Repeat Surgery for Patients with Post-Operative Trichiasis (PTT) Trial Protocol

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Randomized Controlled Trial
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A Collaborative Operational Research Project between SNNPR, Oromia and Amhara Regional Health Bureau, Orbis International Ethiopia, Fred Hellows Foundation, The Carter Center and University of North Carolina (UNC)

Version Number: 4.0

8 May 2020

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

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List of Abbreviations and Acronyms

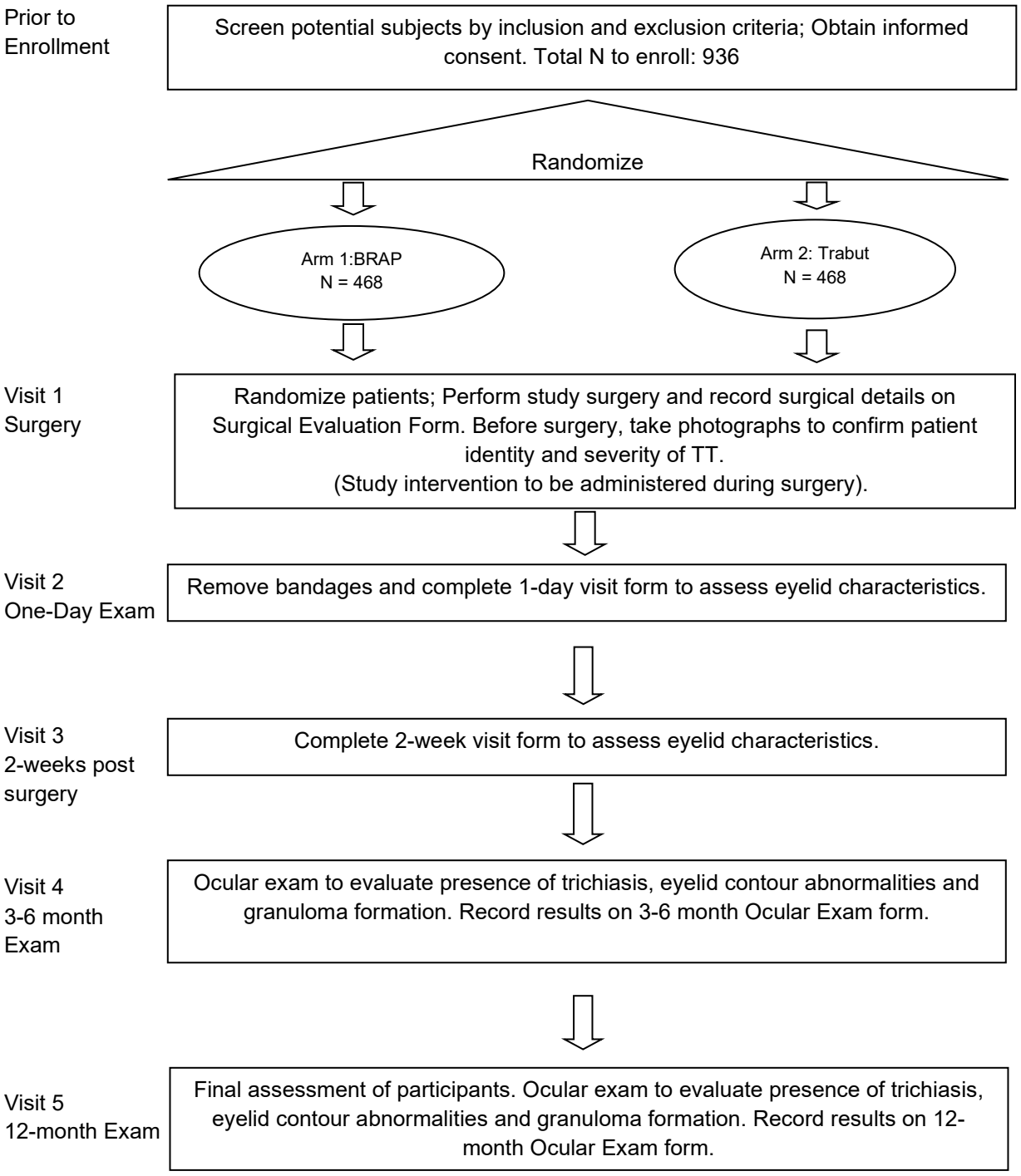
Abbreviation and Acronyms	Name
BLTR	Bilamellar Tarsal Rotation
BRAP	Bevel/rotate/advance procedure
CHW	Community Health Worker
DSMC	Data Safety and Monitoring Committee
ECA	Eyelid Contour Abnormality
FMHACA	Food Medicine and Health Care Administration and Control Authority
FTP	File Transfer Protocol (method for securely transferring data electronically)
IRB	Institutional Review Board
JHU	John Hopkins University
MTSS	Maximizing Trichiasis Surgery Success (clinical trial)
MTSS-PTT	Maximizing Trichiasis Surgery Success – Post-operative Trachomatous Trichiasis (clinical trial)
NEI	National Eye Institute
NIH	National Institutes of Health
PTT	Post-operative Trachomatous Trichiasis
SNNPR	Southern Nations Nationalities and Peoples Region
TT	Trachomatous Trichiasis
UNC	University of North Carolina
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	*Randomized Control Trial of Repeat Surgery for Patients with Post-Operative Trichiasis*
Précis:	In this trial we will randomize 936 individuals with post-operative trichiasis on a 1:1 basis to standard Trabut surgery or the recently developed bevel/rotate/advance procedure (BRAP). Participants will receive trichiasis surgery and will be followed at 1 day, 2 weeks, 3-6 months and 12 months after surgery. The primary outcome is development of post-operative trachomatous trichiasis (PTT) within 12 months after surgery. Logistic regression analyses will be performed to compare the rates of PTT between the two procedures, controlling for demographic characteristics and pre-operative trichiasis severity.
Objectives:	Primary objective: 1) To determine whether the rate of post-operative trichiasis (PTT) differs significantly at 12 months after repeat surgery with the Trabut procedure compared to surgery with a recently developed procedure, the bevel/rotate/advance procedure (BRAP). Secondary objectives: 1) To determine whether the frequency of moderate/severe eyelid contour abnormalities 12 months after surgery differs between the two procedures. 2) To determine whether the frequency of pyogenic granulomas within 12 months after surgery differs between the two procedures. 3) To determine whether the frequency of PTT differs between the two procedures at 3-6 months after surgery.
Endpoints	The primary endpoint for this study is presence of one or more eyelashes touching the globe or signs of epilation after repeat trichiasis surgery.
Population:	Participants will be recruited from three regions in Ethiopia: Southern Nations Nationalities and Peoples Regional State (SNNPR), Oromia, and Amhara. Some participants will be

