FLuorometholone as Adjunctive MEdical Therapy for TT Surgery (FLAME) Trial

Manual of Procedures

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A. BACKGROUND AND SIGNIFICANCE

Burden of Trachomatous Trichiasis (TT)

Trachoma is the leading infectious cause of blindness worldwide.[1-4] Trachomatous trichiasis (TT), a sequela of conjunctival scarring resulting from repeated infection/chronic inflammation, is a key mechanism leading to blindness, and also causes severe chronic eye pain: ~1.9 million people are visual impaired from trachoma, including 0.45 million who are irreversibly blind; approximately 3.2 million people have untreated TT and are at risk of blindness in addition to having eye pain.[4] A manuscript currently under review provides an updated figure of 2.8 million with untreated TT.[5]

Surgery for TT

Surgery to relieve trichiasis is one of the four World Health Organization (WHO)-endorsed "**SAFE**" priority interventions for programs aiming to prevent trachoma blindness.[2] The elements of the strategy under the acronym "**SAFE**" include: **S**urgery for trichiasis (inturned eyelashes), **A**ntibiotics, **F**acial cleanliness and **E**nvironmental improvement. Unfortunately, an undesirably high recurrence rate following trichiasis surgery limits the benefits of surgery and also reduces community confidence in the surgery, resulting in less utilization by people who could benefit from it. Reports of the incidence of recurrence of TT after TT surgery ("post-operative TT) have been highly variable, and are hard to combine due to heterogeneous methods used in reporting and especially variability in the severity of TT which is a strong predictive factor for recurrence.[6] In a comprehensive review summarizing reports through 2012, nine of 11 reports of outcomes using the currently WHO-recommended procedures (bilamellar tarsal rotation and posterior lamellar tarsal rotation) had 25% or more incidence of postoperative TT; programmatic results tended to be less favorable than clinical trial results that involved selection and intensive training of TT surgeons (see Table 3, parts A and B, in reference).[6] Reports based on selection and intensive training of TT surgeons would not be expected to be representative of typical programmatic conditions. Clinical trials which did not undertake such training also had higher incidences of postoperative TT.[7,8] A Cochrane review also reported a 20-40% one year incidence of postoperative TT.[9] Taking a conservative interpretation of the available data, we assume that the incidence of postoperative TT, on average, is at least 20% in current TT programs.

Recurrence of TT after TT Surgery ("Postoperative TT")

Post-operative TT is a difficult problem, with worse outcomes of surgical repair than primary TT.[10] According to WHO, repeat TT surgery should be performed by an ophthalmologist,[11] but ophthalmologists rarely are available in the impoverished communities typically afflicted by trachoma. Because of the dire situation of patients who have postoperative TT—with high risk of blindness,[6] ongoing pain,[6] and limited management options—prevention of postoperative TT is of paramount importance.[12]

Reported risk factors for postoperative TT include surgeon skill, severity of preoperative disease, patient age, and ongoing inflammation during the perioperative period.[6,9,13-15] Optimization of surgical

quality is critical for obtaining good results of surgery, and a subject of considerable programmatic effort, but such efforts do not completely eliminate postoperative TT. While large-scale programmatic surgical programs are ongoing (such as that by the Fred Hollows Foundation, see Section 3.3.1.3), because trachomatous trichiasis is driven by repeated trachomatous inflammation while young,[2] new cases of TT are likely to occur for years to come.

RATIONALE FOR THE FLAME TRIAL

Inflammation and TT

Ongoing inflammation in the setting of trachoma is associated with progressive conjunctival scarring,[16] and often is seen in persons with trachomatous trichiasis.[7,14,17-22] Such inflammation only rarely is associated with Chlamydia trachomatis infection;[18,23] the specific causes thereof are incompletely understood. In the National Eye Institute-sponsored STAR Trial, where azithromycin therapy was associated with reduced risk of postoperative TT even though detectable *C. trachomatis* infection was rare, anti-inflammatory effects of azithromycin were cited as one potential mechanism of the benefit observed.[13]

Fluorometholone 0.1% as Adjunctive Medical Therapy for Lid Rotation Surgery in Trachomatous Trichiasis

We are pursuing an agenda to evaluate a new potentially cost-effective approach to improving trichiasis surgery outcomes: perioperative topical anti-inflammatory therapy. Inflammation—potentially induced by the trachoma disease process or surgery itself—most likely contributes to progressive scarring leading to failure of lid rotation surgery in a clinically important proportion of TT cases, and might be susceptible to adjunctive therapy.[9] We hypothesize that adjunctive topical fluorometholone therapy following trichiasis surgery will reduce the risk of recurrent trichiasis and will be acceptably safe. The rationale for the efficacy aspect of this hypothesis is that interruption of inflammation postoperatively would reduce postoperative scarring/contracture driven by ongoing disease-driven inflammation and/or surgically-induced inflammation thus reducing the incidence of TT recurrence (post-operative TT) and other inflammation-related outcomes.

Regarding safety, topical corticosteroid therapy is associated with potential risks, primarily of cataract induction and intraocular pressure (IOP) elevation in susceptible individuals. However, fluorometholone has much lower intraocular penetration than alternative corticosteroids;[24] Its poor delivery of corticosteroid into the eye itself provides an advantage in the setting of TT surgery because the major anticipated side effects of therapy are the result of intraocular effects, whereas therapy only is needed to the conjunctiva/superficial layers of the ocular surface. Fluorometholone indeed has favorable effects on conjunctival inflammation[25,26] such as episcleritis[27] and outcomes of trabeculectomy surgery,[28] and therefore is likely to suppress the perioperative inflammation which we hypothesize may drive the incidence of postoperative TT in a clinically important proportion of cases. In developing countries, fluorometholone is a low-cost generic drug, costing less than USD $1 per 5 mL bottle in some settings, not counting expenses of distribution.

Thus, we hypothesize that fluorometholone will be effective and safe enough for widespread perioperative programmatic use. Given the additional cost that would be incurred by adding

fluorometholone to TT surgery programmatic expenses, we aim to study the cost-effectiveness as well as efficacy and safety of fluorometholone therapy as Adjunctive Medical Therapy for Lid Rotation Surgery in Trachomatous Trichiasis.

Preliminary Data

As an initial step toward evaluating this treatment modality, we conducted a safety-oriented, dose-finding fully masked clinical trial with parallel treatment design and one year anniversary closeout.[29] In this safety-oriented study, one eye undergoing TT surgery was randomized to one drop of fluorometholone 0.1% administered either two times daily for four weeks, or four times daily (for either four or eight weeks); or else a matching frequency placebo (artificial tears).

Patients were randomized 39:39:37:39 to these respective groups, where the placebo group was the aggregated placebo at frequencies of twice or four times daily for four weeks or four times daily for eight weeks (13:13:13). Active treatment was associated with minimal side effects (one elevation of IOP above 30 mmHg in a 4x/day group, which resolved without sequelae after treatment discontinuation; and one allergy to active treatment). The incidence of postoperative TT in the placebo group was 29.3%, vs 17.7%, 19.3% and 23.2% in the respective active treatment groups, an approximate 1/3 lower risk of postoperative TT in the active treatment groups combined than in the placebo group. Postoperative TT occurred in 31.3% of contralateral eyes (which received neither active treatment nor placebo). Thus, while all three active treatment groups had similar efficacy results, the twice daily group had the lowest TT recurrence rate by a slight margin at one year and also had the best safety profile in the preliminary study and based on theoretical considerations. As per design, which exposed a limited number of eyes to the treatments in the safety-oriented study, the differences in postoperative TT incidence were not statistically significant (p=0.29 for the aggregated active treatments vs. placebo). However, the incidence of repeat surgery was significantly less in the active treatment groups compared with the placebo group combined (5.7% vs. 18%, p=0.018, surgery done per masked ophthalmologist's judgment).

B. OVERVIEW OF TRIAL DESIGN

The **FL**uorometholone as **A**djuntive **ME**dical Therapy for Trachomatous Trichiasis (TT) Surgery (**FLAME**) Trial is a prospective 1:1 randomized, parallel design, double-masked, placebo-controlled clinical trial of fluorometholone 0.1% eye drops vs. placebo in eyes with trachomatous trichiasis (TT) undergoing lid rotation surgery. It has a fixed sample size with anniversary closeout. Key aspects of the design and rationale that have major bearing on the approach to data analysis, statistical issues, and data monitoring are noted below:

B.1. FLAME Trial Summary
The Trial's basic design is summarized in Tables 1 and 2:

Table 1: Protocol Summary

Protocol Title:	**FLuorometholone as Adjunctive MEdical Therapy for TT Surgery (FLAME) Trial**
Study Design:	1:1 randomized, parallel design, double-masked, placebo-controlled clinical trial of fluorometholone 0.1% eyedrops twice daily vs. placebo (artificial tears) twice daily in eyes with trachomatous trichiasis (TT) undergoing lid rotation surgery. Fixed sample size with anniversary closeout.
Primary Study Objective:	To assess the efficacy and safety of fluorometholone 0.1% vs. placebo as ancillary therapy for TT surgery
Number of Subjects:	up to 2,500 Patients (~3,250 eyes), 1,250 patients (~1,625 eyes) per group
Study Population:	Subjects with trachomatous trichiasis (TT) undergoing lid rotation/correction surgery at participating sites.
Test Articles:	1) Fluorometholone 0.1% one drop two times daily for four weeks 2) Placebo (artificial tears) one drop two times daily for four weeks Commercial product will be donated (FML® (fluorometholone) Ophthalmic Suspension, USP 0.1%, Allergan, Dublin, Ireland) sterile and repackaged into identical treatment bottles by the University of Pennsylvania Investigational Drug Service.

Visit Schedule:	Study visits at Baseline, four weeks, six months, and one year; -additional visits for clinical care are permitted, as needed, but data collection will not be conducted at such visits. -Patients will be followed until the anniversary closeout at one year after randomization, even if they do not follow the study protocol otherwise.
Primary Outcome Variable:	Incidence of postoperative TT by one year, as determined by trained study team members, defined as: -one or more lashes touching the globe in an eye operated for TT; *and/or* -history of repeat TT surgery; *and/or* -evidence of epilation on clinical examination
Secondary Outcome Variables	
Efficacy *(objective variables we hypothesize may improve with fluorometholone):*	-Incidence of reoperation for postoperative TT (recommended or done) within (w/in) one year -Number and location of lashes touching the globe within ≤1yr -Entropion (presence and extent) within ≤1yr
Safety/adverse outcomes:	-Corneal opacity (Δproportion from baseline) within ≤1yr -overcorrection within ≤1yr -eyelid notching/eyelid contour abnormalities within ≤1yr -lid closure defect within ≤1yr -granuloma within ≤1yr -Pain score over 1 year postoperatively -IOP elevation over 1 year postoperatively -Occurrence of cataract surgery within ≤1yr -Adverse events attributed to study treatment within ≤1yr
Patient-reported outcomes:	-patient satisfaction over 1 year postoperatively -cosmetic outcome over 1 year postoperatively -health utility over 1 year postoperatively
Additional variables:	-Visual acuity with presenting correction over 1 year postoperatively -Compliance of treatment (assessed by study treatment bottle weights) measured at four weeks (completion of treatment)
Health Economic Analysis:	-Costs will be modeled, based on: -Cost of fluorometholone 0.1% acquisition, importation and distribution required to follow the protocol (for a range of countries)

-Observed use of other medications started following baseline in the alternative groups

-Cost of healthcare due to surgical failure and adverse events in the two groups

-The health program's and the patient's perspective will be considered in calculating costs

-Benefit will be based on trial results regarding the reduction in incidence of post-operative trichiasis associated with treatment with fluorometholone 0.1%

-Cost per episode of recurrent trichiasis avoided will be the primary health economic outcome; cost to avoid one repeat surgery will be a secondary health economic outcome.

Masking	- Placebo controlled, double masked. Patients, surgeons and study staff at field sites will be masked. Study Officers also will be masked except Data Center Co-PI is unmasked. Masters level statisticians at the Data Center will be unmasked, but the Data Center PI will be masked. The Data and Safety Monitoring Committee will be unmasked.
Regulatory Status:	Because fluorometholone 0.1% is an approved treatment for the broad indication of eye inflammation in Ethiopia, exemptions for study of investigational new drugs are not required. Regulatory approval by Ethiopian authorities is required for all clinical trials conducted in Ethiopia (Regional Health Office [Oromia in this case], National Research Ethics Review Committee of the Ethiopian Ministry of Science and Technology, and the Food, Medicine, Health Care Administration and Control Authority of Ethiopia).
Stratification Variable:	1) By surgeon/geographical area. Because each surgeon at each region will use medication boxes that contains 20 randomization assignments with equal number for FML and placebo and new medication boxes will be used at each geographical area, the randomization thus will stratified simultaneously by geographical area and surgeon.

STUDY FLOW CHART (Table 2):

Table 2: Visit and Data Collection Schedule					
Assessments	Visit 1 Baseline	Visit 2 Surgery	Visit 3 4 weeks	Visit 4 6 months	Visit 5 12 months
Timing/Interval (Days[D]) pre/post surgery (=D 0)	D -7 to 0	D 0	D 28-35	D 180±60	D 365 ± 90
Informed Consent, Demographics, Randomization	X				
Medical and Ophthalmic History	X			X	X
External Examination using 2.5x magnifying loupe	X			X	X
Visual Acuity, Trachoma & Trichiasis Grading; IOP; Patient reported outcomes (pain, EQ5D)	X		X	X	X
Medication Review	X	X	X	X	X
Adverse Event Review; medical care utilization		X	X	X	X
Surgical Details		X			
Assessment of Treatment Adherence			X		
Subject Exits Study					X
*D=days post TT surgery; IOP=intraocular pressure; EQ5D=EuroQol health utility (Ethiopian form)					

C. MOBILIZATION OF COMMUNITY SUPPORT AND OF PATIENTS

Ethiopia is the home of more patients with both trachoma and trachomatous trichiasis than any other nation in the world, with a burden of 1.2 million cases of TT in 2005 at the time of the latest national blindness survey; trachoma was the second leading cause of blindness in Ethiopia at that time.[30] Oromia is the largest Regional state of Ethiopia, home to nearly 1/3 of the nation's population. Despite its size and proximity to Addis Ababa, it has been relatively underserved by trachoma programs until recently. In the last few years, the Fred Hollows Foundation (FHF) in partnership with the Ethiopia Federal Ministry of Health has been carrying out large scale TT surgery programs, with 68,142 TT surgeries on 46,793 people carried out in 2017, and large scale work ongoing for the foreseeable future.

Anticipated Site for the FLAME Trial

We anticipate working in districts selected from Jimma and East Wollega zones, districts found by the Global Trachoma Mapping Program to have a high prevalence of trachomatous trichiasis (TT),[31] in which a large amount of TT backlog has yet to be cleared as of the time of the study. The districts/"evaluation units" in these zones were found to have a prevalence of TT from 1.0-4.1% of the total population, with the majority of the evaluation units 2% or higher—an exceptionally high prevalence of TT. Based on the FHF current implementation calendar, a sufficient number of districts in these areas will not yet have had high volume outreach, such that we anticipate it will be feasible to carry out surgeries in these zones with a field office based at Jimma, a city with a population of over 200,000 which is home to one of Ethiopia's five ophthalmology residency training programs at Jimma University. The proximity of this relatively large city with a major health training center will help with finding qualified staff for the Field Teams, as well as helping with retention. Jimma also has two

nonstop Ethiopian Airlines flights per day (morning and evening; 55 minutes) from Addis Ababa which will simplify travel for site visitors (such as the principal investigators, supervisors, internal and external monitors) back and forth when needed. Enrollment will take place in Jimma zone first, and if the study sample size is not reached and the TT backlog was cleared, the Field team will continue enrollment in East Wollega zone.

Steps to Implement the Surgical Team Program:

The FHF Surgical Team has responsibility to carry out all steps prior to the day of surgery for FLAME Trial prospective subjects, as well as conducting surgery and any follow-up care needed per medical indications.

The FHF has developed a highly successful approach to finding and operating TT cases in Oromia, which FHF has agreed to employ in collaboration with the FLAME Trial Research Group to carry out the FLAME Trial as the FLAME Trial Surgical Team. These steps, which will be conducted in the Trial by the FHF Surgical Team, include the following:

1) Liaise with Ethiopian authorities to obtain approvals and support for TT surgery mobilization and implementation at the village, kebele (community), zonal, regional and federal levels:

- 6 months before launch of FLAME Trial recruitment: the Surgical Team to inform federal and Oromia regional health authorities of the plan to carry out services in the selected districts (see next section), building upon the favorable relations FHF has with these authorities already.
- 5 months before launch of FLAME Trial recruitment: After informing the high level authorities, and receiving their support, inform zonal health officials (Jimma and East Wollega) of the program and obtain their support.
- 4 months before each of the outreach surgical programs: Inform kebele and village leaders of the upcoming program at each of the 46 sites at which programs will be carried out, and obtain their support

The FHF program also already carries out Zonal Level Planning Meetings, which include Zonal and Woreda level neglected tropical disease leaders as well as kebele (community) administrators and integrated eye care workers, to develop microplans for TT alleviation and other SAFE programs.

2) Establish a Field Office in Jimma (in the same building as the FLAME Trial Field Team office): 4 months before opening enrollment.

3) For each of the outreach sites, mobilize patients from communities to present themselves for TT surgery, including the conduct of an extensive publicity campaign to make the details of the opportunity known and employment of community mobilizers to seek out people who likely have TT and to bring them to the outreach surgical site.

- 2 months before outreach at each of the sites: After obtaining necessary permissions in Step 1 above, organize publicity campaign in each area.
- Hire mobilizers at least two months in advance
- Finalize agreements for short-term employment using standard rates of payment

- Train and deploy mobilizers at least six weeks in advance, to allow time for them to find patients with TT to bring to the outreach. These trained Health Extension Workers (HEW) in communities or other key community persons (kebele leaders or gare leaders) will visit all of the households in their catchment area to find and register suspected TT cases, and inform them of the opportunity to have their TT fixed, and facilitate their transport to the outreach site.
- Pay mobilizers; organize and implement the carrying out of any tax-related and other employer obligations
- Approximately two weeks in advance of the outreach surgical program: Organize a publicity campaign using local media, generalizing the strategies FHF has used previously to the specific context

4) Temporarily deploy TT surgeons from amongst Integrated Eye Care Workers (Eye Nurses) in the area—who typically perform TT surgery in extant Ministry of Health facilities—to carry out the surgeries;

- Organize deployment of TT surgeons beginning three months before each outreach
- Obtain any necessary permissions from surgeons' employers to use their surgeons (typically surgeons will use annual leave for this purpose)
- Finalize agreements for per diem payments using standard rates of payment
- Because the goal of the study is to assess the value of the intervention added to existing programs, the surgeons will receive no further surgical training as part of this program. However, they will receive training regarding the research protocol (see page 41).
- Distribute per diems; organize and implement the carrying out of any tax-related and other employer obligations related to dispensing per diems.

5) Organize and be financially responsible for the TT surgery outreach programs in which FLAME Trial subjects will be treated using standard surgical care, including obtaining permissions from local leaders for each outreach;

- 3 months prior to each of the 46 outreaches: After obtaining permissions, work with the local health center or post and Ministry of Health officials to obtain a site at which to carry out the surgical services.
- Coordinator visits site no less than two months in advance to organize logistical arrangements
- Team convoy, including two TT surgeons who will work in tandem, arrives early on Monday morning and sets up the site for screening and surgery (in cooperation with the Field Coordinating Center's Field Team partnering with them)
- Screen patients for TT
- Operate TT cases (informing the Field Team in advance that surgery is planned, so that they can recruit the patient for the FLAME Trial)
    - Supply azithromycin to those patients undergoing surgery unless they are pregnant or breastfeeding or some other contraindication exists
    - Note that cases not enrolled in the FLAME Trial still will be operated, but will not receive the experimental study treatment or protocol assessments
- Provide prescriptions for patients presenting with non-TT conditions, or refer them to appropriate providers

- Provide follow-up care. Follow-up care is conducted uniformly on postoperative day 1 and also offered within a 7-14-day window.

6) Provide the consumables on site needed to conduct the surgical program;

- 2 months before each of the 46 outreaches, organize consumable and re-usable supplies for providing service to the anticipated number of subjects, including a cushion on the anticipated number of cases lest more than anticipated come
- The budget includes nearly twice as many units of consumables as patients to be prepared for wastage and bilaterality
- Consumables include sutures, surgical sets, ointments, etc on the FHF SOP for TT surgery.[11]

7) Provide routine postoperative care of these patients, including post-operative medications other than the study drug.

- Organize a facility postoperative patients can go to should problems arise, and inform all subjects of its existence (enrolled FLAME Trial patients also can contact the Field Team members should problems arise)
- Organize a place and time for any follow-up visits needed. Typically, FHF uses patient appointment reminder cards and provide them to patients during the post-operative counseling. Suture removal typically is not needed since the team uses dissolvable sutures.

8) Surgical Team Management is responsible to monitor all of the above, provide any corrective actions needed to ensure accomplishment of the goals, and report on progress at least monthly, and initially twice monthly, to the FLAME Trial Executive Committee.

At each of the 46 outreach surgical sites, based on FHF experience in carrying out large-scale TT programs in Oromia, we anticipate that an average of 8 surgeries per day can be carried out.

D. PRE-IMPLEMENTATION TRIAL PREPARATION

Upon receipt of Notice of Grant Award, we will proceed to prepare the trial for implementation. Ten months is budgeted for this activity.

