between 6 weeks and 12-18 months, , or at last visit before repeat surgery using the photograph grade, which will be based on the definitions below. For the purposes of this analysis, mild will be combined with "no abnormality" and moderate and severe will be combined to form the "moderate/severe contour abnormality" group.

Abnormality	Definition
Mild	Vertical deviation from the natural contour, 1 mm in height (less than half the pupil height in daylight) and affecting 1/3 of horizontal eyelid length
Moderate	Vertical deviation from the natural contour 1–2 mm in height (about the pupil height in daylight) or affecting 1/3–2/3 of horizontal eyelid length
Severe	Vertical deviation from the natural contour 2 mm in height (more than the pupil height in daylight) or a defect >2/3 of the horizontal eyelid length

(Gower et al. 2012 *PLoS Negl Trop Dis* 6(6): e1713)

Secondary analyses will explore the relationship between incision height and the full range of eyelid contour abnormalities, which will require use of the photographic grade that will be graded centrally.

Targeted versus Actual Incision Height:

We will conduct an analysis to compare the assigned incision height against the actual incision height measured during surgery. If more than 10% of the heights vary by more than 0.5 mm, we will conduct secondary analyses for each of the above analyses to determine whether the results of the actual incision height analyses are similar to the per-protocol analyses. If differences exist, we will report these analyses separately, but will emphasize that the per-protocol analyses are the primary analyses.

New Versus Conversion Surgeons

Analyses will also be conducted stratifying based on surgeons' prior experience. Specifically, we will conduct all above analyses based on whether surgeons were trained on both bilamellar and Trabut simultaneously, or whether they first learned bilamellar and received additional training in Trabut at a later time.

1-day Surgical Corrections

Finally, we will conduct an analysis to determine whether there is a difference in the rate of 1-day surgical corrections by study arm.

10 QUALITY CONTROL AND QUALITY ASSURANCE

We will ensure high quality data collection through the course of the trial by ensuring adequate training of all staff on human subjects research and their roles in the trial. All staff must be certified in their respective roles by the project leaders before interacting with study participants and handling study-related data.

10.1 Training

All personnel will undergo extensive training to ensure consistency in data-collection procedures. We will begin with an ethics training session for all study staff, and ethics certification will be required from each staff member before the study begins. We will then provide an overview of the study design, each team member's responsibilities, and how members integrate to form a cohesive data-collection team. Then, a two-day training session will be held for each data-collection group to ensure they understand forms completion and the details of the data that they are supposed to collect.

The recruitment team, surgical assistants, and study coordinators will be trained on appropriate methods for conducting in-person interviews and use of the data-collection forms. Training for all personnel will include didactic instruction and clinical demonstration with live subjects. Upon completion of training, all personnel will be evaluated for all procedures that they will be asked to perform. Only those who pass certification will continue with the study team.

An independent evaluator will critically examine all surgeons to ensure that they perform high-quality surgery and follow recommended WHO procedures. Each surgeon will be evaluated using the WHO certification checklist and only certified surgeons will be allowed to participate in the study. Dr. Merbs will train the surgeons on how to consistently measure incision heights and incision lengths. We will require kappas>0.7 for each measurement comparing the individual surgeon to Dr. Merbs before the surgeon will be considered proficient in collecting these measures.

The outcomes examiner will be trained on how to grade trichiasis and eyelid contour abnormalities using photographs and actual trichiasis patients. Kappas of 0.7 will be required before the examiner is certified. In the second year of the trial, recertification for all patient examiners will be held at the start of the second series of surgical camps and 12-month follow ups.

10.2 Quality Monitoring

To ensure data integrity and study participants' safety, our plan for data and safety monitoring involves several levels. The first level is the extensive set of data-management activities (see Protocol and Manual of Procedures) to help ensure data integrity. These include daily field-based review of data collection to ensure completeness and accuracy before submitting the data to the data entry team, redundant systems to check randomization schemes, double data-entry practices, and

continuous data-quality monitoring through generation of regular reports. These reports are reviewed by the data manager to initiate data cleaning operations, and by the Principal Investigator, who may initiate re-training exercises or change supervisory practices as needed.