	recruited from within the US National Eye Institute (NEI) funded clinical trial of incident trichiasis surgeries, the Maximizing Trichiasis Surgery Success (MTSS) Trial, currently taking place in SNNPR. Other non MTSS post-operative trichiasis (PTT) cases from the 3 regions will also be recruited. All individuals with PTT in at least one eye, aged >18 years, and living in the area will be eligible to participate. We aim to enroll 936 individuals during the 2019-2020 surgical campaigns being supervised by Orbis International, The Carter Center and the Fred Hollows Foundation.
Description of Sites/Facilities Enrolling Participants:	Recruitment will take place at rural health centers and health posts in the SNNPR, Amhara, and Oromia Regions of Ethiopia.
Description of Intervention:	A new surgical procedure, the bevel/rotate/advance procedure (BRAP), for the correction of post-operative trichiasis (PTT) will be compared against Trabut surgery (posterior lamellar tarsal rotation)
Study Duration:	1.5 years
Subject Participation Duration:	12 months
Estimated Time to Complete Enrollment:	Recruitment is scheduled for April 2019 through December 2020.

STUDY DESIGN SCHEMATIC:



1.1 Timeline and Feasibility of Adhering to Study Schedule

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

	Year 1 (Sept 2018 – Aug 2019)				**Year 2 (Sept 2019 – August 2020)**				**Year 3 (September 2020-August 2021)**				**Year 4 (September 2021-August 2022)**			
Activity	Q1 (Sept-Nov)	Q2 (Dec-Feb)	Q3 (Mar-May)	Q4 (Ju-Aug)	Q1 (Sep-Nov)	Q2 (Dec-Feb)	Q3 (Mar-May)	Q4 (Jun-Aug)	Q1 (Sep-Nov)	Q2 (Dec-Feb)	Q3 (Mar-May)	Q4 (Jun-Aug)	Q1 (Sep-Nov)	Q2 (Dec-Feb)	Q3 (Mar-May)	Q4 (Jun-Aug)
Ethics Applications	X	X														
Case identification	X	X	X	X	X	X	X		X	X						
Randomization, Surgery, 1-day follow up visits			X	X	X	X	X		X	X						
2-week follow up visits			X	X	X	X	X		X	X						
3-6-month follow up visits				X	X	X	X	X	X	X	X	X				
12-month follow up visits						X	X	X	X	X	X		X	X		
Data cleaning and analyses					X	X	X	X	X	X	X	X	X	X	X	X
Dissemination of Study Findings (manuscripts and presentations)									X	X	X	X	X	X	X	X

2. KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Emily W. Gower, PhD Gillings School of Global Public Health University of North Carolina at Chapel Hill Chapel Hill, North Carolina egower@email.unc.edu
Clinical Site Investigators:	Alemayehu Sisay, MD; Orbis International
Institutions:	Orbis International Rebecca Building Addis Ababa, Ethiopia University of Maryland School of Medicine Baltimore, Maryland Fred Hollows Foundation Addis Ababa, Ethiopia The Carter Center Addis Ababa, Ethiopia
Other Key Personnel:	Shannath L. Merbs, MD PhD (University of Maryland School of Medicine site PI) Belay Bayissasse, MPH (Project Director, Orbis International) Scott Nash, PhD (Carter Center PI)

Personnel	Job Title	Affiliation	IRB of Record	Study Responsibilities
Emily Gower	Associate Professor, Overall study PI and coordinating center director (Coordinating Center is housed at UNC)	UNC	UNC	Assume primary leadership for the study; manage budget; liaise between other organizations; lead manuscripts; report to DSMC and UNC IRB.
Alemayehu Sisay	Country Director, Orbis PI for this Study	Orbis International	UNC	Assume primary responsibility for Orbis team. Manage Orbis budget. Assist in manuscript preparations. Occasionally observe field team activities to ensure protocols are being followed.
Belay Bayissasse	Project Director	Orbis International	UNC	Oversee field-based study team; oversee on-site day-to-day operations; Field team will perform the screening of study participants; establish their eligibility and consent them; follow participants after surgery; report adverse events to the Coordinating Center; send accumulating data to Coordinating Center.

Shannath Merbs	Professor	University of Maryland School of Medicine	University of Maryland School of Medicine	Perform surgeries in Ethiopia; train another oculoplastic surgeon to perform surgeries in Ethiopia; Report to University of Maryland IRB; assist with manuscript preparations
Demissie Tadesse	Ophthalmologist; Independent consultant	Independent consultant	UNC	Observe subset of surgeries to ensure they are being performed in a consistent fashion across surgeons; observe other field activities on a periodic basis.
Scott Nash	Epidemiologist	The Carter Center	Emory	Will provide technical and scientific support to the study staff in Amhara for the duration of the study as needed

3. INTRODUCTION

3.1 MTSS Trial

The Maximizing Trichiasis Surgery Success Trial (MTSS Trial) is an ongoing US National Eye Institute (NEI) clinical trial evaluating 3 methods for performing incident trichiasis surgery in Ethiopia. The study is enrolling roughly 5000 individuals with previously unoperated trichiasis and following them for 1 year. We anticipate that 15-20% of these individuals will develop trichiasis again during the course of the MTSS trial and these will need repeat surgery. We plan to investigate ways to perform repeat surgery.