Steps to be taken include:

1. Grant implementation:
   a) Chair's Office and Vice Chair:
      - Implement subcontracts and consultant agreements
      - Begin acquisition of study equipment
      - Appointment of to-be-named staff (Study Coordinator; and Post-doctoral Fellow if funds permit)
      - Complete consent forms and updated version of protocol
      - Submit to MEE and LSHTM IRB's for approval
      - Complete launch version of Manual of Procedures (with Field Coordinating Center, Data Center)
      - Develop and implement communication system for the FLAME Trial
      - Organize the stream of Executive Committee meetings
      - Register the FLAME Trial on www.clinicaltrials.gov

   b) Data Center:
      - Inform Allergan of the notice of grant award; organize final agreements with Allergan and arrange for shipment of FML® for the use of the Investigational Pharmacy
      - Begin acquisition of any study equipment, e.g. investigational pharmacy supplies.
      - Arrange ceding of IRB approval to MEE in order to comply with the Single IRB approval requirement for the study protocol
      - Develop study forms and implement them in REDCap using the Mobile App
      - Develop study database systems, including data stream surveillance programs
      - Begin implementing the Statistical Analysis Plan
      - Pilot test REDCap system from Ethiopia with Field Coordinating Center team
      - Proof the data systems in Philadelphia to ensure no data are being lost and backups are occurring
      - Work with the EC to recruit the DSMC, and organize the stream of DSMC meetings

   c) Investigational Pharmacy:
      - Initiate stability/shelf life testing for study drug
      - Obtain the drug supply from Allergan
      - Begin preparing study drug at an appropriate time before randomization begins.

   d) Surgical Team:
      - Implement the Chair's Office Subcontract
      - Take the actions described in MOP Section C.

e) Field Coordinating Center

- Implement the Chair's Office Subcontract
- Begin acquisition of any study equipment
- Appointment of to-be-named staff (Senior Study Coordinator and the entire Field staff)
- Translate and backtranslate the consent and assent forms from English into Amharic and Afaan Oromoo
- After the first University IRB approval is obtained, submit and obtain IRB approval from regional and federal authorities
- Develop (with the DC and CO) the training and quality control/monitoring programs for the Field Teams/FCC staff
- Implement vehicle and office rental in order to have them place at the right time to begin enrollment.
- Implement an Ethiopian investigational pharmacy to receive study drug from the Penn Investigational Pharmacy, and clear the first batches of medication boxes.

2. Confirmation of Trial Site(s)

Prior to study implementation, we will confirm that the Jimma and East Wollega Zones selected still are appropriate frames from which to select Districts for the study in terms of expected numbers of study participants, and other social and environmental factors: political stability, acceptance by communities, and access to sites. If conditions have changed and selected districts are not available for the study, we will choose other districts in collaboration with the Oromia Regional Health Bureau, the Zonal Health Office and the Fred Hollows Foundation Ethiopia.

3. Obtain Approvals

a) University IRBs

Initial approval will be sought from Massachusetts Eye and Ear/Partners Healthcare, Boston, Massachusetts (Dr. Kempen); and the London School of Hygiene and Tropical Medicine (Prof. Burton). As per NIH "Single IRB" requirements, the University of Pennsylvania will cede IRB supervision to Partners, which will serve as the IRB of record for University of Pennsylvania investigators.

b) Oromia Regional Health Bureau

After obtaining the first academic approval, regional approval will be sought from the Oromia Regional Health Bureau (ORHB). The OHRB will provide approval and provide letters of support to the national/federal review committees. Once approval is obtained from national/federal committees, ORHB will provide a letter to the zonal and district health offices instructing them to collaborate with the research project.

c) NRERC and EFDA:

All clinical trials in Ethiopia have to be reviewed by the National Research Ethics Review Committee at Ministry of Science and Technology; and also the Ethiopian Food and Drug Administration. Approval will be obtained from both committees.

d) Importation of Study Drug and Drug Accountability:

Medication boxes may not be imported until EFDA approval is obtained. Once the approvals mentioned above and logistical preparations are in place, the study may commence.

4. Study Team Recruitment and Training

a) Project Team Recruitment

(1) For the Chair's Office (CO), the CO Study Coordinator will be appointed from the pool of coordinators that exists at Massachusetts Eye and Ear immediately; a recruitment process for the Post-doctoral Fellow will be initiated when/if funds permit.
(2) Senior staff of the Field Coordinating Center include the Senior Study Coordinator who will be recruited at Addis Ababa, and Junior Study Coordinator, a Site Supervisor and Site Administration/Logistics coordinator will be recruited from Oromia Region near the study area.
(3) Senior staff of the Surgical Team, the Data Center and the Investigational Pharmacy at Penn already are employed.
(4) Field Coordinating Center Field Team, four pairs (or more, as needed), made up of a Recorder and an Ophthalmic or Clinical Nurse trained Integrated Eyecare Worker (IECW), who will all be recruited from the Oromia Region, at an appropriate interval before trial implementation to allow training and pilot testing to occur.

b) Project Team Organization:

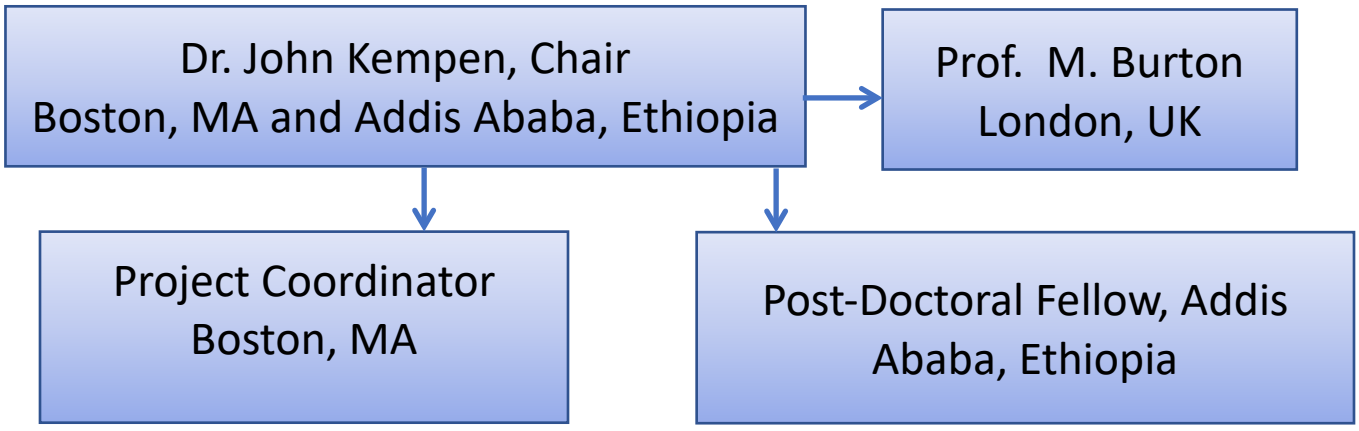
(1) Chairman's Office (Boston, MA, USA and Addis Ababa, Ethiopia):

The Study Chair will directly train and supervise the Study Coordinator (and, if applicable, the Postdoctoral Fellow). The Vice-Chair will provide input through the Study Chair and Executive Committee meetings and in an *ad hoc* manner, sharing his wisdom and materials from the four prior trials about TT surgery he has chaired in Ethiopia, as well as sharing wisdom from his ongoing implementation of the Stronger SAFE research program in the Oromia Region of Ethiopia in partnership with the Fred Hollows Foundation.

- The Study Chair will periodically attend Field Coordinating Center staff meetings when present in Ethiopia, in order to strengthen this unit. The Vice-Chair also will attend in person when in Ethiopia. The Study Chair will carry out some site visits with the Field Coordinating Center Director, especially in the early stages of the FLAME Trial implementation.

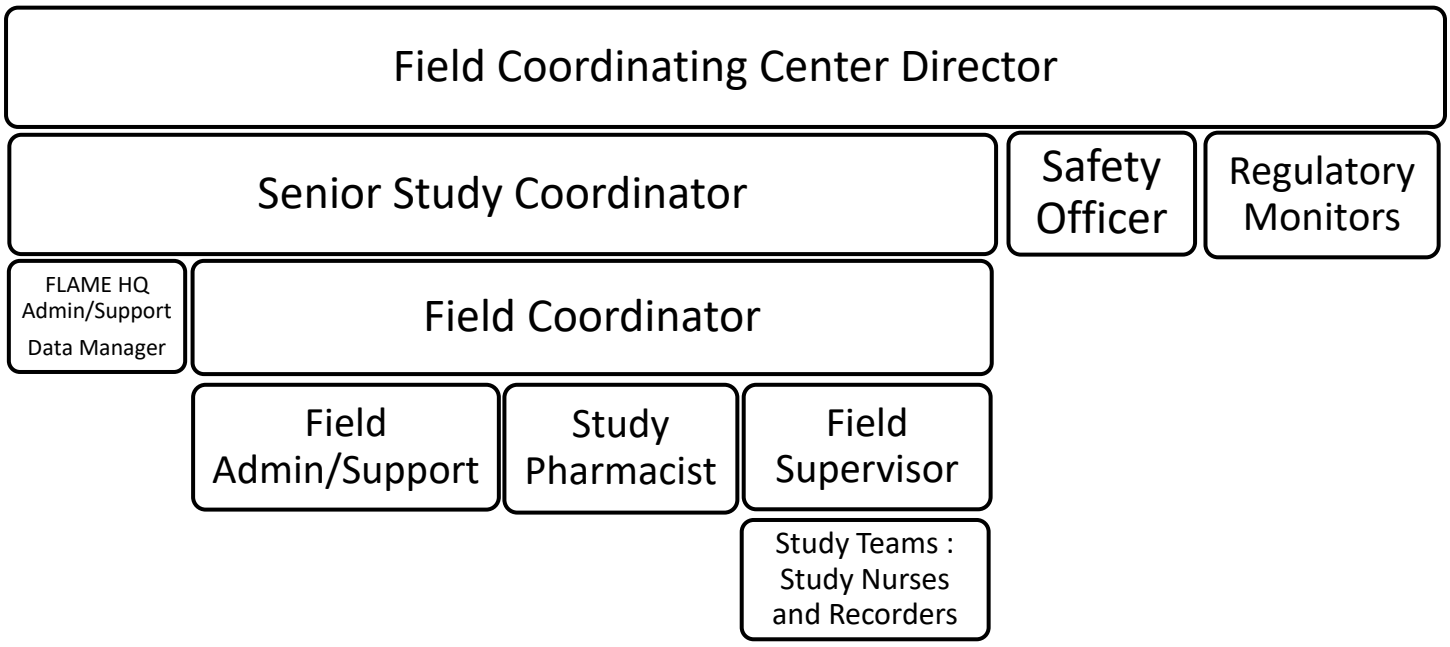
- The Study Chair also periodically will attend administrative meetings of the Surgical Team in Addis Ababa while in Ethiopia, and field site meetings during site visits.

- When present in Ethiopia, the post-doctoral fellow (if applicable) with join the Study Chair at some of these meetings.



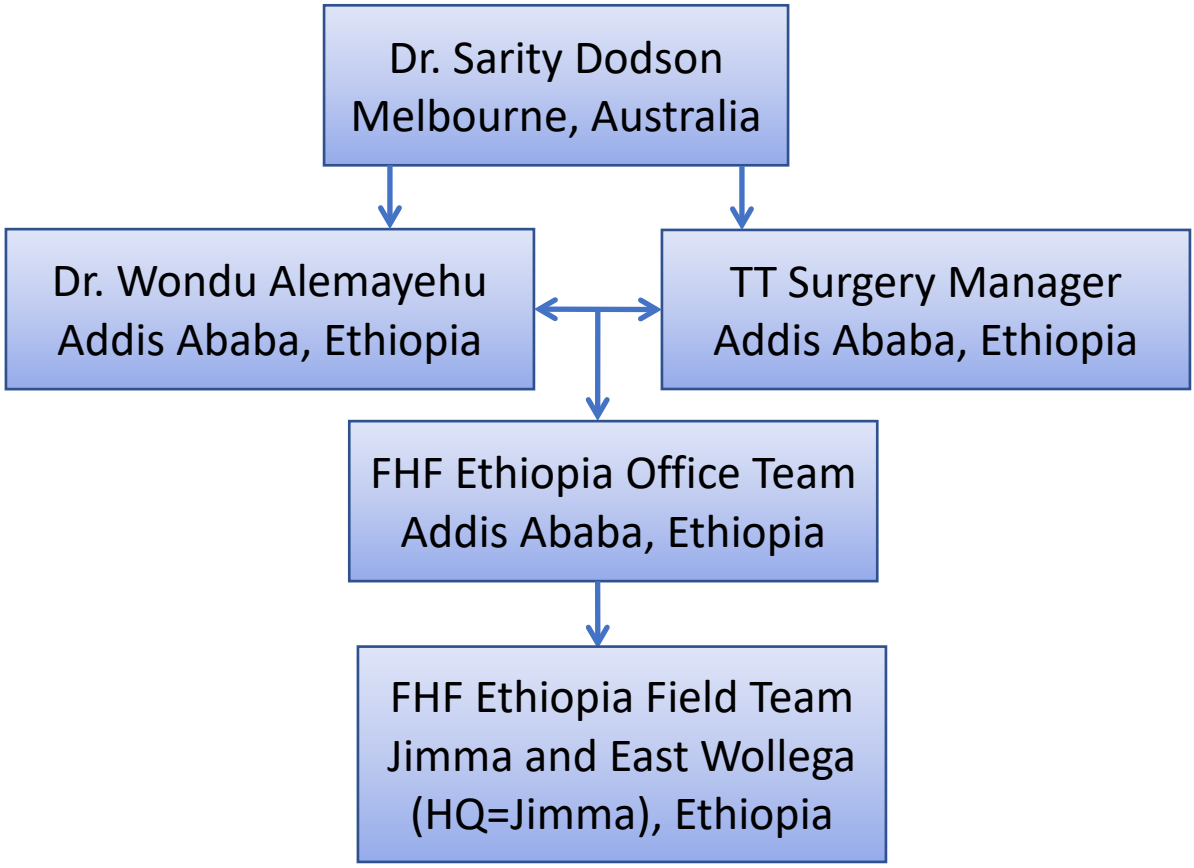
(2) Field Coordinating Center (Ethiopia)

The chain of authority is described in the following Figure. The headquarters staff are located in Addis Ababa, Ethiopia. The Field Team/Staff are located in Jimma, Ethiopia, and travel to outreach and follow-up sites.



(3) Surgical Team (Addis Ababa, Ethiopia and Jimma, Ethiopia)

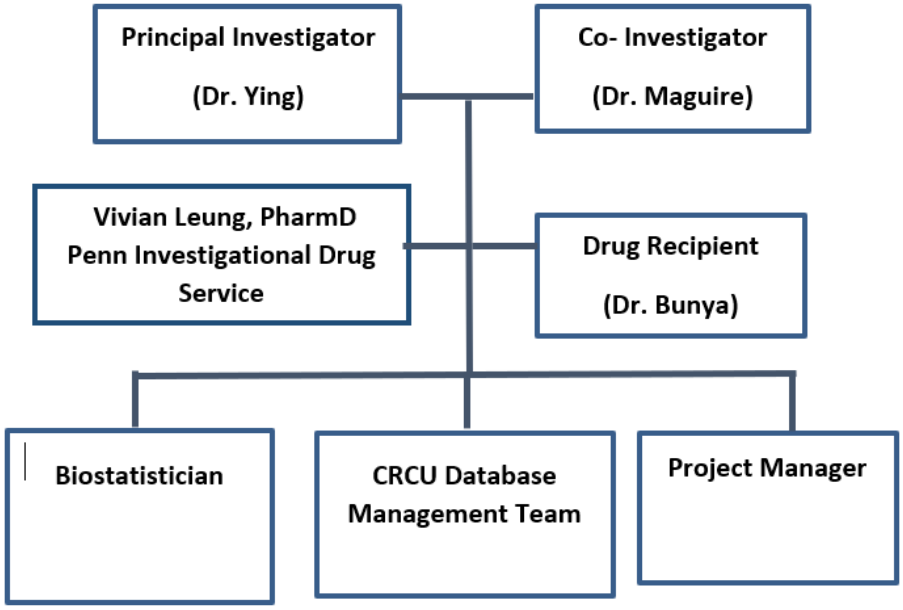
The chain of authority is described in following Figure.



:

(4) Data Center (Philadelphia, PA, USA):

The chain of authority is described in the following Figure:



c) FCC Office and Field Team Training

Live training in Ethiopia will be held for all study staff prior to study initiation. General Training on the Protocol and Manual of Procedures, Good Clinical Practice (GCP), and human subject ethics training will be given by senior investigators, study coordinators, and regulatory staff in person. As in the preliminary trial, Human Subjects and GCP training will be provided by investigators and staff will be certified by the investigators after passing a short test. Role specific training will be provided to each group using the Manual of Procedures. Training techniques will be adapted to this protocol from those employed training staff of the Global Trachoma Mapping Program, which Dr. Abashawl implemented in a region of Ethiopia adjacent to the planned study area, available at: http://tropicaldata.knowledgeowl.com/help/training-system-for-trachoma-prevalence-surveys.

Study nurses who will do the eye examinations will be trained on how to make the various assessments including the TT patients eligibility for the study and how to conduct interviews. While they typically will know how to carry out such activities already, and will be hired partly on the basis of the extent of such knowledge, further training will be implemented to make doubly sure that they are capable of making the assessments, and understanding how they relate to data documentation in the FLAME Trial, so that they can provide valid data and supervise their paired recorder to make sure it is being entered accurately. Prior to the study initiation, the study nurses will all be standardized in their grading capabilities against a gold standard, which is also the ophthalmologist serving as the Safety Officer in the case of the FLAME Trial. Recorders will be trained on how to complete study forms on both androids and paper forms. Practical training will be conducted at JUDO and in the field at one or more non-study outreaches in collaboration with the Fred Hollows Foundation and Jimma districts officials. A two weeks training is planned with protocol and ethics training, data entry and mobile softwares and IOP iCare tonometer use, followed by role specific training at JUDO and field practice

training. The study nurses will also be certified on grading by the gold standard, a certified ophthalmologist trainer.

Training for the use of REDCap and Mobile App will be given using a video prepared in advance and a practical training will follow. In addition, patients' ocular and face photo capturing on ODK application will be demonstrated. The field study team will also be trained in the use of the Peak Acuity app for visual acuity measure. The measurement of intraocular pressure (IOP) using an iCare tonometer will be included in the classroom and a practical training on study team members, and patients at the Jimma University Department of Ophthalmology (JUDO) will take place.

d) Surgical Team Training

Community based case finders will be trained by the Fred Hollows Foundation staff carrying out this activity throughout Oromia. Training follows the Training Curriculum for Trichiasis Case Identifiers developed by the International Coalition for Trachoma Control and adopted by the Ethiopia National Trachoma Task Force (NTTF), available at http://www.trachomacoalition.org/sites/default/files/content/resources/files/ICTC%20TrichiasisCaseFindersTrainingCurriculum%20111915%20v6.pdf. Training will ensure case finders are capable of conducting systematic searches for trichiasis in their catchment area, identification of trichiasis, counseling of trichiasis patients and mobilizing suspected trichiasis patients on surgical outreach days.

TT Surgeons**:** Pursuant to the study's plan to assess the study drug's impact on an extant program, TT surgeons will not receive special training as part of the study (over and above their prior training and certifications).

Other Surgical Team staff are already trained and well-practiced at implementing programs of this nature. However, supervision will be carried out and remedial training implemented as necessary.

5. Replacement of Resigned Team Members:

If any study team member leave, a replacement will be recruited and trained prior to being deployed in the role for which they have been hired. The field supervisor or trained backup nurses from the JUDO and additional backup recorders will fill in until replacements are hired. A higher level of supervision by the field supervisor (and as needed by the senior study coordinator and FCC director), and site visiting will be given in the first six months after hiring.

E. CLINICAL TRIAL IMPLEMENTATION

The "**FL**uorometholone as **A**djunctive **ME**dical Therapy for TT Surgery (**FLAME**) Trial will be conducted in field sites in Ethiopia. The patient interaction activities will be primarily performed by the **Field Teams** from the Field Coordinating Center (FCC) and **the Surgical Team,** which is a subset of an extant trachoma control program in the Oromia Region of Ethiopia implemented by the Fred Hollows Foundation dedicated to the purposes of the FLAME Trial. Their responsibility of Field Teams and Surgical Teams are described below. Standard Operating Procedures are given in Annex**.**

1. Responsibilities by Field Teams and Field Coordinating Center (FCC):

The FCC is located at Berhan Public Health and Eye Care Consultancy in Addis Ababa, Ethiopia, led by Berhan's Director of Programs, Dr. Aida Abashawl, MD, MPH and funded by a Chair's Office subcontract. The FCC performs typical coordinating center functions within Ethiopia, with direct, regular involvement of the Study Chair, and supported by the Data Center's form and REDcap data system. The FCC oversees field implementation of the trial in Ethiopia, employing and supervising all Ethiopian team members except those involved in mobilization and surgery under the Surgical Team. Under Ethiopian regulations, it is necessary for a registered Ethiopian entity to carry out these functions, as only such an entity can employ staff. The roles and activities of the FCC specifically include:

(1) implementing study enrollment and data collection, including employing, overseeing, training/certifying, and supervising the Field Teams—which will have primary responsibility for enrolling, following and collecting data from study participants;
(2) implementing an Ethiopian investigational pharmacy, based in the Jimma Zone, to receive Study Drug from the investigational pharmacy at the University of Pennsylvania, clearing customs, and maintaining Study Drug accountability and distribution in Ethiopia;
(3) implementing in Ethiopia the financial logistics for the study, such as vehicle and office rental and purchasing/maintaining office equipment;
(4) assisting the Surgical Team liaison with Ethiopian authorities (as needed) regarding the study implementation including village, kebele (neighborhood), regional and federal leaders and oversight bodies;
(5) leading the effort to obtain support from and Ethiopian institutional review boards and regulatory approvals at the Oromia Regional and Ethiopian Federal levels (National Research Ethics Review Committee of the Ministry of Science and Technology (primary federal IRB); Ethiopian Food and Drug Administration (which like the FDA in the Unites States, is the authority that regulates drug trials in Ethiopia, implementing a similar level of regulation as an FDA IND Exemption for all drug trials even of Ethiopia-approved drugs like the one studied here), and process yearly renewals of IRB approvals;
(6) implementing and maintaining quality assurance and monitoring procedures for the field teams;
(7) contracting with the Chairman's Office to receive funding to cover these expenses.