The second level of monitoring includes regular site visits by our senior study team members. Our team of experts will ensure all staff members are proficient in necessary procedures before the study begins. During recruitment, Drs. Bedri and Alemayehu will alternate making monthly visits to the study team to monitor surgical procedures and correct any drift or modifications that have inadvertently arisen. At the start of the 6-week and 12-month visits, Dr. Merbs will return to Ethiopia to evaluate the outcomes assessor and ensure kappas are at least 0.7 for key outcomes (PTT and ECA). Dr. Gower also will visit Ethiopia at the start of 12-month data collection to provide refresher training to all study team members and to monitor data-collection procedures.

10.3 Data and Safety Monitoring Board

With input from NIH, we will assemble a data and safety monitoring board (DSMB) to oversee the study. At a minimum, the committee will consist of a trialist, a statistician, and content experts, including someone with local cultural expertise. We will plan for one DSMB meeting prior to study initiation, and then in-person meetings annually, with at least one scheduled teleconference between in-person meetings, and more as needed or desired by the DSMB. We will prepare summary reports of accumulated data for each meeting.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standards

The investigators will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki and The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

11.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Wake Forest, University of North Carolina, and Johns Hopkins IRBs as well as the National Health Research Ethics Review Committee, Ministry of Science and Technology, Ethiopia for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form written in Amharic and describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign (typically through providing a fingerprint) the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the research record.

11.4 Exclusion of Women, Minorities, and Children (Special Populations)

We will not limit enrollment based on sex or racial/ethnic background. Children will not be enrolled in the clinical trial because trichiasis is uncommon in this age range, and general anesthesia is required for trichiasis surgery on children. Children with trichiasis

will be referred to the nearest location that can safely provide the necessary surgical services.

11.5 Subject Confidentiality

All patient data will be kept secure at all times. Paper-based forms will be stored in locked file cabinets and access will be limited to those who have a specific need to review patient-level information. All study computers will be encrypted following the UNC guidelines and will require passwords for logon to the computer, with a separate password to access the study database.

12 COMMUNITY INVOLVEMENT PLAN

This project will be conducted in Hadiya, SNNPR. The project will actively involve members of the community in several ways. First, we will utilize community members such as trained community based screeners (Eye Ambassadors) to identify potential trial participants. Additionally, during the recruitment and surgery phase of the trial we will employ several individuals from the SNNPR region and provide them with on-the-job training that will provide long-term skills development for them. Specific skill sets that we will develop in the staff are how to conduct clinical research, how to properly collect data, and how to utilize a computer for data entry and management (specifically MS Access). Field staff will be taught how to evaluate trichiasis and how to be a surgical assistant (preparing equipment, recording data, etc). We will also utilize local staff to serve as the follow up evaluators for 18 months following the start of recruitment.

Community members with trichiasis may also benefit by taking part in the clinical trial (receiving trichiasis surgery) itself. These individuals will be followed regularly in their communities, which should allow them to be able to be monitored closely and to quickly identify any additional trichiasis management needed.

13 PUBLICATION/DATA SHARING POLICY

The Executive Committee will be responsible for developing publication procedures and resolving authorship issues. At the start of the trial, the committee will outline the expected primary papers for the trial, and will make initial assignments. As additional papers are identified through the course of the trial, authorship will be discussed at the next Executive Committee meeting. This procedure was followed in our most recent trial, and the investigative team (who comprise the majority of the current team) was happy with this approach. Because the scientific team is relatively small compared with other clinical trials, it is anticipated that all publications will follow traditional authorship instead of corporate or modified corporate authorship.

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. This study will be registered in ClinicalTrials.gov.

The trial investigators fully support the dissemination of data from this clinical trial. In accordance with NIH policies, we will prepare a de-identified dataset for public use. The de-identified data, study protocol and annotated case report forms will be available through a website hosted by the University of North Carolina, and data release will coincide with publication of the primary and pre-planned secondary results, estimated to be completed in 2020. Photographic images of study eyelids will not be shared on the website, as these cannot be completely de-identified. Hence, photographic images will be made available through formal requests from researchers to the University of North Carolina. Researchers requesting these images will be required to sign a data use agreement adhering to the School's and NIH's requirements for maintaining strict confidentiality of all images.