3.2 Background and Rationale

The World Health Organization (WHO) has set 2020 as the year by which programs should eliminate trachoma as a public health problem. Many countries are rapidly scaling up trichiasis surgery programs to meet this goal. Significant progress has been made, yet much remains to be done, and trichiasis surgery will likely be needed for at least another decade. Post-operative trichiasis (PTT), or the presence of trichiasis after surgery, is a problem that plagues most national programs. In some regions, rates of PTT as high as 50% have been reported[1–7]. However, consensus has not been reached on how these patients should be managed.

Repeat surgical management of these cases is more challenging than primary surgery because of increased scarring resulting from the first round of surgery plus continued disease progression, both of which cause the tarsus to become thicker and more irregular. In most settings where repeat surgery is performed, patients are operated with the same procedure that they received for their initial surgery. Research indicates that second surgeries using currently available procedures have higher rates of poor outcomes than initial surgeries, with over 40% of patients having repeat PTT within 6 months after surgery and 45% experiencing an eyelid contour abnormality (unpublished data).

Recent WHO guidelines indicate that repeat TT surgery should be performed by the most highly skilled health workers available. Furthermore, at the 2017 annual meeting of the Alliance for the Global Elimination of Trachoma by 2020 (GET 2020), significant discussion focused around the need for identifying an appropriate method for management of PTT cases. It has been proposed that a regional training session should be held to train higher cadres of medical staff on how to perform repeat surgery. Before that time, however, it is critical that the best possible method for addressing these cases is determined. To that end, a clinical trial investigating approaches to improving repeat trichiasis surgery outcomes is urgently needed. Here, we propose to conduct a clinical trial comparing a recently developed procedure, the bevel/rotate/advance procedure (BRAP), to the current standard of care used to treat PTT patients.

Surgical Procedure Comparison

The Trabut procedure is the WHO-recommended standard procedure used for initial trichiasis surgeries and is also widely used for PTT[8]. The bevel/rotate/advance procedure (BRAP) is a procedure developed by Dr. Shannath Merbs and colleagues in Colombia. They worked together to develop the BRAP by combining steps from existing procedures in order to address multiple challenges associated with conducting repeat trichiasis surgery utilizing current TT surgical procedures. Specifically, in the typical upper eyelid with PTT, the tarsus is thick and scarred, especially near the previous incision. Additionally, the tarsus thickness can be quite variable across the width of the eyelid. These factors make a repeat Trabut or Bilamellar Tarsal Rotation (BLTR) procedure[9] more challenging to perform successfully because it is more difficult to make a uniform incision across these eyelids and the variability of the thickness makes it challenging to stably rotate the inturned eyelashes.

To address these challenges, BRAP employs a beveled full-thickness incision at a location, slightly different from the incision of the original surgery, and utilizes a different approach for repositioning the inturned eyelashes. BRAP was first evaluated in Mitu, Colombia (see letter from Columbian MOH). Then, following training by Dr. Merbs, Ethiopian surgeons performed BRAP procedures in SNNPR, Ethiopia. Specifically, 23 patients were operated with BRAP. Among these, 31 eyelids were assessed 3-6 months post-surgery. These surgeries were performed through the Orbis program to provide care for these patients, not as part of a research project. Of these eyelids, 16% had PTT, and 84% had **no** evidence of trichiasis at follow up. Of those with PTT, 2 had central trichiatic eyelashes (1 with 1 lash and 1 had 3 lashes). Comparatively, among 4 eyelids operated with Trabut during the same period, only 50% had no evidence of trichiasis at follow up. These initial surgeries suggest that this procedure is likely to have a lower rate of second post-operative trichiasis. We believe this procedure may have more success than currently available TT surgery procedures because of the incision location and orientation and the manner in which the eyelashes are repositioned during the procedure.

3.3 Potential Risks and Benefits

Potential Risks

The risks associated with this study are minimal. Repeat surgery to treat post-operative trichiasis is a standard practice commonly performed in many countries, and all subjects enrolled in this study would be offered repeat surgery regardless of whether they participate in the clinical trial. Theoretically, a newly-developed procedure utilizing a new method for repositioning lashes could ultimately be found to have higher rates of post-operative trichiasis or eyelid contour abnormalities. Preliminary data suggest that this new procedure is not associated with an increased risk of eyelid contour abnormalities or of higher post-operative TT rates. 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. The team will give patients surgery even if they decide not to participate in the study. In the study, we will evaluate patients at 3-6 months and 12 months after surgery. Participants may view this as a benefit.

OBJECTIVES AND ENDPOINTS

3.4 Study Objectives

This study has one primary objective:

1) To determine whether the rate of post-operative trichiasis (PTT) differs significantly at 12 months after repeat surgery with the Trabut procedure compared to surgery performed with a recently developed procedure, the bevel/rotate/advance procedure (BRAP).

This study has three secondary objectives:

1) Determine whether the frequency of moderate/severe eyelid contour abnormalities at 12 months after surgery differs between the two procedures.
2) Determine whether the frequency of pyogenic granulomas within 12 months after surgery differs between the two procedures.
3) Determine whether the frequency of PTT differs between the two procedures at 3-6 months after surgery.

3.5 Study Endpoints

Post-operative Trichiasis

We will evaluate post-operative trichiasis at two time points after surgery: 3-6 months and 12 months. A patient examiner 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 3-6 months or 12 months, 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 3-6 month visits. For primary analyses, the eyelid contour grade at 12 months will be used.

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 3-6 months and 12 months. All granulomas will be noted, regardless of size.

4. STUDY DESIGN

4.1 Overall Design

This study is a randomized controlled trial comparing two surgical procedures for the management of post-operative trichiasis. Individuals are eligible if they have at least one eye with post-operative trichiasis. Participants are identified either from the MTSS cohort at the MTSS 12 month visit or from screening patients for PTT using surgical logs from existing country programs throughout the three regions and/or conducting screenings during household visits. Individuals will be consented and enrolled on the day they have surgery. We will enroll up to 936 individuals and randomize them on a 1:1 basis to surgery with BRAP or surgery with Trabut. They will be followed for 12 months to assess development of repeat post-operative trichiasis and eyelid contour abnormality.

4.2 Scientific Rationale for Study Design

The BRAP has been used in two countries and initial study outcomes are excellent. A larger, randomized study is required to determine whether BRAP is superior to Trabut.

4.3 End of Study Definition

Each study participant reaches the end of the study at 12 months after surgery.