2. Responsibilities of Surgical Team:

The Surgical Team is a subset of an extant trachoma control program in the Oromia Region of Ethiopia implemented by the Fred Hollows Foundation in partnership with the Ethiopia Federal Ministry of Health dedicated to the purposes of the FLAME Trial. The offices of the foundation are in Addis Ababa, and field operations are throughout the Oromia Region of Ethiopia. The Surgical Team subset dedicated to work on the FLAME Trial is directed by Sarity Dodson (Melbourne, Australia), and co-led by co-investigators Wondu Alemayehu, MD, MPH and the FHF TT surgery manager at the time of study implementation, both based in Addis Ababa, Ethiopia, and funded by a Chair's Office subcontract. Specific responsibilities of the Surgical Team are to carry out patient mobilization and implementation of trachomatous trichiasis surgery program for the study, including:

(1) liaison with the Oromia Health Bureau and Zonal health office authorities to obtain approvals and support for TT surgery mobilization and implementation at the village, kebele, zonal, regional and federal levels;
(2) mobilization of patients from communities to present themselves for TT surgery, including the conduct of an extensive publicity campaign to make the details of the opportunity known;
(3) organizing and being financially responsible for the TT surgery programs in which trial subjects will be treated using standard surgical care, including obtaining permissions from local leaders;
(4) employing TT surgeons from amongst Integrated Eye Care Workers (IECW)—who typically perform TT surgery in extant Ministry of Health facilities—to carry out the surgeries;
(5) providing the consumables on site needed to conduct the surgical program;
(6) providing routine postoperative care of these patients, including post-operative medications other than the study drug and post-op visits.

3 Selection of Field Sites

The FLAME Trial was implemented in Ethiopia's Oromia Region, which the Global Trachoma Mapping Program found to have high levels of TT.[31]

In consultation with ORHB and the FHF Ethiopia, the study was decided to be conducted in Jimma zone, with plans to move the study to East Wellega only if enough study participants are not enrolled to reach sample size.

4 Mobilization

SOP-1: Patient Recruitment/Mobilization

1.1. Purpose- To describe the standard operating procedure for study participants' mobilization and community level sensitization.

1.2. Scope- All the population suspected /confirmed of trachomatous trichiasis shall be mobilized

1.3. Procedures-

a. The zonal health department in liaison with the FHF-E and Berhan Public Health and Eye Care Consultancy (BPHECC) field coordinator carries out mobilization with the site/district(s)
b. The prospective woreda health office personnel, generally the NTD focal person, will be notified and **coordinate activities** with the zonal health department office personnel, the FHF-Ethiopia advisor in Jimma and the BPHECC FLAME Field study team in locating the appropriate sites/kebeles for the study
c. The respective kebele community leaders, health extension workers, teachers, and other local stakeholders (if any) will be notified and receive a quick orientation about the FLAME Trial
d. Then house to house case finding and/or mass mobilization (e.g., using town criers and megaphones, especially during market days or after Friday prayer near mosques or Sunday mass near churches), or else another means of community mobilization will be used for the mobilization
e. The specific time, date and site will be scheduled for preliminary screening and enrollment
f. The BPHECC FLAME field study team will move to the prospective site ahead of time to conduct the study procedure
g. If the study team does not have enough eligible study participants, then the field coordinator and/or the study supervisor will communicate with the woreda health office, zonal health office and the Fred Hollows Foundation-Ethiopia personnel, providing them with a report of the daily outcome and requesting them to take immediate action as needed.

5 Preliminary screening and surgical consent

SOP: Preliminary Screening and participant triaging

Preliminary Screening

1. **Purpose**- To describe the standard operating procedure for triaging surgery eligible participants during each recruitment day. The purpose of preliminary screening is to identify potential study participants who will best fit for the trachomatous trichiasis (TT) surgery.

2. **Scope**- All the people visiting the selected site due to suspected TT complaining of inwards growing lashes, or other people who have interest in being screened due to eye pain or concerns shall be involved in the preliminary screening process.

3. **Responsibilities**- The Integrated eye care workers (IECWs) are responsible and in charge of performing the preliminary screening for the identification of the potential participants eligible for TT surgery and counsel/guide other patients with a non-TT eye problem.

4. **Materials and Facilities required**
   - Examination loupes 2.5x
   - Examination torches
   - Infection prevention kits such as gloves, face masks, alcohol, cotton swab
   - Chairs and tables
   - Patient screening log
   - Pen
   - Separate room(optional)
   - Patient referral form- for postoperative trachomatous trichiasis (recurrent TT cases) and other non-TT cases that require further medical support and management

5. **Procedures**-
   a. The prospective IECWs will go to the selected enrollment site (either a hospital, health service center, health post, or a school) with necessary materials and equipment ideally prior to the Field study team's arrival at the site to begin preliminary screening and setting up for surgery, or otherwise go with the study team, especially at sites that are hard to access
   b. The IECWs will perform their preliminary screening with potential TT patients and pre-surgery activities in a quiet area away from other people at the site
   c. The IECWs will provide health education on trachoma prevention, control, and treatment to the present patients and inform them about the FLAME Trial study briefly if they would like to take part
   d. The patients will line up based on their arrival time, to take turn to be examined by the IECW

e. The IECWs or assistants will register the patients on the patient screening log then will take each participant to the examination room to proceed with the eye examination
f. Patients have to be examined indoors or under a shade to avoid bright sunlight which produces shadows that make the edge of the eyelid difficult to see. Patients may also be very sensitive to sunlight.
g. Assist the patient to sit on the examination chair in front of the examiner's chair.
h. Greet the patient and explain what they are going to do and the benefits and risks of the examination beforehand
i. Ask the patient to look straight ahead with his eyes open in the normal way.
j. Use a torch and light up the edge of the eyelid from below.
k. Look at the eyelid from below, and examine the edge of the eyelid, where the lashes emerge. A 2.5X magnifying loupe is helpful to clearly see the trichiasis.
l. Have the patient look up. Sometimes, it is easier to see dark lashes against a white conjunctiva. While still looking from below and from the side, look for lashes that are pointed downward. There may be need to also examine the eye from the side to see if the lash actually touches the eye.

Examination of the cornea: Look directly at the cornea and see if a white or hazy area is present, especially one that covers part of the pupil.

Examination for defective eyelid closure: If the eyelid does not close properly, either because of trachoma or because of previous surgery, a more complicated operation will be needed. Defective eyelid closure is present if the eyelids do not meet completely when the eyes are gently closed, as during sleep. The sclera (the white of the eye) will still be seen in between the eyelids.
Ask the patient to close both eyes gently, and then light the torch from below towards the eye to look for any part that is exposed (not covered by the eyelids).
Patients with an eyelid closure defect need referral to an experienced TT surgeon or an ophthalmologist whether or not they have trichiasis.

5.1. INDICATIONS FOR EYELID SURGERY

5.1.1. Definite indications for eyelid surgery in the community are:

a. one or more eyelashes which turn in and touch the cornea when the patient looks straight ahead
b. evidence of corneal damage from trichiasis
c. severe discomfort from trichiasis
d. TT patient requesting surgery

5.1.2. Contraindications *to performing surgery in the community*:

a. Defective eyelid closure or repeat trichiasis after surgery
b. Childhood. Children need surgery in hospital, possibly with a general anaesthetic.
c. Poor general health
d. TT of the lower eyelid. This is rare but it does occur and will require more assessment by an ophthalmologist.
e. The cases above require referral to an ophthalmologist for management.

5.2. FITNESS OF PATIENTS FOR SURGERY*:*

OBJECTIVE: To be able to assess the fitness of TT patients for surgery. The procedure must cause only minimal risk to the general health of the patient. The patient must be questioned for general fitness.

a. Ask the patient if he or she has any shortness of breath that results in difficulty lying flat for 30 minutes. These symptoms may indicate evidence of heart failure.
b. Ask the patient if he or she knows if they have diabetes ("sugar"), or high blood pressure, and if they are taking medication for these conditions.
c. Very rarely, a person may be allergic to local anesthetic, or have a bleeding disorder. Ask the patient if he or she has received surgery before or experienced any problems with injections of local anesthetic or with excessive bleeding if cut (this does not relate to menstrual bleeding).
d. Does the patient have difficulty in cooperating and following instructions? Be certain this is not simply an issue of differences in dialect or language between the patient and surgeon. If heart failure, known but untreated diabetes or untreated hypertension,
e. Allergy to local anesthetic, or a bleeding abnormality exists, the operation should not be done in a community clinic.
f. Refer the patient to a doctor for management of the condition first, and to consider whether the operation can be performed under medical supervision in hospital. If the patient seems to be unable to follow instructions, the patient may not be able to give a true informed consent and may not be able to cooperate during surgery. Engage the patient in sufficient discussion to decide if the procedure can go forward.
g. If the surgeon identified a patient who qualifies for an upper eyelid TT surgery:
    - Briefly explain to the patient about the possible treatment
    - Explain to the patient that the only treatment option is surgical outward rotation of an in-turned eye lid margin so that the eye lashes return to their normal position.
    - Explain, if it's not operated, it may damage the cornea which can result in irreversible blindness/visual loss
    - Explain to the patient that surgery will be done under local anesthesia
    - Explain to the patient that the dressing/patch will be removed after one day
h. Take surgical consent. [Refer to the Surgical Consent Form: see the section on *Study Forms Completion Guidelines*]
i. Marking: before entering the operating theatre, the eyelid(s) to be operated on will be doubly marked:
    (a) Use sticky tape "plaster" above the eyebrow so that it does not have to be removed preoperatively (it is easier to see plaster than ink so this will be retained).
    (b) Use a marker pen to mark the surgical eye(s). This will provide a marking that can't be removed in the perioperative period.
j. The surgeons transfer those patients who have provided consent to the study team.

6 Consent for study

Eligible participants willing to participate in the study will be asked to give consent. Informed consent will be sought at the surgical site in a quiet area. Each subject must read (or hear read) and sign an informed consent form prior to any study baseline procedures being performed. Potential risks and benefits to subjects participating in this study as well as the voluntary nature of the study will be detailed in the Subject Informed Consent Form. A witness who is not a member of the Field Team also will sign if the patient is unable to read. Further precautions to ensure enrollment will be informed and voluntary may be added per IRB stipulations. Consent forms will be translated and back translated into Amharic and Afaan Oromo.

When children are asked to join the study, the parent will be asked to sign a consent form, and the child an assent form, which describes the study in a simpler way. The child subject may only be enrolled if the parent consents and the child assents to study participation. They should not be enrolled unless BOTH agree.

1. Purpose

To describe the standard operating procedure for taking informed consent; therefore, every participant will be enrolled in the trial with full knowledge and understanding of what the project is about and its benefits and risks.

2. Scope

This SOP covers the procedures of informed consent process for FLAME trial

3. Responsibility

The Study Nurse or Study Data Recorder.

4. Detailed instructions

4.1 ***General***

4.1.1 Greet participant, introduce yourself, be relaxed and make the patient at ease.
4.1.2 Check if patient heard and understood initial lecture. If not understood, explain about trachomatous trichiasis, blindness and the nature of the trial.
4.1.3 If the patient is not able to read the information provided, then witnessed explanation should be done.
4.1.4 If the patient is not able to understand the information provided, then he/she will be a non-trial patient

4.2 ***Provide the necessary information***

4.2.1 Explain about the need for consent in the trial.
4.2.2 Make sure they understand what consent is and why it is needed. Ensure there are no misconceptions about why consent is being taken, e.g. that the form is not related to voting or government.
4.2.3 If patient can read, provide Information sheet to read. If not, then read to the patient.
4.2.4 Invite the patient to ask questions that need clarification

4.3 ***Check the patient's understanding***
4.3.1 Ask the patient the following questions to confirm that he/she has understood the information
4.3.1.1 What is this study about
4.3.1.2 What benefits are there to take part in this study
4.3.1.3 Are there any risks to take part in this study
4.3.1.4 Why are we requesting you for your consent

4.4 ***Take consent***
4.4.1 Ask the patient if s/he agrees to be enrolled in the trial
4.4.2 If patient is willing to participate in the trial, read the patient the 8 points specified on the consent form one by one and ask if the patient agreed on each point
4.4.3 If the patient agreed in each point, tick the boxes on the right-hand side
4.4.4 Ask them to sign on two copies of the consent form with signature or thumb print
4.4.4 Provide the patient a unique reference number and write the name of the patient and date the consent is given (signed) on the two consent forms
4.4.5 Witnessed informed consent is needed if the person is unable to read the information / consent form. The witness will need to sign both consent forms
4.4.6 Make sure you (the consent taker) sign the two consent forms and document the date the consent is taken
4.4.7 Provide one copy of the completed and signed consent form to the patient and keep the second signed form for the study record

5 Procedure for patients declining consent
5.1.1 If patient does not consent after discussion or if a patient is not competent to consent, patient becomes non-trial patient.

6 Documentation
Update the Screening Log as applicable.

7 Eligibility, Enrollment and Randomization

Purpose: To describe the standard operating procedure for checking eligibility and enrolling patients in the FLAME trial.

Scope: This section of the manual of procedures covers the steps starting from eligibility evaluation to point of enrollment.

To be eligible for enrollment into the FLAME Trial, all the following inclusion and exclusion criteria must be met.

Inclusion Criteria
Subject is ineligible for the study if either of the question is answered No:

1. Did the subject sign the consent form consent (and assent, when applicable)?

2. Is the subject aged 15 years or older?

Eye is ineligible for the study if any of the following two criteria are answered No:

3. Diagnosis of upper eyelid trachomatous trichiasis (TT)?

4. Is lid rotation surgery planned on an upper eyelid with TT?

Exclusion Criteria:
The subject is ineligible for the study if any of the following five criteria are answered Yes:

1. Contraindication(s) to the use of the test articles, including a known allergy or sensitivity to the study medication (fluorometholone) or its components.

2. Contraindications to the use of Azithromycin (including known pregnancy).

3. Any significant illness or condition that could, in the study clinician/coordinator's opinion, be expected to interfere with the study parameters or study conduct; or put the subject at significant risk?

4. Any severe / serious ocular pathology or medical condition which may preclude study completion or increase the risk of harm in the study (e.g., suspicion of non-trachomatous active ocular infection or suspicion of glaucoma where an intraocular pressure spike would be vision threatening?

5. Any condition present at baseline for which it is anticipated ocular or systemic corticosteroid therapy will be required.

Eye is ineligible for the study if any of the following criteria are answered Yes:

6. Previous upper lid eyelid surgery for trachomatous trichiasis?

7. Currently using ocular anti-hypertensive medication? (prior intraocular pressure (IOP) lowering surgery is acceptable)

8. Glaucoma sufficiently advanced that an intraocular pressure spike potentially would put the patient at substantial risk of vision loss, per study clinician/coordinator's judgment.

9. Other than trachoma, any active ocular infections (bacterial, viral, or fungal), or any active ocular inflammation (e.g., scleritis, iritis).

10. Is there Phthisis bulbi in either eye?

11. Intraocular pressure (IOP)≥22 mmHg

Persons responsible:

Person	Responsibility
Study recorder	Ensures eligibility form is properly labeled. Checks the eligibility form for completion. Enters Eligibility form data into RedCap
Study nurse	Checks for eligibility using the eligibility form Enrolls patient to the study and assigns a Study Id number to the participant

a. Materials required:

CRF and other Forms	
1. Eligibility form	To evaluate patient for eligibility and document assignment of study ID
2. Screening log	To indicate if a screened patient has been enrolled
3. Enrollment log	To list who has been enrolled and key information for follow-up
4. Enrollment folder	A folder with all the enrollment forms to be assigned to a patient
5. Patient tracking form	For purposes of follow-up, to document case finder/HEW and date of follow-up
6. Referral form	As needed to refer patients for care
Other Materials	
Labels	Enrollment labels for assigning study ID
Loupe	To check if patient has TT
I-care IOP measuring instrument	To measure IOP
Android phone	For RedCap entry

b. Detailed Instructions:

i. Checking for eligibility

Patients selected for TT surgery by the IECW and given consent to participate in the study are checked for eligibility.

a. The patient who has given consent goes to the study nurse with his/her screening folder and a blank eligibility form
b. The patient's screening number is written or a label affixed to the eligibility form
c. The study nurse goes over the eligibility form addressing each question to evaluate the patient's eligibility [*See* in *Study Forms Completion Guidelines*]. The eligibility form covers all the inclusion and exclusion criteria for each eye.
d. At the completion of the eligibility form, it will be determined if the patient is eligible to enroll and which eyes are eligible.

ii. Enrolling the patient

2.1 If the patient has an eligible eye then the patient can be enrolled.
2.2 Based on the sequential ID numbers assigned for that team, the next ID number is given to the patient.
2.3 The patient ID label is affixed at the end of the eligibility form
2.4 An enrollment folder is assigned to the patient with Study ID label on the folder
2.5 If a patient is not eligible for enrollment, then the study nurse informs the patient that he/she cannot be enrolled in the study but can proceed with their surgery and with the usual care for TT patients. Enrolled participants proceed with baseline evaluations, randomization/treatment assignment, followed by surgery. [Refer to the instructions of the visit # 1 assessments]
2.6 After completion of baseline evaluation, randomization and surgery, the study participant is seen by the study nurse before leaving the health facility
2.7 The study nurse gives a plastic bag labeled with the participant's id number and containing:
- A completed study ID card
- A copy of the signed consent form
- Eye Drop Dairy
- The study medication, and
- All the medication given by the TT surgeon to the patient

2.8 The study nurse or data recorder update the screening log and enrollment log

iii. Documentation

3.1. The Study Nurse or Recorder updates the Screening log indicating if the patient is enrolled or not, and the reason why if not enrolled
3.2. The Enrollment log is also updated with patient's information by the study nurse or recorder
3.3. The study participant's name is entered into the tracking form with the appointment date for the next visit.
3.4. A copy of the tracking form with the list of enrolled participants and their next appointment is given to the health extension worker/case finder at the end of the day

iv. Referral

4.1. If during eligibility assessment a patient is found to have medical conditions that require care, a referral form is completed by the study nurse.
4.2. Referral forms are completed for both enrolled and non-enrolled patients.

8 Visit number 1 assessments

SOP for the visit # 1 assessments of FLAME trial.

Purpose: To describe the standard operating procedure for the conduct of the assessments of visit # 1.
Scope: This document covers the steps starting from Baseline Information Form to the end of the study activities by the study team right before surgery.

Responsible: Study field team

Procedure:

1. Height & Weight measurement is taken by the study data recorder. [Refer to instructions for Height & Weight measurement: see *Annex AA*]
2. The Study Data Recorder performs the visual acuity test and documents the results. [Refer to Instructions of taking visual acuity measurement with Peek Acuity: see *Annex A*] Also, he/she takes face and ocular pictures. [Refer to instructions for capturing the facial and ocular pictures: see *Annex B]*
3. The following get filled out by the study nurse or study data recorder. [Refer to form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]
   - Baseline Information Form
   - EQ-5D Form,
   - Eye Pain Impact Questionnaire,
   - Ocular Surface Disease Index,
   - Visual Function Questionnaire and
   - Poverty Questionnaire

4. The following get filled out by the study nurse. [Refer to form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]
   - Baseline Eye Examination Form
   - Randomization & Initial Treatment Form
5. After randomization the study nurse puts the medication label on the study medication. The study nurse demonstrates how to instill an eye drop in the participant's study eye[s].
6. The study nurse applies one drop of the study medication in the participant's eye and documents the follow up appointment date.

7. An Eye Drop Dairy sheet will be provided to the study participant along with demonstrations on how to use it. [Refer to instructions associated with the Eye Drop Dairy: see *Annex D*]
8. The study nurse informs the patient the week-4 follow-up visit date.
9. The patient will be linked to the relevant TT- surgeon by the study nurse for TT surgery.

i. Trichiasis Surgery

Subjects undergo trichiasis surgery by a participating outreach TT surgeon. The standard programmatic treatment used by the Fred Hollows Foundation in this region is implemented: posterior lamellar tarsal rotation (Trabut) with use of dissolvable sutures on each affected eye. Lower lid TT is referred for ophthalmologist-performed lower lid surgery. Azithromycin is used for all patients except women reporting pregnancy or lactation.

The following data will be collected on this visit:

- Surgical details, in order to obtain any data about variances in surgical technique and their possible relationship to relapse of trichiasis or adverse events
- Medication review
- Adverse event review (for the brief period since randomization)

The subject will be provided a refresher - biscuits and a soft drink - by the study data recorder.

ii. Follow-up and Data Collection Schedule

Each subject participates in five visits (see following re-presentation of Table 2). Visit 1 (to collect baseline data, ensure eligibility and complete enrollment); Visit 2 (to conduct surgery and collect information on surgical details—usually on the same day as Visit 1); and three follow-up visits (Visits 3-5) to obtain outcome and adherence data. Additional contact with the Field Teams or Surgical Team for clinical care is permitted, as needed, but data collection is not to be conducted on such visits. Patients are followed until the anniversary closeout at one year after randomization, even if they do not follow the study protocol otherwise.

Table 2: Visit and Data Collection Schedule

Assessments	Visit 1 Baseline	Visit 2 Surgery	Visit 3 4 weeks	Visit 4 6 months	Visit 5 12 months
Timing/Interval (Days[D]) pre/post surgery (=D 0)	D -7 to 0	D 0	D 28-35	D 180±60	D 365 ± 90
Informed Consent, Demographics, Randomization	X				
Medical and Ophthalmic History	X			X	X
External Examination using +2.5 magnifying loupe	X			X	X
Visual Acuity, Trachoma & Trichiasis Grading; IOP; Patient reported outcomes (pain, EQ5D)	X		X	X	X

Table 2: Visit and Data Collection Schedule					
Assessments	Visit 1 Baseline	Visit 2 Surgery	Visit 3 4 weeks	Visit 4 6 months	Visit 5 12 months
Timing/Interval (Days[D]) pre/post surgery (=D 0)	D -7 to 0	D 0	D 28-35	D 180±60	D 365 ± 90
Medication Review	X	X	X	X	X
Adverse Event Review; medical care utilization		X	X	X	X
Surgical Details		X			
Assessment of Treatment Adherence			X		
Subject Exits Study					X
*D=days post TT surgery; IOP=intraocular pressure; EQ5D=EuroQol health utility (Ethiopian form)					

9 First follow-up visit procedures

Purpose: To describe the standard operating procedure for the conduct of the assessments of visit 3.

Scope: This document covers assessments from the beginning to the end of week 4 follow up visit.

Responsible: Study field team

Procedure:

1. The study team will reach out to study participants and /or case finders three to four days before the appointment date to remind the subject of his/her scheduled follow up visit.
2. The study nurse or the study data recorder greets the subject and kindly asks for the plastic bag containing the medication diary, medication bottle and identification card (ID) that the subject received during enrollment.
3. The study nurse or study data recorder verifies subject's identity through full-face picture (captured at visit 1) and his/her full name and address.
4. The study nurse or study data recorder explains to the patient the purpose of the visit including procedures to be conducted and obtains verbal consent.
5. The Study Data Recorder performs the visual acuity test and documents the results. [Refer to Instructions of the visual acuity assessment: see *Annex A*] Also, he/she takes facial and ocular pictures. [Refer to instructions for capturing the facial and ocular pictures: see *Annex B*]
6. The following get filled out by the study nurse or study data recorder. [Refer to form filling out instructions for each: see the section in *Study Forms Completion Guidelines*]
   EQ-5D Form,
   Eye Pain Impact Questionnaire,
   Ocular Surface Disease Index,
   Visual Function Questionnaire

7. The following get filled out by the study nurse. [Refer to form filling out instructions for each: see the section in *Study Forms Completion Guidelines*]
   Treatment Adherence Form
   Week 4 Eye Examination Form
   Primary End Point Assessment form
8. The study nurse or the study data recorder will provide the patient with soap.
9. The study data recorder will have participant's transportation expenses refunded (if any).
10. The study nurse or the study data recorder will thank the participant for coming, inform him/her of the next appointment date and conclude the visit. The appointment date is written down and provided to the participant.
11. The study nurse gives the subject a referral slip, if any complication has been discovered.

10. Second follow-up visit procedures

SOP for the visit # 4 assessments of FLAME trial.

Purpose: To describe the standard operating procedure for the conduct of the assessments of visit 4.

Scope: This document covers assessments from the beginning to the end of month 6 follow up visit.

Responsible: Study field team

Procedure:

1. The study team will reach out to participants and /or case finders three to four days before the appointment date to remind the subject of his/her scheduled follow-up visit.
2. On the day of the follow up visit, the study nurse or study data recorder will meet and greet the subject and kindly ask for the plastic bag, which contains the participant identification Card (ID) that the subject received during enrollment.
3. The study nurse or study data recorder verifies subject's identity through full-face picture (captured at visit 1) and his/her full name and address.
4. The study nurse or study data recorder explains to the patient the purpose of the visit including procedures to be conducted and obtains verbal consent.
5. The Study Data Recorder performs the visual acuity test and documents the results. [Refer to Instructions of the visual acuity assessment: see *Annex A*] Also, he/she takes facial and ocular pictures. [Refer to instructions for capturing the facial and ocular pictures: see *Annex B*]
6. The EQ-5D Form, Eye pain impact questionnaire, Ocular Surface Disease Index, Visual Function Questionnaire get filled out by the study nurse or study data recorder. [Refer to the form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]

7. Follow Up Health Review form, Month 6 &12 Eye Examination form, Satisfaction with TT Surgery form and Primary End Point Assessment form get filled out by the study nurse. [Refer to the form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]
8. The study nurse or the study data recorder will provide the patient with soap.
9. The study data recorder will have participant's transportation expenses refunded (if any).
10. The study nurse or the study data recorder will thank the participant for coming, inform him/her of the next appointment date and conclude the visit. The date is written down and provided to the participant.

11. Third follow-up visit procedures

SOP for the visit # 5 assessments of FLAME trial.

Purpose: To describe the standard operating procedure for the conduct of the assessments of visit 5.

Scope: This document covers assessments from the beginning to the end of month 12 follow up visit.

Responsible: Study field team

Procedure:

1. The study team will reach out to participants and /or case finders three to four days before the appointment date to remind the subject of his/her scheduled follow-up visit.
2. On the day of the follow up visit, the study nurse or study data recorder will meet and greet the subject and kindly ask for the plastic bag, which contains the participant identification Card (ID) that the subject received during enrollment.
3. The study nurse or study data recorder verifies subject's identity through full-face picture (captured at visit 1) and his/her full name and address.
4. The study nurse or study data recorder explains to the patient the purpose of the visit including procedures to be conducted and obtains verbal consent.
5. The Study Data Recorder performs the visual acuity test and documents the results. [Refer to Instructions of the visual acuity assessment: see *Annex A*] Also, he/she takes face and ocular pictures. [Refer to instructions for capturing the facial and ocular pictures: see *Annex B*]
6. The following get filled out by the study nurse or study data recorder. [Refer to form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]
    - EQ-5D Form
    - Eye pain impact questionnaire
    - Ocular Surface Disease Index
    - Visual Function Questionnaire

- Poverty questionnaire
- Exit Form

7. The following get filled out by the study nurse. [Refer to form filling out instructions for each: see the sections in the *Study Forms Completion Guidelines*]
   - Follow Up Health Review form
   - Month 6&12 Eye Examination form
   - Primary End Point Assessment form
   - Satisfaction with TT surgery form
8. The study nurse or the study data recorder will provide the patient with soap.
9. The study data recorder will have participant's transportation expenses refunded (if any).
10. The study nurse or the study data recorder informs the subject that he/she now has completed(exited) the study.

12. Monitoring and Supervision

The field study supervisors (field coordinator and study supervisor) will monitor the activities of the study coordinators, ensuring adherence to protocol in screening, enrollment, study intervention assignment, and follow-up procedures. Field site supervisors also will review all adverse events and report to the Study Safety Officer and Field Coordinating Center director and senior study coordinator. Monitoring visits will be documented and reported to the Field Coordinating Center and Chairman's Office. Site supervisors will be health professionals experienced in the conduct of clinical trials.

A senior study coordinator who is a health professional experienced in Neglected Tropical Diseases (NTDs), eye health, clinical trials will provide overall management, coordination, and constant supervision of the Field work by visiting study sites approximately bimonthly and oversee the FLAME Clinical Trial. FCC Director Dr. Aida Abashawl and/or Study Chair Dr. John Kempen will visit sites and monitor study procedures quarterly.

F. STUDY DRUG AND TREATMENT

1. Preparation of Study Drug

The FLAME Trial Investigational Pharmacy (Penn Investigational Drug Service) prepares Medication Boxes, each with its own unique number associated with the study number of subjects enrolled in the clinical trial in Ethiopia. The numbers are created in advance of enrollment based on the randomization schedule created for each participating surgeon (because randomization is stratified by surgeon). Each medication box will contain fluorometholone 0.1% or artificial tears (placebo). With the 1:1 randomization schedule of the FLAME Trial approximately half will be each, but the contents of each will be masked by the Investigational Pharmacy placing them in identical bottles. Sets of 20 bottles will be packaged into boxes to simplify stratification by geographical area/surgeon.

The source of fluorometholone 0.1% will be a donation of 2300 10 mL bottles of FML® (fluorometholone) Ophthalmic Suspension, USP 0.1% sterile from the drug company Allergan (Dublin, Ireland). The Data Center, which receives funding for the Investigational Pharmacy for administrative convenience since they area at the same institution, will contract with Allergan to govern the donation of FML, which will be obtained as a grant to a Penn Clinician Co-Investigator, Dr. Vatinee Bunya. Allergan will ship the drug on a schedule that is convenient for the Investigational Pharmacy (to avoid the need to keep bottles in inventory that are at risk of expiry).

The source of artificial tears (Soothe® XP, Bausch & Lomb, which resembles the appearance of the FML® drops) is by purchase at a convenient commercial pharmacy.

Bulk drug product are stored in a secure, temperature-controlled storeroom at 20-25C while at the Penn Investigational Drug Service (IDS). The temperature in this area is closely monitored and materials are tracked in a 21CFR11-compliant electronic inventory system. During preparation of the masked product, batch records following cGMP format, reviewed by a quality assurance officer pre-batch and post-batch, are used to document the entire process. Finished records as well as results from any release testing, are logged in a 21CFR11-compliant LIMS (laboratory information system) and electronically signed by the quality assurance officer before any product is released for use. The drug and placebo are packaged in identical bottles under sterile conditions, which in turn are placed in medication boxes, each labeled with study number as described above. The IDS will follow its usual Standard Operating Procedures in repackaging the study drug.

a. Expiry of Study Drug

The IDS will immediately set up experiments to assess the shelf-life of its repackaged study drug, to the time points of 6 and 12 months after preparation. In the preliminary study, shelf-life of 6 months was proven, and 12 months was not assessed. Upon completion of the experiments, the shelf-life will be established. If study drug is shipped prior to completion of the 12 month time point assay, the expiry label will be updated for affected lots.

b. Shipping of Study Drug to Ethiopia

The IDS uses the fastest available shipping (3-4 days) and sends the designated drug recipient at the Investigational Pharmacy in Ethiopia information to track the package(s). Shipments will be sent approximately every four months in order to assure that the study will be adequately supplied with drug. The recipient pharmacy must track packages not received by the expected time, and the IDS needs to be immediately notified about lost shipments. The IDS ships the drug in a foam shipper with cold packs. The staff at each receiving site will inspect the conditions of each shipment of medication boxes upon arrival, and immediately transfer the contents into appropriate, temperature-controlled storage locations. Kits received with warm or broken cold packs will be rejected, placed in quarantine, and the IDS notified. Study drug should be kept at 2°-25°C. DO NOT FREEZE. Do not use drug beyond the date printed on the packaging. Packages should be kept upright. The transfer of materials to the clinical site will be documented in a chain-of-custody document which includes an itemized list of materials; this list will be reviewed by two staff members (one being a licensed

pharmacist) prior to shipment, then reviewed and signed by the recipient at the pharmacy in Ethiopia, providing clear documentation of the transfer.

c. Distribution of Study Drug in Ethiopia

This activity will be managed by the Field Coordinating Center, which will hire an Ethiopian investigational pharmacist to carry out the activities.

Medication boxes must be stored securely at all locations. It is important that study drug is not accessible to non-study staff. If the medication must be stored in a location that is accessible to other staff, it is recommended that a separate locked box be used. All medication kits received must be logged in and documented on the Medication Box Inventory Form at each location.

First, shipments will be received by customs. While kept in customs, they are kept at room temperature, within the range of acceptable storage temperature for fluorometholone. The Field Coordinating Center will clear the shipment from customs as quickly as possible, typically in 1-2 weeks. The shipment will be immediately transferred to the Ethiopian Investigational Pharmacy, tentatively in Jimma. Study drug will be kept at 2°-25°C in the investigational pharmacy in a locked location.

Medication boxes will be taken from the field office to field sites in an air conditioned vehicle inside of coolers (or cold boxes) with room temperature conditioned gel packs from Cold Chain Solutions, and stored indoors in a cool area at the site. From this cold box, the medication boxes will be dispensed to patients during randomization.

d. Dispensing Study Medication to Study Patients

Each time a medication box is dispensed to a FLAME Trial patient, it must be documented on the Inventory Log indicating the patient's study ID number, date dispensed.

As described elsewhere, Field Team members will carefully instruct the patient on how to place eyedrops, which eye(s) to place them in, how often (twice daily) and for how long (exactly 28 days including the day of surgery as day 1) using the Ethiopian calendar. The study team will place the first drop in the subject's study eye(s) prior to TT surgery as an example. The subject will be instructed to begin placing the eyedrops in the study eyes twice daily beginning from the point any bandages are removed. If no bandages are placed, a second drop can be placed on the study eyes later on the day of surgery. After that, one drop should be given in the morning and one in the evening. Patients should practice applying eyedrops before the drop is placed.

e. Spoiled and Expired Drug

Upon expiry or spoilage at field sites (e.g., accidental freezing of study drug stored in a refrigerator), the medication kit will be returned to the Ethiopian Investigational Pharmacy. Because medication kit numbers differ from patient ID numbers, it will be possible for the IDS to revise the dispensing list indicating a new medication kit number within 1 working day, so as to avoid cessation of enrollment during a planned outreach.

G. ADVERSE EVENTS

All members of the FLAME Trial Research Group have a duty to protect human subjects participating in the trial. Part of that duty extends to monitoring and assessing adverse events to assess their relationship to the study treatments. This section of the Manual of Procedures gives the approach that will be taken. Analytic contributions to safety monitoring also are summarized in Data Management and Analysis sections of the MOP.

FLAME Trial Executive Committee has a duty to assess the safety outcomes of the subjects enrolled in the Trial, and will meet approximately monthly. The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing the study design and regularly assessing the study data with special attention to adverse events and/or beneficial effects of treatment. The DSMC will meet approximately every six months and will review all accumulated study data including adverse events.

The Field Team, Field Coordinating Center, and Safety Officer provide the information needed for these committees to carry out their duties to the study subjects, as described here. In addition, the Safety Officer will communicate with the DSMC contact expeditiously regarding specific, severe and unanticipated adverse events, on a case-by-case basis.

All adverse events (AEs) must be described in detail in the source documents and documented in the case report forms (CRFs). AE's meeting criteria for urgent reporting will be reviewed promptly by the ophthalmologist Safety Officer, who also will review quarterly summary reports of AEs prepared by the data center. The Safety Officer will be responsible for meeting reporting requirements of the IRBs and Ethiopian government agencies overseeing the study, as well as the DSMC. The Safety Officer will maintain a reporting protocol to ensure the Field Team promptly reports required events, including training in response to any errors in such reporting, with each revision requiring approval by the Executive Committee. The Data Center will develop a system to incorporate relevant analytic details into the central study database using REDCap and Mobile App.

See source forms from which the AE forms will be developed in the appendices.

1. Definition of Adverse Events

An adverse event (or adverse experience) is any untoward medical occurrence in a clinical investigation subject in the FLAME Trial, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be <u>any</u> unfavorable and unintended sign (including an abnormal laboratory finding, should any subjects undergo lab testing outside of the study), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition.

Abnormal Findings

The criteria for determining whether an abnormal objective finding should be reported as an AE are as follows:

- Finding is associated with accompanying symptoms, and/or,

- Finding requires additional diagnostic testing.
- Finding requires significant additional concomitant drug treatment or other therapy or intervention.
- Finding leads to a change in study dosing or discontinuation from the study.
- Finding is considered to be an AE by the Surgical Team, Field Team or Field Coordinating Center.

Merely discovering an abnormal finding, in the absence of any of the above conditions, does not constitute an AE. An apparently abnormal finding that is found to be a false result (such as false laboratory result) does not require reporting as an AE.

Note: All Adverse Events must be reported on the Case Report Forms (CRF) provided by the Study (FLAME Study Forms). Follow the guidance of the Study Form to determine if expedited reporting to the Safety Officer is required. If in doubt, contact the Safety Officer to discuss the event and get his/her input.

f. Grading of Adverse Events

Adverse events will be graded in regard to maximum intensity and relationship to study treatment, and the information entered on the Adverse Event form:

i. Maximum Intensity

All AEs will be graded according to the following:

- Mild: Event requiring no special treatment and generally does not interfere with usual activities.
- Moderate: Event that impairs usual activities but may be ameliorated by simple therapeutic maneuvers.
- Severe: Event which impairs usual activities and requires intervention greater than that described in the Moderate category.

Note that “severe” intensity and “serious” nature are different things.

ii. Relationship to Study Treatment

All AEs will be evaluated by the Investigative team/Safety Officer for potential relationship to the study treatment using the following recognized method of the WHO-UMC system:

- Certain/Definite: Event with a reasonable temporal sequence from administration of the study treatment; or that follows a known or expected response pattern to the study treatment and was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
- Probable/Likely: Event with reasonable temporal sequence from administration of the study treatment; or that follows a recognized response pattern to the study treatment; was confirmed by withdrawal but not by exposure to the drug; and could not be reasonably explained by the known characteristics of the patient’s clinical state.
- Possible: Event that follows a temporal sequence after administration of study treatment; possibly followed a recognized pattern to the study drug but could also be explained by disease or other drugs
- Doubtful/Unlikely: Event was likely related to factors other than study drug

- Unable to assess: Event report suggesting an adverse event with insufficient information where data cannot be supplemented or verified

The Field Team should discuss the classification with the Study Safety Officer before coming to a final conclusion about causality. For AEs that are assessed to be related to the study treatment, the Safety Officer must determine whether to continue or discontinue the study treatment.

iii. Adverse Event Designation

All adverse events, irrespective of severity, will be classified as either EXPECTED or UNEXPECTED. Any adverse therapeutic experience that is specifically investigated as a study variable in this protocol or in the study information/consent form is an expected event. In general, events listed as potential effects of study drug in the consent form are expected events. In contrast, any other adverse event is an unexpected event. The Executive Committee may add to list of expected events over time

g. Eliciting Adverse Events

At each study visit, the subject must be questioned about AEs in a non-leading manner, in their preferred language. All AEs, whether observed by the Investigator, elicited by the Investigator, or spontaneously reported by the subject, will be documented in the AE case report form (CRF).

h. Follow-Up of Unresolved Adverse Events

All AEs should be followed until they are resolved or until a stable clinical endpoint is reached. This follow-up often will require extra contact with the subject

i. Serious Adverse Events

Each AE is to be classified further by the Field Team Eye Nurse as SERIOUS or NONSERIOUS. **Reporting a Serious Adverse Event (SAE) requires review with the study Safety Officer within 24 hours** to confirm it is appropriately reported, and to ensure he can report it to regulatory groups in a timely manner (see below). Proper classification of SAEs is an important matter, because it is one of the major protective mechanisms for study subjects (should the study treatments prove to have unanticipated and serious adverse sequelae on patients) and has significant regulatory reporting implications for that reason.

i. Definition of a serious adverse event (or serious adverse experience)

Although this is not an FDA regulated study, we are following the precedent established by US Food and Drug Administration regulations (as per 21 CFR 312.32 (Investigational New Drug Application [IND], safety reports), in which a SAE is defined as any untoward medical event occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE (immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (including need for surgery)
- A persistent or significant disability or incapacitation

- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may also be considered SAEs (i.e., clinically significant AEs) when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse. Note: an SAE likely to be encountered fairly often in this study is the need for reoperation for TT. This, and other expected AE's determined by the Executive Committee, will be reported on forms but its reporting will not be expedited unless required by a report recipient.

Please note: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on a set of subject/event outcome and/or action criteria usually associated with events that pose a threat to a subject's life or functioning (including visual functioning). Seriousness (not severity) is what serves as a guide for defining regulatory reporting obligations.

Hospitalization as a result of an Adverse Event
AEs reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any formal admission (even if less than 24 hours) to a healthcare facility meets the criteria of hospitalization. Prolongation of hospitalization is when a subject is ready for discharge, but then develops an event that prolongs his/her hospital stay.

However, please be aware that there are circumstances that should be distinguished from hospitalization for an adverse event:

Hospitalization does not include the following (all of which are rare in the study context, but mentioned for completeness):
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:
- Admission for treatment of a preexisting condition not associated with the development of a new AE or without a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Administrative admission (e.g., for yearly physical exam)

- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

j. Serious Adverse Event Reporting

If a SAE occurs, the study team must verbally and/or in writing (via email or phone) notify the study Safety Officer within 24 hours of the occurrence of the SAE. This will be facilitated by having an Ethiopia-based ophthalmologist serve as the Safety Officer in the FLAME Trial. The initial SAE report must be followed by a written report, signed by the Study Team Member who detected the adverse event, and received by the Safety Officer via email or other channel within three working days (reports will only use study numbers to identify subjects). If the internet is not "live" at the time the Field Team is ready to make a report, the Team Member also can call the Safety Officer and read the report over the phone, sending a copy later. The Study Team Member must provide written follow-up reports until the SAE or clinically significant AE has resolved or until a stable clinical endpoint is reached. If required by an Institutional Review Board (IRB)/Ethics Committee, government regulatory agency or DSMC or other recipient of reports, notification of an SAE or clinically significant AE must also be submitted in accordance with the overseeing body's requirements, which will be managed by the Safety Officer.

k. Reporting Period for Adverse Events

All AEs occurring from the time that the subject provides informed consent through the last study visit must be reported.

Should the investigator become aware of a SAE that occurs within 30 days after the last study visit, it must be promptly reported in the event a causal relationship to investigational product is suspected. It is unlikely that such SAE's will occur because treatment is finished after the first four weeks of the study.