4.4 Data Collection and Management

Data will be collected primarily electronically through customized Open Data Kit (ODK) forms on Motorola Moto X Pure Edition, Samsung S8, and Samsung A9 phones. At the end of each day, data from the phones will be downloaded to a customized Access database. The Access database will be stored on a UNC approved, encrypted laptop. Both the laptop and the database will include password protection. Each week, the project director will transfer accumulated data to the UNC Coordinating Center. This transfer will be done via a secure File Transfer Protocol (FTP) connection.

All data will be collected by trained staff members who have completed human subjects' research training.

Data will primarly be collected on encrypted mobile phones. All devices will be encrypted and password protected. They will be stored in locked offices each night.

Adverse events (AE) will be monitored throughout the study. At surgery, the data collection form will have specific questions regarding each of the possible adverse events that could happen during surgery (excess bleeding, division of the eyelid margin). If an event is encountered, the project director will report it to FMHACA in writing, within 48 hours of occurrence of the event according to the authority guideline, and to the PI (Dr. Gower) within 72 hours. This report will include measures taken to mitigate the event. At the 2-week and 3-6 month and 12 month visits, deaths and

hospitalizations will be proactively collected (the data collector will ask the participant if they have been hospitalized; death will be noted if a family member reports the participant has died). Any AEs occurring at these visits will be reported to the Coordinating Center within 72 hours. At all visits, deaths will be noted and reported to the Coordinating Center within 72 hours. Whenever an AE is reported to the Coordinating Center, Dr. Gower will assume responsibility for sharing with the appropriate parties. If an event could possibly be related to the study treatment, she will share the details of the event with the study monitor, who will review the data in a masked fashion to determine whether it could be related to the study procedure. He also monitors all aspects of the study assuring Good Clinical Practice (GCP) of the trial. Therefore, he will have responsibilities with direct accountability to the sponsor with periodic monitoring, reporting the findings to the sponsor. We will follow the Data and Safety Monitoring Board's guidelines on reporting these events to them.

5. STUDY POPULATION

Participants will be recruited from three regions in Ethiopia: SNNPR, Oromia and Amhara. Some participants will be recruited from within the US National Eye Institute (NEI) funded clinical trial of incident trichiasis surgeries, the Maximizing Trichiasis Surgery Success (MTSS) Trial, currently taking place in SNNPR. Other non-MTSS post-operative trichiasis (PTT) cases from the 3 regions will also be recruited. All individuals with PTT in at least one eye, aged >18 years, and living in the area will be eligible to participate. We aim to enroll 936 individuals during the 2019-2020 surgical campaigns being supervised by Orbis International, The Carter Center and the Fred Hollows Foundation. The Carter Center will be responsible for the screening and identification of patients in Amhara, while the Fred Hollows Foundation will be responsible for conducting screening in Oromia.

We will not exclude subjects based on race or gender.

5.1 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 post-operative upper eyelid trichiasis needing surgery
- Willing to comply with all study procedures and be available for the duration of the study

5.2 Subject Exclusion Criteria

Any individual who is unable to provide informed consent will be excluded from participation in this study.

5.3 Strategies for Recruitment and Retention

Subjects will be identified on the day that they present for their 12-month follow up visit for the MTSS Trial in the SNNPR region or from surgery logs from programs conducting village-based screening in all three regions. List of patients previously identified to have PTT during survey activities or programmatic follow-up activities may be consulted to determine potential study candidates. Trained case finders may also be used to conduct house-to-house visits to identify potential study candidates. Patients found to have post-operative trichiasis in at least one upper eyelid that had surgery performed in the MTSS Trial will be eligible to have repeat surgery performed as part of the PTT trial. Patients suspected of having PTT (and thus may be eligible for the study) will be assessed by surgeons to confirm eligibility. Surgery will not be performed that day. Instead, the team will schedule surgery days for that district after determining how many patients in the area have PTT of sufficient severity to warrant surgery. All recruitment and screening activities will be conducted by the coordinating partner in that region—The Carter Center in the Amhara Region, the Fred Hollows Foundation in Oromia, and Orbis in SNNPR.

On the day of surgery, an examiner will visit the patient and discuss the study as well as the opportunity to have repeat surgery. If the patient agrees to repeat surgery s/he will be brought to the surgery site where she will meet with a consent specialist who will provide a full description of the study and will complete the consent process if the patient is eligible and interested.

All repeat surgery trichiasis patients will receive surgery free of charge, regardless of participation in the trial. If a patient has patient has bilateral post-operative trichiasis and elects to have surgery on both eyes, both eyes will be enrolled in the study. Patients that are not eligible for the study but are presenting with TT will be offered surgery at no cost by the program staff of the coordinating organization.

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.

6. STUDY INTERVENTION

6.1 Study Intervention Description

Participants will undergo either the Trabut procedure or the BRAP. Both procedures are performed under local anesthesia.

6.1.1 *Trabut*

The Trabut procedure is the WHO-recommended standard surgical procedure used for initial trachoma trichiasis surgeries and is also widely used for PTT[8,9]. The eyelid is fixed on the Trabut plate and an incision 3 mm from the eyelid margin is made through the conjunctiva and tarsal plate, without cutting the orbicularis muscle. The muscle is dissected from the tarsal plate in both fragments, and the fragments are re-sutured so that the eyelid margin is rotated outwards and the eyelashes no longer touch the globe. For further details, refer to the WHO Yellow Manual.

6.1.2 *BRAP*

Beveled Incision

A Trabut plate is used to evert the upper eyelid in the standard fashion for Trabut surgery. (Fig. 1A, and Fig. 22 and 23 in yellow manual). A caliper is used to measure 3 mm (“C” in Fig. 2C) superior to the eyelash follicles on the conjunctiva across the width of the eyelid. The sharp point of the caliper or the scalpel blade can be used to make small scratches in the conjunctiva to delineate this position. This often corresponds to the scar or a portion of the scar from the original TT surgery (“scar” in Fig. 2B). A scalpel is used to make a tarsal incision along the marked position, beveled towards the eyelash follicles with care not to cut the follicles (the incision is the line between “B” and “D” in Fig. 2). Note that this beveled incision is in contrast to the typical Trabut incision that is made perpendicular to the plane of the upper eyelid tarsus. Upon completion of the tarsal incision, sharp dissection between the scarred orbicularis and the scarred and thickened proximal tarsus is performed (Fig. 2D). White scar contributing to an eyelid contour abnormality is resected (Fig. 2E), and dissection is continued between the orbicularis and tarsus to the top of the tarsus (Fig. 2D). After dissection and release of the scar from the original TT surgery, the contour of both the beveled, distal fragment and the larger, proximal fragment should be normalized (Fig. 1B) The Trabut clamp and traction suture are removed.