All AEs (serious and non-serious) should be recorded on the study case report forms from the time of randomization until the patient exits the study.

It is anticipated that most AEs related to treatment will be detected at the four week visit, which is in place largely to detect such events. This is because the treatment is stopped after four weeks, and it is hypothesized that the treatment will have few downstream long-term effects. However, this hypothesis should not prevent the Field Team from reporting adverse events or considering the potential relationship to study treatment, as downstream side effects could exist.

<u>Pregnancy and Breast Feeding:</u>

Because corticosteroid eyedrops are permitted for early childhood treatment, breastfeeding will not entail any adverse event reporting. Pregnancy reporting (occurring during follow-up) is required pursuant to the Penn agreement with Allergan. Therefore occurrence of pregnancy during follow-up must be captured and reported to Allergan.

There is some concern that azithromycin may be bad for babies, so the policy of the Fred Hollows Foundation is not to use it in pregnancy. However, these women still are operated, so as not to lose the opportunity to be cured of TT. Given that this is the standard SAFE programmatic practice in the study area, pregnant women will receive a slightly different treatment than non-pregnant persons. Because of concern about potential bias in including them in the study analysis, self-reported pregnancy is an exclusion criterion for enrollment in the study since pregnant women will not be given azithromycin.

Reporting Requirement of Adverse Events

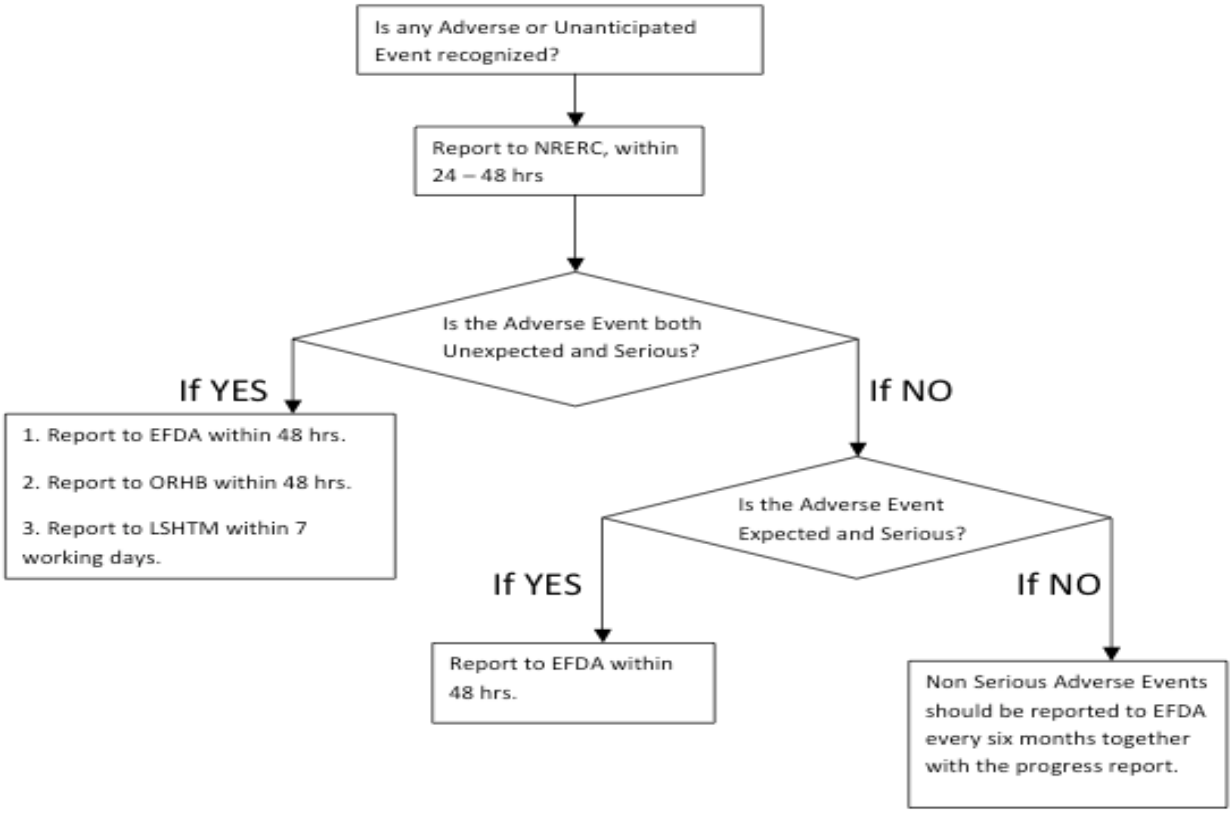
The following chart summarizes the reporting requirement of adverse events by the various IRBs.

Adverse Event Reporting Chart

Items to be reported				Institution/Committee 1: FLAME (Chair, Senior Coordinator and FCC Director)	2: Allergan/ Abbvie	3: NRERC	4: EFDA	5: Partners/ Mass General Brigham IRB	6: LSHTM IRB	7: ORHB	8: DSMC
1	Suspected/ Related	Serious Adverse Events	Unexpected	x	X	X	X		X	X	X
			Expected	x	X	X	X		N	X	X
	Not Suspected/ Not Related	Serious Adverse Events	Unexpected	x	X	X	X		N	X	X
			Expected	x	X	X	X		N	X	X
2	Suspected/ Related	Non-Serious Adverse Events	Unexpected	x	X	X	X		N	N	X
			Expected	x	N	X	X		N	N	X
	Not Suspected/ Not Related	Non-Serious Adverse Events	Unexpected	x	N	X	X		N	N	X
			Expected	x	N	X	X		N	N	X
3		Protocol Deviation	Minor	x	If related to study drug	N	N		N	N	N
			Major (violation)	x	X	X	X		X	X	X
4		Other Event to report		x	Pregnancy, Breastfeeding, Misuse, Abuse, Overdose, Medication error	1. Protocol Amendments, 2. Premature suspension or termination of research	1. Protocol Amendments, 2. Premature suspension or termination of research		N	N	N
5.1		Who Reports	Serious Events	Safety Officer for serious events and major violations; Field supervisor for the rest	Safety Officer	Safety Officer	Safety Officer		Safety Officer	Safety Officer	Chair or Upenn
5.2		Who gets report; email address		saba.badawi@gmail.com; ahlam.awad@gmail.com;hlikono@gmail.com; John_Kempen@meei.harvard.edu	1. To Allergan->> Patient Safety Operations Fax: 1-714-796-9504 Back-up fax: 1-714-246-5295 or email IR-Clinical-SAE@Allergan.com 2. To Upenn->>	nrpca@ethernet.edu.et	TBD		matthew.burton@lshtm.ac.uk	[illegible]@gmail.com	jeremy.keenan@ucsf.edu
Period for Reporting	Suspected/Related	Serious Adverse Events	Unexpected	24-48 hr	within 7 Days	24 - 48 hrs	48 hr		with in 7 working days	With in 48 hrs	With in 48 hrs
	Not Suspected/Not Related	Serious Adverse Events	Expected	24-48 hr	within 7 Days	24 - 48 hrs	48 hr	Annual summary report with renewal of IRB approval	Annual summary report	24-48 hrs	With regular scheduled reports
	Suspected/Related	Non-Serious Adverse Events	Unexpected	every month	every six months with report	24 - 48 hrs. (have asked to go by EFDA Rule)	every 6 months with the progress report		Annual summary report	every six months	With regular scheduled reports
	Not Suspected/Not Related	Non-Serious Adverse Events	Expected	every month	every six months with report	24 - 48 hrs (have asked to go by EFDA rule)	every 6 months with the progress report	Annual summary report with renewal of IRB approval	Annual summary report	every six months	With regular scheduled reports
7	Format to use		Serious	FLAME Form	Allergan format	EFDA Format	EFDA Format	FLAME Form	FLAME format	EFDA Format	FLAME Format
			Non-serious	FLAME/EFDA form	FLAME/EFDA Form	EFDA Format	EFDA Format	FLAME/EFDA Form	FLAME/EFDA Form	EFDA Format	EFDA format

Reporting of Adverse Events Flow

The flow chart below summarizes the flow of reporting of adverse events by the Safety Officer.



l. Executive Committee Review of AEs

The Executive Committee (study leaders) will meet at least monthly during the trial, and will review unexpected SAEs when they occur. The Executive Committee also will review aggregated adverse event outcomes that were pre-specified and a summary of AE reports approximately semi-annually.

m. Data and Safety Monitoring Committee Review of AEs

A Data and Safety Monitoring Committee (DSMC) convened by the National Eye Institute (See Section N, Organizational structure of the Study) will review the implementation, progress and results of the study (including considering the safety of subjects) at intervals to be determined by the DSMC, tentatively twice annually, once by phone/media and once in person in conjunction with a conference (due to cost constraints). Phone service, electronic media, or similar approaches will be used for meetings otherwise.

H. FIELD COORDINATING CENTER POLICIES ON AVOIDANCE AND MANAGEMENT OF LOSSES TO FOLLOW-UP

1. Strategy for Preventing Missed Visits and Dropouts

The study team will use various means to ensure all visits are done and to avoid dropouts, as previously done in the four trials conducted by Prof. Burton, and the preliminary fluorometholone trial, all of which obtained well over 90% follow-up through one year. These include:

- Easy access to the study team: **provide phone numbers and information regarding the location of the field office to participants.**

- At the time of enrollment: obtain contact information from study participants including address-equivalent and as many phone numbers as possible. **Enter this information the Enrollment Log**. Make sure to protect the Enrollment Log from loss. Completed enrollment logs (when a surgeon completes his/her work with the study) should be kept in a locked area unless being actively used. Copies thereof may be kept on your Android behind password protection, so that you can use the information in finding and following up patients.

- **Community facilitators** will be engaged to assist the team in bringing participants for follow-up. We will give preference to using the same community facilitator as had been used by the Surgical Team to mobilize patients at the time of the original outreach program. Please send a reminder by phone to the community facilitator just ahead of a visit to make arrangements for follow-up.

- **Subjects will be reimbursed** by the Field Coordinating Center for any travel costs and meals will be provided should mealtimes occur during follow-up visits.

- **Conduct follow-up visits in villages close to subject residences**, or at subject homes, to facilitate easy attendance.

- **Subjects who miss a visit:** Contact Subjects by phone (either their own phone or often that of a family member or friend) if they miss a visit and arrangements will be made to either bring the patient to a follow-up site or the team will go and visit the study participant at their home. (We have found that in 2018 virtually all TT patients even in rural Ethiopian communities have access to a cellular phone, either directly or through a friend or neighbor).

- **Home visits.** Should reminders fail, the Field Teams will visit patients at their homes. When logistically convenient, home visits may be conducted before failure of reminders, as Field Teams will be in the near vicinity of subjects' homes at the time of follow-up visits. When applicable, subjects will be notified in advance of this possibility.

n. Missed Visits, Study Withdrawal and Termination

i. Missed Visits:

Missed visits are defined as no visit within a study visit window. To avoid missing a visit, the Field Team will schedule a time to see the patient within the window for the next visit, preferably more toward the beginning of the window so that there is time to reschedule if the first appointment is missed. The Community Facilitator and/or Field Team then will remind the patient of the appointment, either in person or by phone respectively. If the initial appointment is missed, they will reach out to the patient to schedule a visit for at least one more and typically two more potential dates within the visit window. If the team is unable to find a participant and a visit is missed, a "missed visit" form is completed documenting which visit was missed, attempts at contact and any comment regarding why visit was missed.

ii. Unscheduled Visits:

Unscheduled visits are visits outside the study visit window. If an unscheduled visit is occurring in place of a missed visit (protocol deviation), then all the procedures for the missed visit will be done. Otherwise, we do not anticipate collecting data from unscheduled visits, other than for adverse event reporting (initial or follow-up reporting for adverse events for which the unscheduled visit is occurring). Unscheduled visits may occur as a result of a medical problem a subject is having, e.g. if they need to be brought to a Health Center for evaluation of a problem that comes up (e.g., suspected cataract).

iii. Loss to Follow-up:

Loss to follow-up is determined at the end of the follow-up period (1 year follow-up). A participant who misses an interim visit is held as 'missed visit' and all efforts expended in locating the participant for the subsequent visits. If the study participant still is missing by the end of the 1 year follow-up window, then the participant will be considered to be lost to follow-up. Great efforts, along the lines described in the previous section, will be made to avoid losses to follow-up, especially for the one year visit.

iv. Voluntary withdrawal:

Participants have the right to withdraw from the study. A participant exit form is completed for those participants who elect to withdraw from the study. If a patient has voluntarily withdrawn from the study, do not attempt to contact them further. The Field Coordinating Center and Data Center will adjust follow-up lists to remove a voluntarily withdrawn patient from the list. If you notice such a patient still on the list, reach out to the Field Coordinating Center (headquarters) to point out the discrepancy, so that the list can be updated.

v. Withdrawal as a Result of Regulatory/Oversight Requirements:

Participants may be withdrawn from the study as a result of regulatory/oversight requirements such as protocol deviation in enrollment procedures, severe adverse events, or other reasons such as government, IRB, or DSMC mandate. Complete adverse event forms if needed and complete a Termination Form.

vi. Deaths:

If a study participant dies, the Field Team should attempt to get all information related to the death and complete an adverse event form and report the death to the Safety Officer as soon as possible, who in turn will report it to the relevant authorities. A study exit form also is completed.

o. Study Completion and Per-Protocol Termination of Follow up:

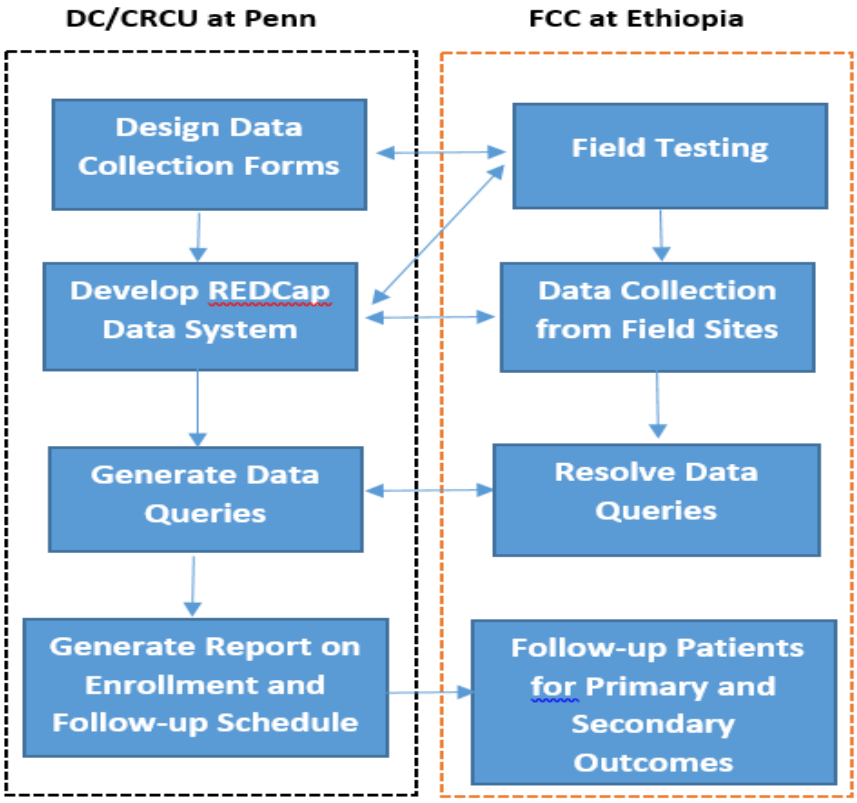
For study participants who complete their one year follow up, in addition to the visit form, a study exit form is completed.

I. DATA MANAGEMENT, DATA QUALITY ASSURANCE AND MONITORING

1. Overview of Database

The FLAME Trial database will be constructed using the Research Electronic Data Capture (REDCap) system (www.project-redcap.org)[32] hosted at the University of Pennsylvania. REDCap is a secure, web-based application designed to support data capture for research studies providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The study Chair Dr. Kempen has used the REDCap and Mobile App successfully for data collection in Ethiopia using the approach proposed herein.

As shown in the following figure, the data collection and data management for the FLAME Trial will be a collaborative effort between the Field Coordinating Center (FCC) in Ethiopia and the Data Center (DC) at the Center for Preventive Ophthalmology and Biostatistics (CPOB) and Clinical Research Computing Unit (CRCU) at the University of Pennsylvania. The FCC will take responsibility for collecting the study data from trial participants; the DC will develop the REDCap database, develop and implement a quality assurance program to ensure data integrity and completeness, perform the data management and statistical analysis of all study data.



The data from the FLAME Trial will include baseline participant characteristics, enrollment, treatment, and follow-up outcome assessment data collected using the REDCap and REDCap Mobile App by Field Teams that are trained, certified and supervised by the Field Coordinating Center (FCC). The REDCap Mobile App will be installed on study-use-only androids (with password protection) so that data can be collected offline at the villages without internet access and stored locally on that device, after which it will be synced back to the main REDCap server once internet access becomes available. The REDCap Mobile App has been proved most useful when data collection is performed in places without internet service (e.g., no WiFi or cellular service) or where there is only intermittent internet service, as is the case in the study area of FLAME trial. The free REDCap Mobile App was launched in April 2015, and it receives around 1000 (and increasing) downloads per month in 100+ countries. There are several studies operating mobile REDCap App successfully in rural areas of Africa using this approach.[33-35]

p. Design of Data Collection Forms

The data collection forms will be designed to facilitate accurate data collection and data entry. The type of variables to be included in the data collection forms are listed in **Table 4** at the end of this Section. The data forms will be designed by the Data Center with input from the Study Chair, Data Center Director (Dr. Ying), and Director of Field Coordinating Center on the specific data fields to be included. The layout of the forms generally will consist of two columns; the left column consisting of items required for all subjects and the right column consisting of items that are answered conditional on the responses to the items in the left column. The correct logical flow is conveyed through use of directional arrows. Multiple choice and check-off responses are used as much as possible; however, unusual findings may be recorded in comment fields that are keyed in their entirety. Key instructions on additional actions to complete the form are included in the form items. English will be used for all study forms; and only fluent English speakers will serve as study coordinators.

Logical sections of the forms are divided into different form sections or components, with numbering of items specific to the component. The component concept allows for modularity of form design and therefore minimizes the impact of form revisions. Form revisions and additions are accommodated by having data management staff at the Data Center modify or create the appropriate data definition.

Forms nearing finalization will be circulated to Field Coordinating Center for review and comment, and pilot tested by the Field Team before finalization.

SOPs for form completion guidelines are listed in VII. Annex F.

q. Development of REDCap Database

The study REDCap database will be developed by the staff in the CRCU according to specifications that describe the features and functions of the data system. The REDCap database will include some advanced features including auto-validation (range/data checks), branching/skip logic, data calculations (e.g., automatically calculate the body mass index) and subject scheduling, all of which will be applied for the FLAME Data System.

Prior to deployment and use of the FLAME Trial's REDCap database, the electronic systems will be subjected to extensive testing. The REDCap data system will be field tested by the Field Team in Ethiopia. Once the system has been tested and validated, it will be migrated from a 'development' environment and deployed in a 'production' environment. Modifications to the database system will be requested using standard operating procedures, resulting in the development of written specifications that explicitly document programming requirements. Following modification of the system, the system will be re-subjected to testing and validation before again being deployed in production mode.

r. Training and Certification of Data Collectors

Users' Manuals for the Field Teams on data collection procedures and troubleshooting for using the REDCap and Mobile APP will be prepared by the FCC in English (to maximize simplicity of making entries in English). Training study coordinators for the use of the REDCap database and Mobile APP will be an essential task for the study. The DC/CRCU will have Webinar trainings with Field Team members for using the REDCap and Mobile App for data collection and transmission. After completing the training, FCC Field Team members will go through certification process by demonstrating sufficient skills of using REDCap and Mobile App for data capture with androids and successfully syncing the data from androids to the main REDCap database. During the FLAME Trial, the CRCU will provide technical support to Field Team members for any problems with the data collection and data transmission using REDCap and Mobile APP.

The FCC will train the Field Teams in the best practices for conducting clinical trials following the study protocol, and for the data collection.

After both training of best practice for clinical trials provided by the FCC, and the technical training on using the REDCap and Mobile APP for data capture and transmission, the Field Team members will be required to go through a certification process. **Certification requirements** for Field Team members include: 1) attendance at a training session provided by the FCC that includes instruction in the FLAME Trial study design and methods, human subjects protection, Good Clinical Practices; 2) complete the Webinar training by DC/CRCU on the data collection using REDCap data system and Mobile App; 2) demonstration of proficiency in using the REDCap Data Management Systems by entering data from mock CRFs and using the Mobile App and syncing the data to the main REDCap database; 3) certificate of completion of training in human subjects protection and Good Clinical Practices; and 4) submission of a signed Data Integrity Statement.

s. Data Collection and Transfer

Study Field Teams consisting of trained and certified study coordinators will go to the field sites to collect all study data at baseline and follow-up visits as scheduled below:

Table 2: Visit and Data Collection Schedule					
Assessments	Visit 1 Baseline	Visit 2 Surgery	Visit 3 4 weeks	Visit 4 6 months	Visit 5 12 months
Timing/Interval (Days[D]) pre/post surgery (=D 0)	D -7 to 0	D 0	D 28-35	D 180±60	D 365 ± 90
Informed Consent, Demographics, Randomization	X				
Medical and Ophthalmic History	X			X	X
External Examination using +2.5 magnifying loupe	X			X	X
Visual Acuity, Trachoma & Trichiasis Grading; IOP; Patient reported outcomes (pain, EQ5D)	X		X	X	X
Medication Review	X	X	X	X	X
Adverse Event Review; medical care utilization		X	X	X	X
Surgical Details		X			
Assessment of Treatment Adherence			X		
Subject Exits Study					X
*D=days post TT surgery; IOP=intraocular pressure; EQ5D=EuroQol health utility (Ethiopian form)					

The data to be collected for the FLAME trial are listed in **Table 2** above that include:

1) Baseline data before surgery: demographics, detailed medical and ophthalmic history data, visual acuity, clinical signs of trachoma, intraocular pressure, use of medications etc.
2) Data on the day of surgery: surgical details, medication review and adverse review.
3) Data at follow-up visits within 1 year: medication review, adverse event review, medical and ophthalmic history, visual acuity, clinical signs of trachoma, patient self-reported outcome, etc.