Rotation and Advancement

The beveled fragment is then externally rotated (Fig. 2D), and the proximal tarsal fragment is advanced downward (Fig. 1C, Fig. 2E). The cut edge of the beveled distal fragment is positioned 1 mm above the cut edge of the proximal fragment (Fig. 2F).

Suturing

If excess upper eyelid skin noted, a horizontal mattress suture (the “high” suture) is placed through the skin 10 mm above the lash line as the approximate position of the upper eyelid crease and through Muller’s muscle just above the top the upper tarsus using 5-0 polyglactin 910 (Fig. 2F). Although, this suture is not tied until the end of the procedure, it is important to check that it is placed properly and does not undo the advancement when it is tightened. The relative position of the tarsal fragments is stabilized with horizontal mattress sutures as follows. Starting centrally, the suture is placed backhand from just above the lash line, through the distal fragment, and through the proximal tarsal fragment. The needle is repositioned in the standard forehand position, and the suture is advanced horizontally by 3 mm and is placed thorough the proximal tarsus, through the distal fragment, and exiting just above the lash line. At least 2 additional sutures are placed in the same fashion, nasal and temporal to the central suture. The 3 sutures are tied. The 1 mm advancement should be uniform across the eyelid. One or two additional sutures can be placed for optimum contour if necessary. The “high” suture is then tied (Fig. 2F).

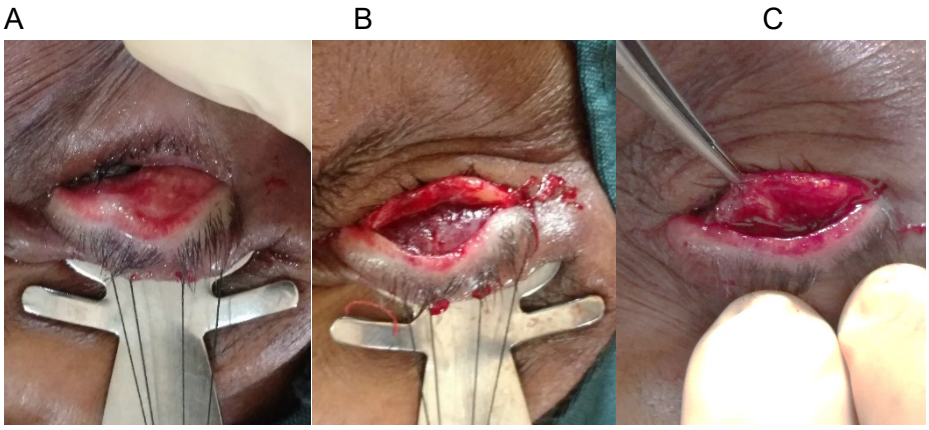


Figure 1. Initial steps of BRAP. A) Eversion of the upper eyelid with an eyelid contour abnormality over a Trabut plate. B) Upper eyelid after completion of the beveled incision, release and removal of the scar tissue, and normalization of the eyelid contour abnormality. C) Demonstration of ability to advance the proximal tarsal fragment, confirming adequate dissection.

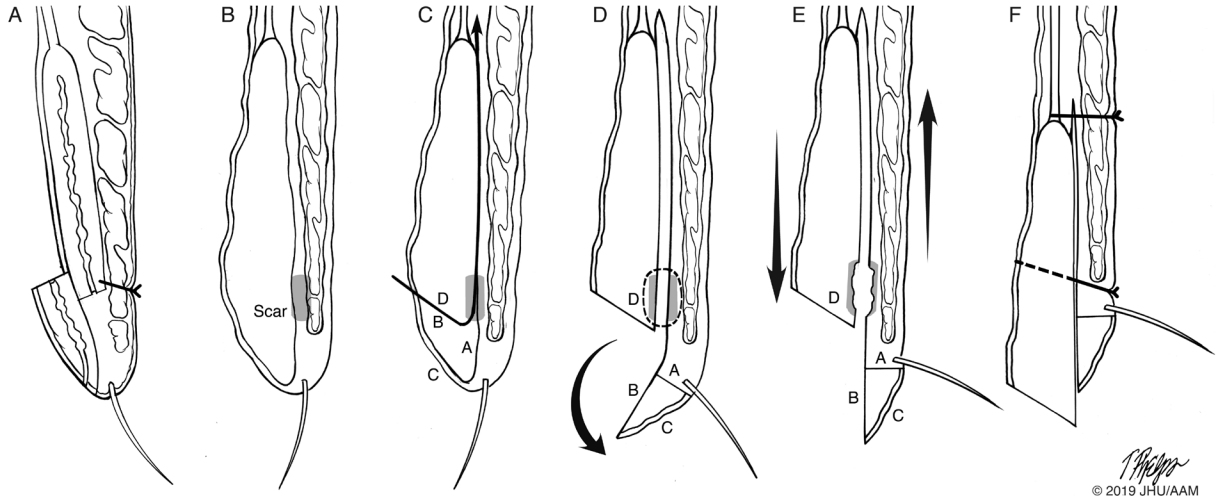


Figure 2. BRAP. A) Sagittal view of an upper eyelid immediately after Trabut surgery. B) Appearance of the upper eyelid after healing from Trabut surgery showing thickened tarsus in the region of the scar and recurrence of the entropion and post-operative trichiasis. C) A beveled incision through the tarsus is made along the line between B and D. The incision is continued superiorly between the orbicularis and tarsus to the top of the tarsus (arrow). D) Scar tissue in the region of the prior surgery (gray shading circled by dashed line) is identified and removed if needed. The distal fragment is externally rotated (large arrow). E) The larger proximal tarsal fragment in advanced downward and the smaller, rotated, distal fragment is recessed upwards. F) The cut edge of the beveled distal fragment is positioned 1 mm above the cut edge of the proximal fragment. The advancement is stabilized with three horizontal mattress sutures (lower suture) placed nasally, centrally and temporally. If needed, an additional horizontal mattress suture is placed centrally from the approximate upper eyelid crease (10 mm) to Mullers' muscle (higher suture).