Data will be collected from all participants who have signed the study consent form. Early in the study, the data will be first recorded into the paper data collection forms. The data recorded in the paper forms will be treated as source data. Use of paper forms will provide added security against data loss if androids were damaged/lost before uploading of data. In some rural areas of Ethiopia, the lack of reliable internet coverage makes it not feasible to use online REDCap for data collection. To make the data transmission in an accurate and timely fashion, the data in the paper forms will be entered into the REDCap database by the study coordinators on the same day. If the internet access is limited in rural areas of Ethiopia, the REDCap Mobile App will be used for data entry offline using an android. When the internet access becomes available, the data will be synced back to the main REDCap database.

At the study site, each data item entered into the paper data collection form will be checked for valid codes, legitimate ranges, legal dates, and completeness by the study coordinators. Any invalid or missing data in the paper forms will be corrected onsite. The paper data collection forms then will be signed off by the study coordinators. Further validation of data will occur during and after the data entry into REDCap database.

T. Data Edits for Data in REDCap

All data recorded into the REDCap database are subject to consistency checks developed by the staff in the CRCU and Data Center. Often these post-entry checks involve cross-checking across several different forms and visits. The Biostatistician will develop the logic for these checks and the comments to be associated with the resulting data queries. The queries then will be sent to the FCC for validation and resolution. The FCC will review the data query and check with the source data (if paper forms still were in use at the time of the data entry). If necessary, the Field Teams will make data corrections (documented with initials and dates on the paper form) and update the REDCap database. The updated data records again will be subjected to the entire data checking system. When extraordinary circumstances arise in which the query may never be able to be resolved to meet the requirements of the edit logic, the biostatistician may, with the approval of the Data Center Director, flag specific items on specific forms as exempt from further edit. The REDCap system generates electronic transaction records after every record correction so that a fully verifiable audit trail is created.

u. Data Back-up and Data Security

REDCap at Penn is administered by Penn Medicine Academic Computing (PMACS). Data for REDCap are stored in a database that is located on PMACS servers in a managed, restricted access data center. The database is backed up nightly. Individual user accounts are required to access REDCap. Those accounts are managed by PMACS and access to the study database is controlled by the study owner through individual study level permissions. The REDCap installation is HIPAA compliant (which will be useful should the HIPAA law come to apply in Ethiopia) and REDCap includes additional features to identify and manage Protected Health Information (PHI) data within studies.

All computers and androids for data entry are username and password protected to protect against intrusion and compromise. Users must log into a computer or android for data entry, thus logging such activity. The computer/android is locked after 15 minutes of inactivity. The FLAME Trial will require the study coordinator to sync data from study androids to study REDCap databases once the internet access is available. The data recorded in the paper forms will be kept in a secure cabinet in the Field Coordinating Center, and all study data entered into REDCap will be backed up daily on the server and their offsite back-up storage servers. A rotation of backup tapes is maintained so that the database can be restored as of the most recent day of the week, week, month, or quarter. A copy of the monthly backup tapes is also stored off site. PMACS uses the University of Pennsylvania's central facility for managing the Data Center servers. The Data Center is an ISO9001:2008 certified Tier 2 Data Center. This secure, limited access facility has high-speed networking and redundant power with battery backup. Data files will be regularly exported from REDCap data system to create analysis data files for data checking and reporting. These analysis data files will reside on the Data Center file server which is backed up nightly. Individual computers will be backed up daily through CrashPlan Pro. In addition, all Data Center personnel are required to keep copies of key documents such as correspondence, statistical analysis programs, and reports on the CPOB file server, which is on an automatic backup schedule. Files of the data system as of the time of each freeze and for each publication also will be archived.

v. Quality Assurance Activities Related to Data Management

The Specific quality assurance features related to data integrity of the FLAME Trial are:

- Standard data collection forms and procedures;
- Standard REDCap data system with the built-in functions for checking of data ranges, consistency and completeness.
- Masking of patients, surgeons and study staff at field site to the assigned treatment group of the subject;
- Training and certification of study coordinators in data collection and data entry.
- Explicit instructions with the release of new/revised data collection forms about new/revised questions and instructions;
- Weekly checking of data by the Data Center to detect any data problems early and provide feedback to the Field Coordinating Center for any correction;
- Timely data detection and edits for missing, invalid, and suspect responses by the collaborative work in Field Coordinating Center and Data Center;
- Regular reporting on performance (timeliness, completeness and accuracy of data) of Field Teams for the data collection;
- Field observation and review of data collection process by the Protocol Monitor from Field Coordinating Center (the study team supervisor, the senior study coordinator, the FCC director, the Trial Chair);
- Checking by the Protocol Monitor of a random sample of entered data by the study coordinators against original source data after data editing has been completed.

w. Patient Enrollment and Randomization to Treatment Assignments

The Data Center will generate randomized treatment assignment (to either fluorometholone 0.1% or to placebo) that will be stratified by operating surgeon. Because the Surgical Team will travel to several field locations for TT surgery, and we anticipate surgeon skills may have more impact on TT recurrence than sites, we plan to stratify randomization by both surgeon/geographical site simultaneously (because surgeons will operate in particular geographical sites). Surgeons will go to a limited number of sites near the health center where they are based, so stratifying by surgeon tends to balance randomization across sites as well. A permuted block method of randomization will be used to ensure balance over time and a randomly selected block size will be used to further thwart attempts to determine the next treatment allocation based on perceived knowledge of previous allocations. The Data Center will generate a unique five-digit medication box number associated with study drug treatment or placebo treatment for each enrolled patient to maintain masking of the Field Team, who will dispense medication box to enrolled patients. Medication boxes will be packaged in sets of 20 within which 10 each will contain active and placebo treatment. Each surgeon (and associated Field Coordinating Center team members) will work through one box of 20 for each surgeon.

At each field site, screened patients will be tracked on a pre-printed screening log (indicating the

enrolling study team number and a four-digit number for the patient), prior to the patient being enrolled if deemed eligible. Enrolled patients will be randomized to receive either the fluorometholone 0.1% or placebo eyedrops immediately before TT surgery and twice daily afterwards for four weeks. When a patient is enrolled and randomized, the Field Team will enter the patient's name, and date of enrollment on the study-supplied paper Enrollment Log prepared for each study team. The enrolled patient will be assigned with a medication box number which will be recorded in the Enrollment Log and randomization form before the medication box is dispensed to the enrolled patient. Each enrolled subject will have a screening ID, an enrollment ID, and a medication kit number (to indicate treatment assignment). To decrease the dependency on the paper Enrollment Log for recording the treatment assignment of each patient, the medication box number assigned to the patient will be recorded in the patient's hard copy case report forms and the REDCap file as well. Identifying details of participants other than the Patient ID and medication box number will be kept in the FCC and will not be entered into REDCap. The treatment assignment information will be kept in the Data Center and will not be entered or shared with the Field Team to minimize the risk of unmasking of treatment assignment. From the moment the subject is randomized and receives the TT surgery, subjects will be considered as enrolled in the study and will be included in efficacy and safety analyses. Patients who have both eyes eligible will have both eyes assigned to the same treatment group and will receive one medication box that has sufficient drug (or placebo) to use for four weeks. While randomization of one eye to fluorometholone and one eye to placebo for patients with both eyes eligible would be a statistically more efficient design, we considered the risk of the patient administering the wrong eye drops to be greater than the benefit and chose randomization by person.

x. Reports Developed by the Data Center

The Data Center will provide study reports based on available data to support the Field Coordinating Center for subject enrollment and follow-up, the quality assurance activities of the study, and the periodic meetings of the Executive Committee and the Data and Safety Monitoring Committee (DSMC). Certain reports designed to check the completeness of activities of Field Coordinating Center will be run on the current database, usually involving the master files and auxiliary files and programs that identify and count specific data collection forms without analyzing the content of the data record. Other reports geared towards a comprehensive summary of the study data require a significant amount of preparation. Therefore a data cutoff date will be chosen (usually the end of the month 30 to 60 days before the report is needed) so that the data files will not be changing while work on the report is ongoing and a "frozen" dataset is created. Before proceeding, checks are run to verify the completeness of available information. The frozen datasets consist of the full complement of SAS system files in the integrated database. During the course of the FLAME Trial, hundreds of tables will be used for the various committee meetings. Some tables will be used in reports to several committees.

y. Safety Data

The FLAME Trial does not involve the use of investigational drugs, investigational devices, or invasive diagnostic or therapeutic procedures as defined by the United States' Food and Drug Administration (FDA) and therefore is not under FDA purview. The FLAME Trial will be subject to regulations for federally funded research as overseen by the Office of Human Research Protections (OHRP). In Ethiopia, although fluorometholone is an approved drug, all clinical trials are under the purview of the

Ethiopian Food and Drug Administration (EFDA), formerly known as the Ethiopian Food, Medicine and Health Care Administration and Control Authority (FMHACA; which has a similar role to the FDA in regulating clinical trials), as well as the National Research Ethics Review Committee (NRERC) of the Ministry of Science and Technology (which functions like an institutional review board for clinical trials) (or their successor organizations should the names of the governing organizations be changed). OHRP, FMHACA and NRERC (as well as the academic institutional review boards (IRBs) involved) require reporting of unanticipated problems, defined as any incident, experience, or outcome that are unexpected, related, and suggest that the research places participants or others at a greater risk of harm than previously known or recognized. Allergan, the drug donor, also requires reporting of certain adverse events on its own form set.

Data regarding anticipated potential adverse outcomes of fluorometholone 0.1% will be collected prospectively, including**:** 1) measured intraocular pressure (median of three measurements, analyzed as the proportion ≥30 mmHg and the proportion with ≥10 mmHg rise in IOP from baseline); 2) cataract surgery: history of cataract surgery (yes/no); 3) infectious eye problem (yes/no, if yes specify); 4) dose-limiting toxicity (see Protocol end of Section 11.2; yes/no, if yes specify); 5) other adverse event attributed to study treatment (yes/no, if yes specify). 6) Any other ocular surgery during study? (yes/no, specify if yes). Examples of dose-limiting toxicity include: a) SAEs (see below) judged as likely related to the treatment by the investigators; b) allergy to the masked study treatment (fluorometholone or artificial tears); or c) when the field investigative team determines that other AEs observed in a subject would make future applications of the treatment contraindicated on the basis of side effects. Observation of such events will constitute “dose-limiting toxicity” for a subject. In addition, irreversible SAEs judged likely to be attributable to study treatment (e.g., a clinically important degree of corneoscleral thinning), also would be considered a dose-limiting toxicity.

All serious adverse events (SAE) will be documented in detail and will be reported to the FLAME Trial Safety Officer, who in turn will report them to the relevant agencies and IRBs as per the agencies’ and IRBs’ requirements. The Study Safety Officer also will notify the Chair of the DSMC when the DSMC’s criteria for such reporting are met; the DSMC Chair will determine whether the entire DSMC needs to be notified and determine whether there is a need for a DSMC conference call to discuss the problem. The DSMC might choose to appoint a DSMC Safety Officer to carry out this process, per the DSMC’s decision on the matter. Unanticipated and anticipated events will be reviewed at the regular DSMC meetings. Few unanticipated events are expected given the nature of the study procedures. A narrative summary of each SAE event will be provided by the Field Coordinating Center to the DSMC at its regular meetings. The non-serious AE will be collected at each study visit by Field Team, and be tabulated by treatment group for the DSMC meetings.

z. RESOURCE SHARING PLAN

i. Data Sharing Plan

NIH Data Sharing guidelines (NOT-OD-03-032: Final NIH Statement on Sharing Research Data - February 26, 2003) encourage discussion of data sharing with program staff. NEI staff have stated recently that NEI does not have a specific policy or preferred method of data sharing. The FLAME

Trial Study Leadership Committee and NEI Project Officer will be in communication during the project period about any emerging policy from NEI.

As described in the Approach section of applications from the Study Chair and Data Center, the FLAME Trial will generate a large database on the incidence of postoperative TT and predictive factors, as well as other outcomes of eyes/patients undergoing TT surgery. Data cannot be analyzed for publication until they are released by the Data and Safety Monitoring Committee. Study guidelines regarding publication include that the primary outcome results will be submitted for publication within 1-year of data release; and that secondary outcome measures and the baseline predictors for treatment outcomes also will be analyzed and submitted for publication, ideally before the end of the planned 5-year study period.

FLAME Trial data will be made available through two modes:

- A summary, de-identified (i.e., no participant names, identification numbers involving codes for Clinical Center and site, examination dates, birthdates, etc.) data set will be made available through direct inquiries to the Study Chair or Data Center Director soon after the time of publication [note: NIH policy advises release at the time of acceptance of publication; however, there are many good reasons for not releasing results in advance of publications that have impact on clinical practice.] The plan is that SAS data sets and the data collection forms (blank) for the eye examinations and other encounters with the participants will be provided in electronic format. FLAME Trial SAS data sets will be largely self-documenting in that an item identifier is embedded within the label for each variable. In addition, key derived variables will also be contained in the data sets.
- The full SAS databases (not fully de-identified) associated with the FLAME Trial will be kept on secured computer systems maintained by the Study Chair and/or by the Director of the Data Center. Researchers may request limited access data sets from the Study Executive Committee. Approved recipients will need to enter into a data sharing agreement. Costs for compilation of the datasets will be the responsibility of the recipients. After completion of activities, relevant documents will be filed on a data sharing service (see MOP Section L).

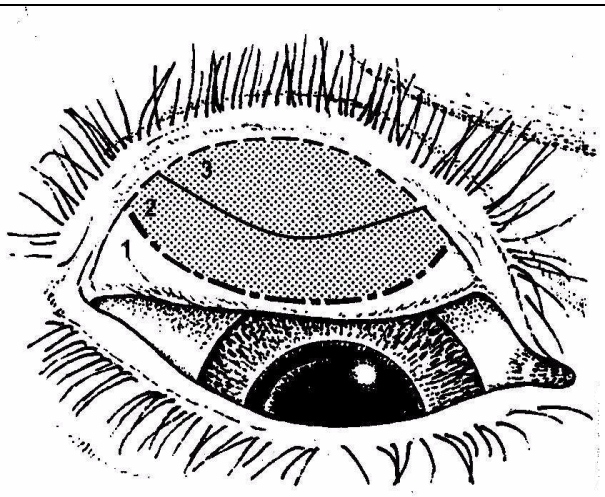
ii. Sharing Model Organisms

Not applicable

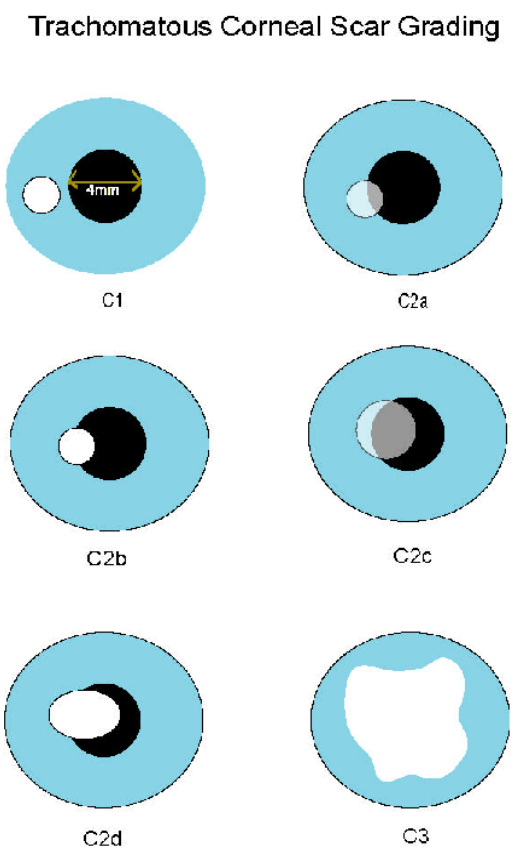
iii. Genome-Wide Association Studies (GWAS)

Not applicable

Table 4: FLAME Trial Data Summary							
Outcome Measures	Variable Description/Definition	Type of Variable	V1	V2	V3	V4	V5
PRIMARY	Incidence of Postoperative TT within 1 year*	dichotomous			X	X	X
SECONDARY							
Eyelid Variables	Reoperation for TT (per eyelid)	dichotomous			X	X	X
Trichiasis	Total number of lashes touching cornea (K) (per eye)	count	X		X	X	X
	Total number of lashes touching medial to K (per eye)	count	X		X	X	X
	Total number of lashes touching lateral to K (per eye)	count	X		X	X	X
	Total number of lashes touching globe**	count	X		X	X	X
	Lashes touching cornea or not**	dichotomous	X		X	X	X
	Trichiasis grade (T0=none; T1=lashes deviated toward globe no touch; T2= Lashes touching globe but not cornea; T3=Lashes rubbing cornea)	ordinal	X		X	X	X
	Extent of Lashes Touching Cornea**: None; Mild (1-5); Moderate (6-9); Severe (10 or more)	ordinal	X		X	X	X
Epilation	Evidence of epilation, per eyelid	dichotomous	X		X	X	X
	Extent of epilation, per eyelid: <1/3; ≥1/3 to ≤2/3; >2/3	ordinal	X		X	X	X
Entropion:	Area of Entropion / Degree of severity: <50% of lid margin / >50% of lid margin	ordinal	X		X	X	X
	None: E0 (none)						
	Without K-lash base touch: E1 (mild) / E2 (moderate)						
	With K-lash base touch: E3 (severe) / E4 (total)						
Adverse Outcomes of TT Surgery	Persistent TT, immediately postoperatively (yes/no)	dichotomous		X			
	If yes, specify	dichotomous		X			
	Late complications of TT surgery not otherwise captured (yes/no)	dichotomous		X			
	If yes, specify	dichotomous		X			
Overcorrection	Per upper eyelid	dichotomous		X	X	X	X
Eyelid notching	Per upper eyelid	dichotomous		X	X	X	X
Lid closure defect	Per upper eyelid	dichotomous		X	X	X	X
Granuloma	Per upper eyelid	count		X	X	X	X

Ocular Surface Variables							
Discharge	Serous (watery)	dichotomous	X		X	X	X
	Purulent (yellowish, thick)	dichotomous	X		X	X	X
	Foamy (foam-like)	dichotomous	X		X	X	X
Conjunctivalization of lid margin, per lid CM 0: None CM 1: muco-cutaneous junction is located anterior to its normal position, but the whole line is still posterior to the line of Meibomian gland orifices CM 2: The muco-cutaneous junction is located anterior to the line of the Meibomian gland orifices for less than 50% of the lid. CM 3: The muco-cutaneous junction is located anterior to the line of the Meibomian gland orifices for greater than 50% of the lid		ordinal	X		X	X	X
Upper eyelid papillary hypertrophy (each eye) PO: Absent: normal appearance P1: Minimal: individual vascular tufts (papillae) prominent, but deep subconjunctival vessels on the tarsus are not obscured. P2: Moderate: more prominent papillae and normal vessels appear hazy, even when seen by the naked eye P3: Pronounced: conjunctiva thickened and opaque, normal vessels on the tarsus are hidden over more than half of the surface		ordinal	X			X	X
Follicles (each upper eyelid) FO: Absent F1: Follicles present, but no more than 5 in zones 2 and 3 together F2: More than 5 follicles in zones 2 and 3 together, but less than 5 in zone 3 F3: Five or more follicles in each of the three zones		ordinal	X			X	X
							
Conjunctival Scarring (each upper eyelid), if NO prior lid surgery		ordinal	X				

	CO:No scarring on the conjunctiva C1: Mild: fine scattered scars on the upper tarsal conjunctiva, or scars on the other parts of the conjunctiva C2: Moderate: more severe scarring but without shortening or distortion of the upper tarsus. C3: Severe: scarring with distortion of the upper tarsus. C6: Not applicable						
	Conjunctival Scarring (each upper eyelid), <u>if prior lid surgery</u> SCO: No scarring on the conjunctiva SC1: Surgical line only. SC2: Surgical scar with widespread trachomatous scarring but no distortion SC3: Severe: scarring with distortion of the upper tarsus. SC4: Surgical scar with distortion immediately around the incision line. SC5: Surgical scar with additional distortion secondary to widespread trachomatous scarring. SC6: Not applicable	ordinal				X	X
<u>Visual Acuity,</u> Presenting (per eye)	Category: Measurable on chart; Count Fingers; Hand Motions; Light Perception Only; No Light Perception	ordinal	X		X	X	X
	Among those measurable on chart, logMAR	numerical	X		X	X	X
	Most likely cause of VA<6/18 (if applicable)	categorical	X		X	X	X
<u>Eye Outcomes</u> (per eye)							
	Corneal Opacity C0: No opacity C1: Opacity not entering central 4mm C2a: Opacity within central 4mm but not entering within the central 1mm of the cornea. The pupil margin is visible through the opacity. C2b: Opacity within central 4mm but not entering within the central 1mm of the cornea. The pupil margin is not visible through the opacity. C2c: Opacity within central 4mm and entering the central 1mm of the cornea. The pupil margin is visible through the opacity. C2d: Opacity within central 4mm and entering within the central 1mm of the cornea. The pupil margin is not visible through the opacity. C3: Opacity large enough and dense enough to make whole pupil margin invisible C4: Phthisis bulbi	ordinal	X		X	X	X