We believe that BRAP may have more success than currently available TT surgery procedures because the margin fragment is recessed away from the eye creating more distance between the trichiatic lashes and the cornea. Additionally, the beveled incision creates a marginal fragment that is thinner and more uniform in thickness than the fragment created in an eyelid with PTT by the Trabut or BLTR procedures, making it easier to rotate, recess and stabilize during the healing period.

6.2 Randomization Procedures

Participants will be randomized at the participant level on a 1:1 basis to one of two arms: 1) the BRAP procedure or 2) the Trabut procedure. If both eyes need surgery, they both will have the same procedure performed. Dr. Gower will oversee generation of the randomization assignments at UNC. We will utilize random, permuted blocks of varying sizes to ensure balance between arms on a frequent basis.

Randomization assignments will be prepared by UNC staff in Chapel Hill, 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.

Randomization will occur on the day of surgery in order minimize chances of randomizing an individual who does not present for surgery.

The envelope will be opened in the surgery room by the surgical assistant. The surgeon and surgical assistant will both confirm verbally with one another the assigned surgical procedure at the start of the procedure. They will be required to indicate the assigned procedure on the surgical evaluation form as well as the procedure they ultimately perform.

The randomization assignments will be developed at UNC. After each surgical outreach camp period, reported assigned surgical procedures will be compared against the master table to ensure the assigned procedure is consistently being reported for each participant. Details on monitoring are available in the quality assurance section.

6.2.1 *Masking Procedures*

The study subject and the outcomes assessor 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.

In order to ensure the outcomes assessor is masked, s/he will not be present at the surgical site, and s/he will not have access to data from the baseline and surgical visit. However, because one procedure involves a full-thickness incision and the other does not, we expect that the outcomes assessor will be able to determine which procedure many of the patients received through visual inspection. Thus, we will use photographs as a backup to verify the outcomes reported, by holding cardstock to cover the skin incision scar in the photographs so that evidence/lack of an incision is not visible.

6.3 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 and are performing the correct procedure. After each surgical outreach period, the Coordinating Center (CC) will compare the assignment reported on the Surgical Evaluation form against the actual assignment.

6.4 Procedures for Training of Clinicians on Procedural Intervention

6.5 Dr. Shannath Merbs will train up to two Ethiopian surgeons (ophthalmologist and IECW) in how to perform the BRAP procedure. Then Dr. Merbs and the Ethiopian surgeons will review/discuss the Trabut procedure steps to ensure that they both plan to perform the procedure in the same way. Dr. Merbs will monitor the surgeries to

ensure that all surgeons are performing the two procedures in the same way.Procedures for Ensuring BRAP Surgery is Performed According to Study Procedure

1) We will provide the study surgeon with professional sketches of the surgery procedure, and Dr. Merbs will review these steps with him. The surgeon will take these sketches with him to the surgery site each time he performs the BRAP procedure.
2) Dr. Merbs will be present for the first two surgery recruitment periods. She will observe the study surgeon closely to ensure all steps of the procedure are understood and being followed. Once he is performing all steps independently and consistently, she will periodically observe his surgery, but she will continue to examine each patient at the end of surgery to ensure that the surgery was performed according to the study procedure.
3) After two surgical periods, if Dr. Merbs is comfortable with the study surgeon performing surgery in her absence, the surgeon may proceed to perform study surgeries independently. At the start of each surgery period, he will review the surgical sketches to refresh his memory on the surgical approach and will be encouraged to have the project manager communicate with Dr. Merbs to address any questions or concerns.
4) In Dr. Merbs absence, a second individual will be present at the surgery site to review completed surgeries and ensure the suture and incision placement follow the protocol.
5) Each week that study surgeries are performed in Dr. Merbs' absence, images of the eyelid immediately after surgery will be uploaded to the study's secure shared folder. Dr. Merbs will review each image to ensure that there are no systematic differences from the study procedure.
6) If systematic differences are noted, Dr. Merbs will contact the project manager and study surgeon to discuss and address them.

6.6 Study Procedural Intervention Description

Surgeons will receive the surgical procedure assignment just prior to surgery for that participant. Immediately before beginning surgery, the surgeon will confirm with the surgical assistant whether the procedure is BRAP or Trabut.

7. STUDY DISCONTINUATION, PARTICIPANT DISCONTINUATION OR WITHDRAWAL

In this trial, all subjects will receive repeat trichiasis surgery using the BRAP or Trabut procedure. The primary study intervention is surgical procedure, with either Trabut or the newly developed BRAP procedure being performed.

7.1 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.

7.2 Lost to Follow-Up

If a participant misses a follow-up visit, the outcome examiner will make arrangements with the Community Health Worker for the two of them to visit the patient's village and home together on one of the 'mop up' days.

If evaluation for a required visit is not completed within the visit window, a Missed Visit form should be completed at the close of the window and submitted with the relevant blank follow up form. At least three attempts should be made to find the participant within the relevant window before a Missed Visit form is completed. If the participant has died, the form can be completed immediately. If the participant has relocated somewhere in the district, efforts should be made to track him/her at the new location. The participant is still eligible for any subsequent visits.

8. STUDY ASSESSMENT PROCEDURES

8.1 Efficacy Assessment

This section lists the procedures and describes the general approach for data collection.

Ocular Examination: The ocular exam will consist of a detailed evaluation of each eyelid. This information will be collected on the day of surgery. At each follow up study visit, the study eye will be assessed for the presence of *repeat* post-operative trichiasis, eyelid contour abnormality and granuloma.