							
Potential Adverse Outcomes of Fluorometholone Therapy:							
Intraocular pressure (per eye)	Measurement, mmHg	numerical	X		X	X	X
	≥30 mmHg	dichotomous			X	X	X
	Elevation ≥10 mmHg above baseline	dichotomous			X	X	X
	Prior filtering surgery	dichotomous					
Cataract, per eye	Cataract diagnosis and visual acuity worse than 6/18	dichotomous	X		X	X	X
	Prior cataract surgery	dichotomous	X		X	X	X
Infectious problem (per eye)	Present or absent?	dichotomous			X	X	X
	If yes, specify	string			X	X	X
Dose-limiting toxicity (per eye)	Present or absent?	dichotomous			X	X	X
	If yes, specify	string			X	X	X
Adverse Events (AE's)							
AE attrib'd to study treatment	Present (1 or more) or absent?	dichotomous		X	X	X	X
	If yes, specify	dichotomous		X	X	X	X

per eye***							
AE attrib'd to study treatment per person	Present (1 or more) or absent?	dichotomous		X	X	X	X
	If yes, specify	dichotomous		X	X	X	X
Specific AEs	Coded as per protocol, Section 11.2	categorical		X	X	X	X
Patient-reported Outcomes							
EQ5D (Ethiopian version)	mobility, 5 levels (none to severe)	ordinal	X		X	X	X
	self-care, 5 levels	ordinal	X		X	X	X
	usual activities, 5 levels	ordinal	X		X	X	X
	pain/discomfort, 5 levels	ordinal	X		X	X	X
	anxiety/depression, 5 levels	ordinal	X		X	X	X
	Derived score	numerical	X		X	X	X
WHO PBD Visual Functioning Questionnaire	20 items, each 1-5 (Never, Rarely, Sometimes, Often, Very Often)	ordinal	X		X	X	X
Pain Impact Questionnaire	6 items, four levels (Never, Occasionally, Often, Constantly)	Ordinal	X		X	X	X
Change in Pain after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X
Change in **Light Sensitivity** after surgery (per eye)	3 levels (none, a little, a lot)	ordinal	X		X	X	X
	If present, how often: occasional, moderate, severe	ordinal	X		X	X	X
Change in **Foreign Body Sensation** after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X
Change in **Watering** after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X
Change in **Discharge** after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X
Change in **Itching** after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X
Change in **Vision Problem** after surgery (per eye)	4 levels (0=worsened, 1=no improvement, 2=some improvement, 3=a lot of improvement); or No symptom preop (8); or No Surgery in this Eye (99)	ordinal	X		X	X	X
	If present, how often: occasional, often, always	ordinal	X		X	X	X

Limitations	Are there things you are unable to do because of your eye problem? (yes/no)	dichotomous	X		X	X	X
	If yes, what are they?	string	X		X	X	X
Satisfaction with **trichiasis outcome**	0 = Very dissatisfied 1 = Dissatisfied 2 = Neither satisfied nor dissatisfied 3 = Satisfied 4 = Very satisfied 99 = NA/No surgery	Ordinal			X	X	X
	If not satisfied (if answer for 2.1 is 0 or 1 or 2), why? (Write reason, or 99 if the answer to 2.1 is 2 or 3 or 4 or 99)	String			X	X	X
Satisfaction with Cosmetic Outcome	0 = Very dissatisfied 1 = Dissatisfied 2 = Neither satisfied nor dissatisfied 3 = Satisfied 4 = Very satisfied 99 = NA/No surgery	Ordinal			X	X	X
	If not satisfied (if answer for 2.1 is 0 or 1 or 2), why? (Write reason, or 99 if the answer to 2.1 is 2 or 3 or 4 or 99)	String			X	X	X
Health care Utilization							
	Excess utilization at the time of TT surgery, yes/no	dichotomous		X			
	If yes, specify	string		X			
	Episode of health utilization 1, 2….	dichotomous			X	X	X
	Nature of health utilization 1,2,…..	string			X	X	X
	Was health utilization 1,2,….. related to TT or treatment?	dichotomous			X	X	X
	Specify outcome of health utilization 1,2,…..	string			X	X	X
Non-outcome Covariates							
Treatment	Assignment (fluorometholone, placebo (masked))	dichotomous	X				
	Dispensed study drug?	dichotomous	X				
	Medicine box number	numerical	X				
	Number of eyes treated (1 or 2)	dichotomous	X				
Adherence	Used treatment assignment? (yes/no)	dichotomous			X		
	Level of adherence by history (none, low, moderate, high)	ordinal	X		X		
	Bottle weight (absolute value)	numerical	X		X		
	Change in bottle weight from baseline (actual value)	numerical			X		
	% of expected change in bottle weight (adjusted for early visits, # eyes)						
	Level of adherence by weight (none, low, moderate, high)	ordinal	X		X		
Other variables							

Age	In years	numerical	X				
Sex	Male or Female	dichotomous	X				
Ethnicity	Oromo or other?	dichotomous	X				
	If not Oromo, specify	string	X				
Race	African or other?	dichotomous	X				
	If not African, specify	string	X				
Education	In years	numerical	X				
Literacy	Able to read and understand consent form?	dichotomous	X				
Medications in use	Yes or no?	dichotomous	X		X	X	X
	Specify medication and dose	String/ numerical	X		X	X	X
Other ocular disease diagnoses	Yes or no?	dichotomous	X		X	X	X
	Specify	String/ ICD code	X		X	X	X
Systemic disease diagnoses	Yes or no?	dichotomous	X		X	X	X
	Specify	String/ ICD code	X		X	X	X
**derived variables							

1. DATA ANALYSIS PLAN

1. Overview of the Study Design from the Statistical Perspective

The **FL**uorometholone as **A**djunctive **ME**dical Therapy for Trachomatous Trichiasis (TT) Surgery (**FLAME**) Trial is a prospective 1:1 randomized, parallel design, double-masked, placebo-controlled clinical trial of fluorometholone 0.1% eye drops vs. placebo in eyes with trachomatous trichiasis (TT) undergoing lid rotation surgery. Fixed sample size with anniversary closeout. Key aspects of the design and rationale that have major bearing on the approach to data analysis, statistical issues, and data monitoring are noted below:

- There are 2 treatments groups.
  - Active treatment group: Fluorometholone 0.1% one drop two times daily for four weeks
  - The placebo control group: Placebo (artificial tears) one drop two times daily for four weeks
- The unit of randomization is person, and one or both eyes will be included into study if eligible.
- The ratio of the number of patients assigned to active treatment group to placebo group is 1:1.
- Stratification: By surgeon.
- The duration of the treatment period is four weeks, and the total length of follow-up is one year after randomization.
- The primary outcome is incidence of postoperative TT by one year as determined by the trained Field Team members at four weeks, six months and one year. Recurrence is defined as the presence of one of the following: (1) one or more lashes touching the globe in an eye operated for TT; (2) clinical evidence of epilation; (3) history of repeat TT surgery.
- Secondary efficacy outcome measures are:
  - Incidence of reoperation for postoperative TT (recommended or done) within one year
  - Number and location of lashes touching the globe within ≤1 year
  - Entropion (presence and extent) within ≤1 year
  - Cost-effectiveness
- Safety outcome measures are:
  - Corneal opacity (change in proportion from baseline) within ≤1 year
  - Overcorrection within ≤1 year
  - Eyelid notching/eyelid contour abnormalities within ≤1 year
  - Lid closure defect within ≤1 year

- Granuloma within ≤1 year
- Pain score over 1 year postoperatively
- IOP elevation over 1 year postoperatively
- Occurrence of cataract surgery within ≤1 year
- Adverse events attributed to study treatment within ≤1 year

- Patient-reported outcomes:
  - Patient satisfaction over 1 year postoperatively
  - Cosmetic outcome over 1 year postoperatively
  - Health utility over 1 year postoperatively
- Additional outcomes
  - Visual acuity with presenting correction over 1 year postoperatively
  - Compliance of treatment (assessed by study treatment bottle weights) measured at four weeks (completion of treatment)

aa. Overview of the Study Design

For the primary outcome measure, the null hypothesis to be tested is:

$H0: \pi_A - \pi_C = 0$

where π is the proportion of patients with recurrence by one year, **A** refers to the active treatment group using Fluorometholone 0.1% eye drop and **C** refers to the placebo control group.

bb. Sample Size Determination

Sample size calculations are based upon the following assumptions:

- Two-sided type 1 error rate of 5%
- Statistical power is 90%. This trial is intended to be considered the definitive clinical trial for assessing the efficacy of fluorometholone 0.1% eye drop for reducing the recurrence of TT; therefore, power is set higher than the traditional 80% level because missing a true treatment effect would be a serious error.
- The comparison of recurrence rate between active treatment group vs. placebo control group will be based on a per eye analysis using generalized estimating equation (GEE) to adjust for the inter-eye correlation
- 25% lower risk of postoperative recurrence of TT in the fluorometholone 0.1% group. In our Phase 2 trial, we observed 29% lower risk of recurrence of TT (21/115 in the aggregated treatment groups, and 10/39 in control group). We anticipate that an absolute difference of less than 25% would be insufficient to motivate uptake of the intervention at programmatic levels.

- Incidence of TT recurrence by 12 months in the placebo group ranges from 15-20%. Our Phase II trial observed recurrence rate of 25% (10/39), and a comprehensive review suggested a typical recurrence rate of 20-30% in studies where surgeons were not especially selected and trained.[6] We choose 15-20% conservatively.
- Correlation for recurrence between two eyes from the same patient is assumed to be 0.46. The inter-eye correlation was 0.15 in our preliminary trial, 0.48 in BLTR-PLTR trial,[36] 0.40 in the Doxycycline trial[50] (from personal communication), and 0.48 from the Clamp trial.[8] The inter-eye correlation from the observed data of the FLAME (as of October 26, 2022) is 0.46.
- Bilaterality of TT surgery is 35% based on the 932 FLAME participants enrolled (as of Oct. 26, 2022).
- Rate of loss to follow up is at 2% based on the FLAME, which is better than that in our preliminary trial (5%) and in Professor Burton's trials (2-7%).[19,22,36,50]

The number of participants for enrollment and number of eligible eyes required are in the following table for the assumed postoperative TT rate ranging from 17% to 20% in the Placebo group. We target to enroll up to 2,500 participants (1,250 participants per group).

TT incidence rate in one year				Number of Participants Enrolled	Number of Study Eyes
Placebo group	FML group	Rate Difference	% Reduction		
20.0%	15.0%	5.0%	25%	2190	2956
19.0%	14.3%	4.7%	25%	2383	3217
18.5%	13.9%	4.6%	25%	2434	3286
18.0%	13.5%	4.5%	25%	2484	3354
17.5%	13.2%	4.3%	25%	2665	3598
17.0%	12.8%	4.2%	25%	2727	3681

cc. Statistical Analyses

i. General Approaches to Statistical Analysis

The general guidelines for all the analyses in the trial include:

- Analyses comparing treatment groups will follow the intention-to-treat (ITT) principle; that is, all patients will be analyzed in the group to which they are assigned regardless of the compliance of using the fluorometholone eye drops. However, exploratory sensitivity analyses will be performed using other approaches including a per protocol analysis.

- For the eye-specific primary or secondary outcomes, both eyes of bilateral patients (i.e., both eyes eligible for the trial) and one eye of unilateral patients (i.e., only one eye eligible for the trial) will be included in the analyses. Statistical methods that accommodate the correlation in outcomes between eyes, such as mixed effects models and marginal models using the generalized estimating equation (GEE) approach, will be used for eye-specific analyses [37-39].
- Because the randomization will be stratified by the surgeon/geographical area, all the patients with surgery performed by the same surgeon are clustered, thus the correlation from this clustering will be accounted for by using generalized linear mixed models (GLMM).[40] Generalized linear mixed effects models allow specification of correlation from clustering with same surgeon and from use of data from two eyes of same patients.

ii. Baseline Descriptive Analysis

Tables will be generated and inspected to compare, by treatment group, the distribution of key baseline variables having descriptive and prognostic importance. These variables will include, but not be limited to, patient age, gender, severity of trachomatous trichiasis (TT), medication use, presence of epilation, presence of entropion, number of eyelashes touching the globe, number of eyelashes touching the cornea, location of trichiatic eyelashes, cornea opacity, visual acuity, etc.

Patient-level comparison of baseline characteristics between two treatment arms will use standard statistical techniques for comparing two independent groups: chi-squared tests for equality of proportions, independent t-test for equality of means, Wilcoxon rank sum test for skewed data. Eye-level comparison of baseline ocular characteristics will use generalized estimating equations to account for the inter-eye correlation.[37] The distribution of continuous variables will be assessed by measures of normality and graphical displays; non-parametric methods or data transformations may be applied when appropriate.

iii. Data Analyses of the Primary Outcome Variable

a. Primary Analysis of Primary Outcome

The primary outcome measure is the postoperative recurrence of trachomatous trichiasis (TT), defined as one or more eyelashes touching the globe or evidence of epilation (lash stubs) on examination, or a history of repeat trichiasis surgery at any time during the one year follow-up period after the baseline surgery.

In this trial, some patients will undergo concurrent surgery in both eyes with TT, and their treatment outcome (i.e., recurrence of TT) is likely to be correlated.[8] The primary assessment of efficacy will be the comparison of cumulative proportion of incident post-operative TT by 12 months post-surgery between the two treatment groups using a repeated measures logistic regression model, where the inter-eye correlation will be accounted for through generalized estimating equations (GEE)[37-39]. The repeated measures logistic regression model will be executed by using PROC GENMOD in SAS with the stratification factor Surgeon as a covariate, and the robust sandwich variance estimate will be calculated by using the option of TYPE=IND in the REPEATED Statement to account for the inter-eye correlation. The difference for cumulative incidence rate of

postoperative TT by 12 months, the odds ratio and their 95% confidence intervals for the comparison between two treatment groups will be calculated from the repeated measures logistic regression model.

It is expected that the important baseline characteristics (those known to affect the risk of recurrence) will be balanced between the two arms by stratified (for operating surgeon/geographical area) randomization. If this is the case, no baseline covariates will be included into the logistic model. If two arms are found to be substantially imbalanced with respect to baseline covariates, the imbalanced baseline variables will be included into the logistic regression model.

b. Secondary analysis of primary outcome:

To fully evaluate the treatment effect on the primary outcome, we will perform secondary analyses of the primary outcome as described below.

i. Effect modification for primary outcome

To check the consistency of results over subgroups, we will assess effect modification of the treatment on the primary outcome (TT recurrence over one year) with the following factors by including treatment group indicator, subgroup indicator and their interaction term in the stratified logistic regression model as described above. This analysis will be done for each of following potential effect modifying variables separately. If we find any important interactions, stratum-specific recurrence rate by treatment group and their odds ratios (ORs) for treatment effect will be reported for each effect modifying variable.

a. Preoperative upper eyelid trichiasis severity with five categories (epilating-less than half the eyelid, epilating half or more of the eyelid, 1-5 lashes, 6 – 9 lashes, 10-19 lashes, 20+ lashes).

c. Preoperative entropion severity (none, mild, moderate, severe)

d. Sex (male, female)

e. Age group—classified based on the age distribution

f. Conjunctival (papillary) inflammation (none, mild, moderate, severe)

g. Corneal scarring (none, mild, moderate, severe)

ii. Predictors for recurrence:

Univariate and multivariate logistic regression models that account for the inter-eye correlation using GEE will be used to identify potential predictors for recurrent trichiasis by one year. Predictors of recurrent trichiasis to be evaluated will include:

a. Pre-operative disease severity (trichiasis, entropion, corneal opacity)

b. Type of trichiasis lashes at baseline

c. Trichiasis lashes location at baseline

d. Surgeon

e. Scarring and/or inflammation status at baseline and follow up time points

f. Sex

g. Age

h. Literacy

i. Surgical complications (these are unusual in our experience, so we will compare any versus none)

iii. Recurrence over time at four weeks, four to six months, and one year

Intention-to-treat analysis will be performed at each follow-up time point separately (four weeks, four-to-six months and one year) to assess the consistency of treatment effect over time on TT recurrence by using stratified logistic regression models. In addition, we will perform logistic regression model analysis for postoperative TT incidence by one year (e.g., ever had postoperative recurrence of TT yes/no during one year follow-up).The stratification variable (surgeon) along with baseline imbalanced or important prognostic factors will be included in this longitudinal modelling to estimate the adjusted odds ratio for comparing the recurrence between fluorometholone 0.1% and placebo.

iv. Analysis for early and late post-operative TT

If primary analysis find fluorometholone 0.1% eyedrops is effective in reducing the risk of post-operative TT, we will investigate whether effect of the fluorometholone 0.1% changes over time by performing the above comparisons between two treatment groups for the incidence of early post-operative TT (defined as TT occurred within 6 months post-surgery) and later post-operative TT (defined as TT occurred after 6 months post-surgery) separately.

v. Analysis by treatment adherence

A secondary analysis also will be performed based on the level of adherence to randomized treatment with fluorometholone 0.1% or placebo. Adherence will be defined as the participant taking his/her drug adequately as prescribed based on bottle weights at four weeks. Sensitivity analysis of this status based on patient self-report also will be conducted.

We will calculate the % of drug consumed vs. expectation as well as the self-reported number of days taking prescribed medication and categorize the level of adherence as >75% compliance, 50-75% compliance, or <50% compliance. We will then compare the recurrence rate by treatment assignment in each of these compliance groups using logistic regression models without and with adjustment of baseline predictors for recurrence of trichiasis.

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vi. Sensitivity analyses

We expect a small percent of patients may be lost to follow-up or will not comply with the trial protocol during the study. Analyses will be performed to assess the robustness of the results with respect to dropouts and non-compliance with the eligibility criteria and the treatment protocol.

Analysis of primary outcome data from all patients who complete the 1-year follow-up (completed cases) will be performed with their treatment group assignment classified as assigned at randomization ("intent-to-treat"). Also, a "per protocol" analysis, including only those patients who met all eligibility criteria at baseline and whose assigned treatment was carried out as specified in the protocol, will be performed.

Sensitivity analyses will be performed using multiple imputation methods [43,44] for those who dropped out of the trial. Both predictive model-based methods and propensity score methods will be used to evaluate the impact of missing data. Further sensitivity analyses will be conducted using pattern mixture models for missing data if there are indications that data are not missing at random.[45]

In addition, the two analyses will be performed by treating those lost to follow-up as all having TT recurrence, and all as no TT recurrence, to see what amount of difference between those followed and those not followed would be needed to change the results qualitatively.

iv. Data Analyses of Secondary Outcome Variables

Specific secondary outcome variables for the study are severity of recurrence based on number of lashes touching the globe after recurrence, location and type of recurrent lashes (e.g., touching the cornea or not), evidence of post-operative epilation, entropion, incident corneal opacity, IOP elevation, need for cataract surgery, change in visual acuity from baseline, eyelid contour abnormality, granuloma, eyelid necrosis, lid closure defect, conjunctival scarring, conjunctival inflammation, and occurrence of adverse events, etc. (see Section 9). These secondary outcomes cover a diversity of data types, including count data, continuous data, categorical data and ordinal data. Descriptive statistics will be used for summarizing these secondary outcomes by treatment arms. For the statistical comparison of these secondary outcomes between treatment arms, we will use the generalized estimating equations of generalized linear model [41,42] to account for the inter-eye correlation (for eye-specific secondary outcomes) and for the repeated measures correlation (for secondary outcomes with repeated measures over time). These comparisons of secondary outcomes will be based on Binomial models for binary outcomes, Poisson models for count data, multinomial nominal models for ordinal outcomes, multinomial ordered models for ordered outcomes, and Gaussian models for the normally-distributed continuous data. For secondary outcomes that are measured repeatedly over time, longitudinal data analysis will be performed by comparing treatment arms by treating time as categorical variables without assuming any linearity.[37] We will adjust the multiple comparisons from evaluating multiple secondary outcomes by grouping the secondary outcomes into various categories, and a false discovery rate approach for multiple comparisons will be used within each category of secondary outcomes.[51]

v. Data Analyses of Safety Outcomes

The safety outcomes include incident corneal opacity within one year, overcorrection within one year, eyelid notching/eyelid contour abnormalities within one year, lid closure defect within one year, granuloma within one year, pain score over 1 year postoperatively, IOP elevation over one year postoperatively, occurrence of cataract surgery within one year, adverse events attributed to study treatment within one year. These safety outcomes include difference type of data (categorical, ordinal, continuous). Descriptive statistics will be used for summarizing these safety outcomes by treatment arms at each follow-up visit. For safety outcomes evaluated at eye-level over time, the statistical comparison of between treatment groups will use the generalized linear model [7, 8] to account for the inter-eye correlation and the longitudinal correlation from repeated measures over time, the time (modelled as categorical variable without assuming linearity) and operating surgeon will be included as a covariate in the model [6]. These comparisons will be based on a Binomial model for the binary safety outcome (e.g. presence of over-correction), multinomial models for ordinal outcome (e.g., extent of epilation, severity level of cornea opacity), and Gaussian model for the normally-distributed continuous outcome (e.g., pain score). For systemic adverse events evaluated at patient level, the stratified logistic regression will be performed. For ocular adverse events evaluated at eye level, the inter-eye correlation will be accounted for using the generalized estimating equations. For the comparison of patient-specific systemic adverse events that is uncommon (for uncommon event <5), we will use Fisher's exact tests for comparing between treatment arms for the incidence of adverse events, serious adverse events, and adverse events attributed to treatment.