Visual Acuity: Visual acuity will be assessed monocularly at baseline and will be assessed again at the post-operative 3-6 months and 12 months visits; it will be assessed using an Early Treatment of Diabetic Retinopathy (ETDRS) tumbling “E” chart on a smartphone, using the PEEK acuity app.

Trichiasis Surgery: All participants will receive trichiasis surgery with either the BRAP or Trabut procedure.

Photographs: Photographs will be taken of the full face (headshot) and of each eyelid preoperatively, during surgery, immediately postoperatively, and at each follow up visit.

9. STATISTICAL CONSIDERATIONS

9.1 Study Hypotheses

Primary Aim:

Null hypothesis:

1) Surgery performed using the Bevel/rotate/advance procedure (BRAP) will have the same rate of post-operative trichiasis as surgery performed using the Trabut procedure.

Alternative hypothesis:

1) Surgery performed using the BRAP procedure will result in a relative 30% reduction in the rate of post-operative trichiasis compared to surgery using the Trabut procedure.

Secondary Aim:

Null hypothesis:

1) Eyelids operated with the bevel/rotate/advance procedure will have the same rate of moderate/severe eyelid contour abnormalities rate as eyes operated with the Trabut procedure.

Alternative hypothesis:

1) Eyelids operated with the bevel/rotate/advance procedure will have fewer moderate/severe eyelid contour abnormalities than eyelids operated with the Trabut procedure.

9.2 Sample Size Considerations

The planned sample size for this trial is 700 participants. This sample size will give sufficient power to detect a 30% relative difference in post-operative trichiasis rates between the BRAP and Trabut procedures. This estimate is based on the following assumptions:

- 35% of eyelids in the Trabut group will develop post-operative trichiasis during the 12 months following surgery
- Two-sided alpha error = 5%
- Power = 80%
- 10% loss to follow up

In the event that the number of participants is lower than anticipated, we are still adequately powered to detect a clinically significant difference (see table below). For instance, if only 600 participants enroll, we have 80% power to detect a relative difference of 32%.

Power to Detect a Difference between Treatment Groups

	Relative Risk				
Number of Participants	**1.2**	**1.3**	**1.32**	**1.4**	**1.5**
560	44%	72%	77%	91%	99%
600	47%	75%	80%	93%	99%
640	49%	77%	82%	94%	99%
720	53%	82%	86%	96%	99%
800	56%	85%	89%	97%	99%

The subset of 186 participants who enrolled and received surgery prior to August 1, 2019 will be excluded from the primary analysis because they were operated prior to precise standardization of the incision and suture placement. These individuals will continue to be followed and cared for in the same manner as all other study participants.

9.3 Analysis Plan

We will follow these general analysis principles:

- The primary analyses will be performed according to the participant's assigned intervention (intention-to-treat).
- All participants who complete randomization after August 1, 2019 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).

We will use logistic regression analysis for each of the outcomes. In previous trials, we have created time-to-PTT models using Cox proportional hazards with PTT as the outcome. However, with the limited number of follow-up visits, Cox proportional hazards models do not provide much additional information. Hence, we do not plan to conduct such modeling for this trial.

Post-operative Trichiasis Analyses:

The **primary analysis** will be based on the dichotomous outcome: presence or absence of post-operative trichiasis noted at any time point beginning with the 3-6 month visit and within 12 months following surgery (trichiasis noted at either the 3-6 month or 12

month visit will be considered as post-operative trichiasis, regardless of whether there is trichiasis at the final visit). Both unadjusted and adjusted analyses will be performed. Adjusted analyses will account for the severity baseline PTT, with severity defined based on the table below.

Trichiasis Severity Classification	**Description**
Mild	1-4 Eyelashes touching globe, no epilation OR < 1/3 of eyelid epilated, no lashes touching globe
Moderate	5-9 Eyelashes touching globe, no epilation OR 1-4 lashes touching globe and < 1/3 of eyelid epilated
Severe	5-9 Eyelashes touching globe and 1-10 eyelashes epilated OR 10+ Eyelashes touching globe, regardless of epilation status OR >1/3 of eyelid epilated, regardless of lashes touching

(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. Additionally, we will assess the frequency of overcorrection performed at the one-day visit.

Eyelid Contour Abnormalities:

Primary analysis of eyelid contour abnormalities will be based on a dichotomous variable: presence or absence of moderate/severe contour abnormality at the final study

visit (12 months) using the field 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. We will adjust for first procedure performed (Trabut or BRAP) and severity of pre-operative trichiasis.

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 procedure and the full range of eyelid contour abnormalities, which will require use of the photographic grade that will be graded centrally.

Treatment of Missing Data

We have had great success in our trials to date, reporting over 95% follow up at 1 year after surgery in each of our prior trials. However, invariably, some participants will be lost to follow up. To this end, we will conduct sensitivity analyses treating all missing data as success and then as failures. Given that we collect limited external information on this population, it would be difficult to impute the values.

10. STUDY ASSESSMENT PROCEDURES

Visit Type	Timing	Window
Eligibility Screening	Day 0	N/A (potential subjects to be seen during MTSS 12-month visit or identified from programs' surgical logs and screening activities)
Eye Exam, Consent, Randomization and Surgery	Within 3 months of eligibility screening	0-3 months after eligibility screening. If surgery must take place more than 3 months after eligiblity screening, a new baseline exam will be done
1 day post-operative visit	1 day after surgery	1 day after surgery
2 week follow up	2 weeks after surgery	10 – 18 days after surgery
3-6 month follow up	3- 6 months after surgery	12-30 weeks post-surgery
12 month follow up	12 months after surgery	11 to 13 months post-surgery

10.1 Eligibility Screening, Eye Exam, and Consent

Potential participants will be identified through review of the MTSS study data, examination of surgery logs, PTT patient lists from surveys, and through screening of patients from household visits.

Patients will be screened for eligibility by a trained eye care worker acting as a case finder and confirmed by MTSS-PTT study team members. Patients will be required to have entropion, and/or lashes touching the cornea, and/or pain that leads them to request surgery. These criteria are based on the definitions determined by a WHO expert panel held in Geneva on Nov 26-30, 2018. If patients are deemed to meet TT severity inclusion criteria, they will be referred to a consent specialist.

The consent specialists will meet with each PTT surgery patient to tell them about the study and then 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.

<u>Required Procedures/Data Collection:</u>

- Complete Eligibility Screening form (Form 1)
- Obtain informed consent
- Confirm demographic and tracking information from MTSS patient list

10.2 Enrollment and Surgery

When patients present for PTT surgery, a trichiasis surgeon or screener will screen them to confirm post-operative trichiasis and to confirm the patient's identity using either a patient list generated from the MTSS Trial or the screening logs.

After having pre-operative photographs taken to confirm patient identity and presence of post-operative trichiasis, the patient will receive PTT surgery.

Required Data Collection:

- Surgical Evaluation Form

10.3 Follow up Visits

Follow up visits occur 1 day, 2 weeks, 3-6 months and 12 months following surgery. At the 1-day visit, bandages 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 1-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, 3-6 month, 12 months form)
- Adverse Event Form (if applicable)

10.4 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

11. 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
- Periodic assessment of compliance with assignment of surgical procedure
- 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.

11.1 Data and Safety Monitoring Board

With input from NIH, we have assembled a data and safety monitoring board (DSMB) to oversee the study. The committee consists 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. All members of the MTSS DSMB have agreed to serve on the MTSS-PTT DSMB. These members include, DSMB chair Maureen Maguire, PhD (biostatistician and clinical trialist), James Tielsch, PhD (epidemiologist and global health expert), Wondu Alemayehu, MD MPH (Ethiopian ophthalmologist and renowned trachoma expert) and Michael Kazim, MD (oculoplastic surgeon). 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.

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 *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 the patient's native language (Amharic and all necessary local languages, including Yem, Gamo, Afan Oromo, Gedioffa, Wolaitegna, Keffa, Konso, Hadiya, 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.

12.1.2 *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. When the team is travelling out of Hadiya zone and Yem special woreda where the project office is located, the team will establish a temporary office at the capital of the woreda where the surgical camp is taking place. All study data will be temporarily stored in this office until the field work at the area is completed and then all data will be stored at MTSS office located at Hossana, Hadiya.
Safety Oversight

An external monitor will be responsible for reviewing any adverse events related to surgery. He will review photograph images and a written summary of events in a masked fashion. If it appears that the event may be related to the study procedure, he will be unmasked for that study participant to further complete his assessment. The study PI will keep track of all adverse events and will report serious adverse events to the DSMB and regulatory boards in a timely manner. If at any time it appears that the

frequency of adverse events is significantly higher in one study arm, the PI will convene a meeting of the DSMB to discuss the events and determine a course of action.

12.1.3 *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.

The trial will also be conducted with full conformity with national GCP and CTA guidelines.

12.1.4 *Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to University of North Carolina, University of Maryland, and Emory University IRBs as well as the National Health Research Ethics Review Committee, Ministry of Science and Technology (MoST) and Food, Medicine, Health Care Administration and Control Authority (FMHACA) of 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 and EFMHACA before the changes are implemented in the study.

12.1.5 *Exclusion of Women, Minorities, and Children (Special Populations)*

We will not limit enrollment based on sex or racial/ethnic background. Both sexes and all races are eligible for participation.

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.

12.1.6 *Quality Assurance and Quality Control*

We will ensure high quality data collection through the course of the trial by using only staff from MTSS who have already been trained in human subjects research, trial procedures, data collection methods, and their role 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.

12.1.6.1 Training

Quality of data in a clinical trial is highly dependent on the competency of the personnel collecting the data and their ability to conduct their jobs. To this end, as part of MTSS, all personnel have undergone extensive training to ensure consistency and accuracy in data-collection procedures. These same personnel will be responsible for data

collection in MTSS-PTT and are already trained in all of the necessary procedures for the proposed study. Just prior to the start of MTSS-PTT data collection, we will host a training meeting for all study staff to provide an in-depth discussion of the MTSS-PTT trial. For those staff who are already part of MTSS, we will conduct a refresher ethics training session to review key aspects of conducting human subjects research. For any new staff hired for MTSS-PTT, we will conduct a full ethics training session, and ethics certification will be required from each staff member before the study begins. Next, we will conduct training on the MTSS-PTT procedures. We will explain what procedures are the same as in MTSS versus what procedures are different in MTSS-PTT and will review how to perform each of the procedures. Next we will work with each individual team member to observe them practicing their role in MTSS-PTT. Each person will be required to pass certification for their specific job responsibilities before initiating work for MTSS-PTT. As with MTSS, we will require kappa agreement of 0.7 or greater for all key variables (specifically trichiasis grading) before staff can participate in study data collection.

12.1.6.2 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** to help ensure data integrity. These include daily field-based review of data collection to ensure completeness and accuracy, redundant systems to check randomization schemes, double data-entry practices, and continuous data-quality monitoring through generation of weekly reports. These reports are reviewed by the data manager to initiate data cleaning operations, and by the principal investigator, who will 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, Dr. Alemayehu will making monthly visits to the study team to monitor study activities. At the start of 3-6 month and 12 month visits, Dr. Merbs or Dr. Gower 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 the study and at least once during follow up data collection to provide refresher training to all study team members and to monitor data-collection procedures.

Finally, with input from NIH, we will assemble a **Data and Safety Monitoring Board (DSMB)** to oversee the study. The details of this committee are described above.

12.1. Community Involvement Plan

This project will be conducted in multiple regions within Ethiopia to ensure representativness. These regions include SNNPR, Oromia and Amhara. 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 Ethiopia 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).

Community members with trichiasis may also benefit by taking part in the clinical trial (receiving PTT 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.

EFMACA has the right to approve the primary results manuscript before submitting the manuscript for publication. The study team will submit the manuscript to EFMACA and will await comments from the committee. If no response is received from EFMACA within 30 days, it will be assumed that the manuscript is acceptable for publication without further comment.

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 requests made to the University of North Carolina, and data release will coincide with publication of the primary and pre-planned secondary results. Photographic images of study eyelids will not be shared widely, 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.

14. CONFLICT OF INTEREST

On a yearly basis, DSMB members and key study team members will be required to report any real or perceived conflicts of interest. Additionally, study team members are required to complete UNC's annual conflict of interest certification.

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