Since we will evaluate multiple safety outcomes, correction for multiple comparison will be made using the false discovery rate approach.

f) Data Analyses of Patient Reported Outcomes

Patient-reported outcomes include: (1) patient overall satisfaction over 1 year postoperatively, (2) cosmetic outcome over one year postoperatively, and (3) health utility over one year postoperativelyies. Per-eye level reported outcomes (e.g. cosmetic outcome etc.) will be compared following the same approaches for eye-specific outcomes in sections 4.4 and 4.5. For patient-level reported outcomes (e.g., patient overall satisfaction score, health utility), the comparison between treatment groups will use the generalized linear models that include the time and surgeon as covariates. Since we will evaluate multiple patient reported outcomes, correction for multiple comparison will be made using the false discovery rate approach.

g) Data Analyses of Exploratory Outcomes

The exploratory outcomes include: (1) visual acuity with presenting correction over one year, (2) compliance of treatment measured at four weeks (completion of treatment). We will check the distribution of visual acuity and compliance rate using histograms. The visual acuity will be summarized using mean (SD) if normally distributed, and using median (inter-quartiles) if not normally distributed. The visual acuity also will be categorized into several clinically relevant levels (e.g., normal vision, vision impairment, blindness). The comparison of visual acuity (in LogMAR) between treatment groups will be performed using generalized linear models that account for both inter-eye correlation and longitudinal correlation) using GEE. For we will summarize the compliance rate by calculating the % of eyes drops administered, and categorize into several levels (<50%, 50%

to 75%, >75%). The two sample t-test will be used for comparing the compliance rate between treatment groups.

vi. Data Analyses for Cost-Effectiveness

The cost of the intervention itself will be calculated as the cost of the drops of flourometholone 0.1% that is prescribed and taken. The price of the generic drug will be based on what is normally charged in Ethiopia. The cost of post index surgery medications related to the eye will be derived from the self-reported medications, a list of which is obtained at each visit. The prices will also be standard prices at clinics in Ethiopia. The cost of any additional medical care utilization (not including study visits) will include utilization based on self-report and a price based on standard use of a clinic in Ethiopia. All costs will be converted to US dollars based on the international exchange rate. The outcomes will be cases of post-operative TT averted. If the proposed intervention is more effective and more expensive, the incremental cost-effectiveness ratio will be calculated as the difference in costs divided by the difference in cases. If one intervention is more effective and less expensive then it will be described as dominating and is the obvious economic choice. We will also calculate quality adjusted life years (QALYs) based on the change from baseline for the intervention and control group and take the difference. The incremental cost-effectiveness ratio can also be expressed as dollars spent per QALY gained. Finally, we will conduct sensitivity analyses varying one variable at a time to determine whether any reasonable variation in costs or any observed variable being at the high or low end of a confidence interval rather than at the mean would change the interpretation of the economic value of the intervention (i.e., it would go from being cost-effective to not or vice versa.) If a change in one variable at a time or a change when making all variables either the most or least favorable to fluoromethodone would change the qualitative interpretation of the results, we will bootstrap the results to characterize the level of certainty about the conclusion using a cost-effectiveness acceptability curve. Dr. K. D. Frick, a well-known health economics and a professor of Carey Business School at Johns Hopkins University will oversee the DC for performing these cost-effectiveness analyses.

vii. Handling Missing Data

Major efforts will be made by the entire study group to avoid loss to follow-up and subsequent missing data. However, despite these efforts some data for the primary and secondary outcome measures may be missing. The percentage of data missing for major analyses will be tabulated. The characteristics at baseline, and during follow-up, of patients who ultimately are unavailable for follow-up will be assessed by comparing distributions between those under follow-up to those who are lost to follow-up. When available, the reasons for losses to follow-up will be reviewed. If missing data account for more than a small percentage of expected data (>5%), key analyses will be performed not only with the actual observed data on patients under follow-up, but also using multiple imputation methods.[43,46] The propensity score method will be used to evaluate the impact of missing data on the key analyses of the study. In the multiple imputation using propensity score method, the conditional probability of missing outcome (i.e., the propensity score) first will be calculated for each subject from a logistic regression model with outcome data missing yes/no as the dependent variable, and the baseline demographic and clinical variables as predictors. The missing outcome data then will be imputed based on the observed outcome data from subjects with similar propensity scores as those with missing outcome data.[46]

viii. Identification of outliers, incorrectly collected data, and possibly fraudulent data

With each freeze of the database, a set of statistical and data analytic algorithms will be applied to detect data warranting further investigation and/or action. The identified outliers or fraud data will be investigated with study coordinators for data recording error, data entry error etc. As part of the preparation for any of the data analyses, continuous variables, including dates, are subjected to the techniques of exploratory data analysis in order to fully understand the distribution of the variable. If the outlier values are valid, statistical methods that minimize the impact of outliers will be used.

ix. Software for Statistical Analysis

SAS/STAT software (SAS Institute, Inc., 100 SAS Campus Dr., Cary, NC, 27513-2414) will be used for performing most statistical analyses. When the application can be accommodated more easily by other software packages, Stata (StataCorp, 4905 Lakeway Drive,College Station, Texas 77845), R (R Core Team, URL http://www.R-project.org/)[48], or Mplus (computer software, Los Angeles, CA) will be used.

2. QUALITY ASSURANCE ACTIVITIES

Quality Assurance also is a fundamental obligation of the FLAME Trial Research Group, as enrolled subjects deserve assurance that the results of the study will provide robust, useful data to inform future programmatic and clinical practices. For this reason, the Executive Committee will develop a comprehensive plan to assure protocol adherence and data quality. The Data and Safety Monitoring Committee also will review and monitor this plan. The plan is outlined here, with emphasis on the activities of the Field Coordinating Center and its Field Teams. Data aspects of Quality Assurance are covered in MOP Section J (especially under heading J.8), which also are summarized here.

1. General Assurances:

x. Training

The protocol, Case Report Forms (CRFs; electronic and hard copy), study drug supplies, and relevant procedures will be explained in detail to study staff during their training period (see MOP Section D).

xi. Monthly Supervision

Subsequent to initiation of subject enrollment, supervisory visits will be conducted at least monthly by the field office supervisor to ensure protocol adherence and to assist in identifying and resolving problems. Supervision visits will be followed up by action items to correct specific and general deficiencies. Follow-up supervisory visits will be conducted at an appropriate interval (shorter if substantial problems are found, longer if not).

xii. Site Visiting by FCC Addis Ababa Team and Study Chair

Periodic visits by the Field Coordinating Center and Study Chair will provide independent observation to ensure that there is standardization of procedures, that study teams have been trained adequately, and that patients and their data are being managed as specified in the protocol. Visitors from the FCC also provide assistance in solving logistical problems by conveying efficient, accurate solutions used from one to the other Field Teams. All Field Teams will be visited within a few months of the initiation of patient recruitment and will then be performed every other year on a staggered schedule. Field Teams may be visited more frequently if the study monitors deem it necessary due to problematic performance of a team or if there is staff turnover.

xiii. Conducting Site Visits

Site visitors (Coordinators from the FCC) prepare for the visit by reviewing previous site visit reports and notes from recent telephone calls. The Data Center will also prepare data to be checked against clinic forms and original source materials.

The Site Supervisor prepares by making sure that study teams are available for the site visitor to observe the teams perform the entire set of study protocols. The site visitors may ask the Site Supervisor to assist in making arrangements for local lodging and transportation.

Site visits will generally require 1-2 days. Strict adherence to the protocol is stressed throughout the visit.

General areas of review during the site visit are listed below:

- Storage and access to study medications and Medication Box accounting procedures
- Throughput process for patients during study visits with special emphasis on procedures for screening, enrollment and examinations
- Presence of up-to-date study documentation including the Manual of Procedures, data collection form masters, Protocol and Protocol memoranda, study medication inventory and tracking documentation, documentation confirming reports of serious adverse events to the local IRB and other regulatory documents.
- Review of signed consent forms for 100% of patients during the enrollment period
- Review of a sample (approximately 5%) of data collection forms for comparison with data in the FLAME database and source documents
- Observation of study procedure during at least one patient visit
- Storage and access to study patient files, including proper storage of signed consent forms and handling of edit messages; verification that storage is secure.
- Discussion of individual patients with follow-up problems
- Discussion of recruitment, follow- up, and areas of concern

A written summary prepared by the site visitor will be sent to the Director of the FCC, and the Principal Investigator. A copy of the report is also maintained in the Field Office library of study documentation.

dd. Data System Quality Checks

The study field teams will direct data enter into a Android-based eCRF system which will implement range checks and other intrinsic quality control mechanisms to allow for correction of data errors in real time. As security against data loss should an Android break, data also will be entered onto paper forms. Because the staff often will be out of range of cellular data systems, a REDCap (Vanderbilt University, Nashville, TN) android operating system-based app will allow for this approach to be implemented, and will upload the de-identified study data to the data center when the device is in range, analogous to the approach Field Coordinating Center Director Dr. Aida Abashawl used in implemented the Global Trachoma Mapping Program project in rural Ethiopia, and which study Chair Dr. John Kempen currently is using for another study. The system will provide for e-signature, date and timing of each form. The Data Center will perform additional data stream monitoring, and provide feedback data quality queries to the study team. Hard copy documents (those containing subject identifiers) will be kept secure by the Field Team at the field office unless in active use so as to avoid misdirection of protected health information.

The Specific quality assurance features related to data integrity of the FLAME Trial are:

- Standard data collection forms and procedures;

- Standard REDCap data system with the built in functions for checking of data ranges, consistency and completeness.
- Masking of patients, surgeons and study staff at field site to the assigned treatment group of the subject;
- Training and certification of study coordinators in data collection and data entry.
- Explicit instructions with the release of new/revised data collection forms about new/revised questions and instructions;
- Weekly checking of data by the Data Center to detect any data problems early and provide feedback to the Field Coordinating Center for any correction;
- Timely data detection and edits for missing, invalid, and suspect responses by the collaborative work in Field Coordinating Center and Data Center;
- Regular reporting on performance (timeliness, completeness and accuracy of data) of Field Teams for the data collection;
- Field observation and review of data collection process by the Protocol Monitor from Field Coordinating Center;
- Checking by the Protocol Monitor of a random sample of entered data by the study coordinators against data recorded in paper forms (if available) after data editing has been completed.

ee. Data Surveillance Approaches: Identification of outliers, incorrectly collected data, and possibly fraudulent data

With each freeze of the database, a set of statistical and data analytic algorithms will be applied to detect data warranting further investigation and/or action. The identified outliers or fraud data will be investigated with study coordinators for data recording error, data entry error etc. As part of the preparation for any of the data analyses, continuous variables, including dates, are subjected to the techniques of exploratory data analysis in order to fully understand the distribution of the variable. If the outlier values are valid, statistical methods that minimize the impact of outliers will be used.

ff. Maintenance of IRBs, DSMC activities in assuring quality

Annual reports will be submitted to all IRBs (US, UK, Ethiopia) and approval sought for the following year. Annual reports will include updates on enrollment and follow-up status as well as a summary of adverse events.

An independent Data and Safety Monitoring Committee (DSMC) will monitor the trial following “NIH Policy For Data And Safety Monitoring” - release date: June 10, 1998) and the “National Eye Institute Guidelines for Data and Safety Monitoring of Clinical Trials” NOTICE: EY-01-002, release date March 2001. DSMC meetings will be held semi-annually (one in-person meeting,

one teleconference each year) throughout 5-year trial to review trial protocol and the accumulated safety and efficacy data.

3. STUDY POLICIES

1. Protection of Human Subjects

The protection of patients participating in the FLAME Trial has been paramount in the design and implementation of the study. This includes consideration of the risks and benefits of participation, plans for the consent process, and inclusion and exclusion criteria.

i. Institutional Review Board Review and Informed Consent

Each patient must provide written informed consent in order to participate in the FLAME Trial. The consent form is prepared locally based on a prototype provided by the Chair's Office and is submitted to the local IRB for approval. A single consent form will be used for the study, with English, Amharic, and Afaan Oromoo versions. The original will be created in English; the Amharic and Afaan Oromoo versions will be created by translation and backtranslation from English, which will be the language of primary review by the University IRBs although we anticipate they also will want to see the translated/backtranslated versions. We expect all three versions to be reviewed by the NRERC and FMHACA by native speakers in the process of approval, which will ensure their veracity.

Consent must be obtained from each patient prior to performing any study-specific procedures. Procedures that are part of routine programmatic/surgical practice by the surgical team may be performed without consent as they are not specific study procedures. If the patient is determined to be eligible after all screening tests have been performed, WRITTEN informed consent must be obtained from the patient before enrollment into the FLAME Trial. Informed consent must be documented through the signature of the participating patient on the approved consent form in the language of their choice. A copy of the signed/dated consent must be provided to the patient and the original will be maintained at by the Field Coordinating Center (with field office documents). The signed consent form must be available for inspection during site visits.

Field Team members are responsible for conducting the consent process, describing study procedures, discussing the risks and benefits and alternatives to participation, and discussing the voluntary nature of participation with the potential subject. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had all questions answered to his or her satisfaction. All FLAME Trial staff must complete training programs in ethics and maintaining the safety of human subjects in clinical research and in complying with applicable regulations prior to becoming eligible for FLAME Trial certification. Training may be provided by the individual institutions' approved training program or by the NIH website for non-Ethiopian investigators and replacement hires in Ethiopia; for Ethiopian investigators we expect to provide live training will be provided during the startup period (see MOP Section D). Certificates documenting the successful completion of ethics and patient safety programs must be submitted to the Chair's Office by all members of the investigative group prior to FLAME certification.

ii. Patient Confidentiality

The Research Group will preserve the confidentiality of all subjects taking part in this study. In the event of subject names inadvertently appearing on any hard copy study documentation where it

should not appear, the identifiers will be obliterated. Patients are assigned a unique numeric and letter code that is not related to their birth date, government identification numbers or name. The REDCap e-CRFs will be designed so that this information cannot be entered into the computer database for this study (e.g., the electronic data entry system will be designed to be unable to accommodate patient names). Hard copy forms are kept in locked file cabinets at a Field Coordinating Center site (the field office until the post-completion of field work portion of the study). As mentioned in MOP Section E, after screening at each of the outreach sites is completed, the names on the Screening Log will be cut off and burned (or similarly destroyed). The Enrollment Log will be retained as the link between patient identifiers and study identifiers. This form will be kept under lock and key until completion of the study, after which it will be destroyed. Electronic copies of Screening log paper forms (photos or scans) may be kept behind password protection on study androids. Study androids will be wiped clean at the end of the study. Electronic devices containing study data will be password protected, with access limited to the appropriate members of the study team according to Executive Committee policy. Two copies of such keys will be kept (one primary copy at the field office, and one backup copy at the Field Coordinating Center headquarters), so as to avoid losing access to study data. As an additional precaution against data loss, data free of patient names and similar identifiers will be uploaded automatically to the Data Center in Philadelphia as soon as devices are online.

Specifically, all study records including local electronic versions of CRFs containing data, IRB approval letters (and all correspondence), and all other documents pertaining to the conduct of the study must be kept on file by the Research Group. The field office/Field Coordinating Center will maintain the records of test article disposition, signed consent forms, correspondences, monitoring visit dates, and records that support this information for a period of at least one year after completion of the protocol, but not less than the minimum amount of time required by current National Institutes of Health regulations.

Representatives of the Executive Committee will seek access to clinical information only if and when the subject and relevant authorities have given them approval to do so. The de-identified data from this study may be used in academic publications and presentations, and programmatic evaluations by the sponsor or other organizations with the Executive Committee's approval. NIH policy regarding making de-identified information available also will be followed. Patient identities are not to be revealed in any publication that may result from the FLAME Trial. Identifiable clinical information in the possession of the FLAME Research Group is not to be released without written permission of the patient, except as required for monitoring by governing IRBs and governmental authorities. All study records are subject to inspection by governmental agencies (when legally mandated) or the Field Coordinating Center (or its designees) at any time. All study documents will be transferred to the keeping of the Field Coordinating Center upon completion of the study.

The Field Coordinating Center must be notified, in writing, when a study team member leaves the Field Team working where the study is being conducted. The Field Coordinating Center then must assign and train a designee to assume that individual's study-related responsibilities on the Field Team. Study passwords must be updated each time this happens in order to prevent data leaks outside the study team.

iii. Patient Costs

Patients do not pay any charges for TT surgery, perioperative medications, or randomized study drug. Likewise, there are no charges for study visits. Travel to study visits will be provided to patients, and food or snacks during time at the study site.

gg. Changes to Study Documents

i. Changes to the IRB-Approved Study Protocol

All protocol amendments will be submitted to the governing IRB(s) for approval of changes. Protocol modifications that impact on subject safety, the scope of the investigation, or affect the scientific quality of the study will be approved by the IRB(s). However, the investigators may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate IRB(s) will be notified subsequently. In the event of a protocol modification, the subject consent form may require similar modifications, implemented in a similar manner.

ii. Study Completion

The IRBs will be notified of the completion or termination of the protocol. Within 12 months of protocol completion or termination, each investigator will provide his/her IRB with a final clinical summary report. Study results also will be posted on www.clinicaltrials.gov (in accordance with NIH regulations current at the time) in addition to any academic publications and presentations.

iii. Approval of Changes in the Protocol

All significant changes to the FLAME protocol must be approved by the FLAME Executive Committee and the DSMC. In some circumstances, approval from NEI may also be required. When a change in protocol is implemented, a protocol memorandum will be issued to the Research Group. During site visits, visitors review whether the protocol, e-forms, paper forms and other documents are up to date.

iv. Changes to the Manual of Procedures

After initial completion, the FLAME Manual of Procedures will be revised to reflect changes to the protocol. All revised MOP sections are distributed by the Field Coordinating Center. Any revisions to chapters that originate in other FLAME resource centers (i.e., the Data Center, Surgical Team, or Chair's Office) must be sent to the Field Coordinating Center for distribution to the entire Research Group.

hh. Study Location Termination

The Executive Committee shall have the right to cease operations at a field site at their discretion. Termination of a particular field site would not alter the above-stated record retention requirements.

ii. Premature Study Termination

Premature termination of this clinical study may occur because of governmental action, safety problems, or upon the agreement of Executive Committee, e.g., upon recommendation the DSMC should there be safety problems or evidence that the study objectives are accomplished prior to completion of elements of the protocol, or based on determination that objectives cannot be accomplished.

If the study is prematurely terminated or discontinued, the Executive Committee promptly will notify all the study team. After notification, the study Field Team must contact all actively participating subjects as soon as possible. All study materials must be collected and all CRFs completed to the greatest extent possible.

jj. Financial Disclosure

Because the drug in question is not patent protected, financial disclosures regarding relationships to drug companies only will pertain to any companies that may be developing a competing product during the time of the study, as determined according to the discretion of the Executive Committee and of the Data and Safety Monitoring Committee. Should such a relationship exist for a member of the study team, it will be reported to the Study Chair; such relationships for DSMC members will be reported to the DSMC Chair. The recipient of such information would evaluate the information, and document the disposition of the information in meeting minutes. If judged of potential problematic impact to the study, the recipient will review it with the IRB governing the individual's activities to discuss the appropriate approach to mitigating potential problems to the study as a result of such a "conflict."

kk. Publicity

All publicity and press releases on behalf of the FLAME Trial are to have prior approval of the Executive Committee. FLAME investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chair.

It is recognized that when information is sought from an individual investigator by the local press in his or her own community, it is sometimes necessary or desirable for the investigator to handle the request him/herself, especially after results of a primary or secondary analysis have been published. In such an event, the participating investigator who gives information should speak as an individual and not as the official representative of the FLAME Trial. This fact should be made clear to the press; however, the information given should be accurate and reflect the general policy and views of the group.

During the recruitment phase of the study, announcements (pre-approved by the Executive Committee) may be placed in local media (newspaper, radio, television; e.g., see Section C). The Field Coordinating Center also will prepare a set of materials to aid the Field Teams in recruitment and study visibility.

On a global level, study publicity will be increased by postings on the NEI and ClinicalTrials.gov web sites and the entities involved (e.g., Mass Eye and Ear, Penn, Berhan etc), by publication in scientific journals, presentation in scientific meetings, and through press releases/interviews of study leaders.

ll. Scientific Publication and Presentation Policy

The Executive Committee members, under the leadership of the Study Chair, jointly have the ultimate responsibility and authority regarding the decision and responsibility to publish results from the FLAME Trial. Additional investigators also will participate in publications per the consensus of the

Executive Committee. Sponsors will not be able to influence publication content, but have the privilege of 30 days' advance review of primary result manuscript contents (results containing presentations of the results related to the study's three specific aims). An exception will be made if mandated by NIH policy; also, given that the study Project Officers are members of the Executive Committee, some influence may exist from the NEI sponsor, subject to NIH's policies on the matter.

The clinical trial registration at clinicaltrials.gov will be kept current in accordance with NIH policy. Publications will be posted at PubMed Central open access within 12 months of initial publication in accordance with NIH policy.

i. Publication Plan

FLAME Trial scientific publications are defined as those that use data, documents, or other information collected during the course of the Study. **Primary publications** are related to primary reporting of results related to the specific aims of the Trial. **Secondary publications** are those which are primarily executed by the members of the Research Group primarily using FLAME Trial data. **Ancillary studies/reports** are those which are primarily executed outside the main FLAME Trial (see below) using FLAME Trial resources to some extent, and approved by the FLAME Executive Committee. **Related studies** are studies by FLAME investigators about trachoma but which are separate investigations NOT requiring approval of the FLAME Executive Committee. In uncertain cases, the Executive Committee may need to make the determination which of the four categories an investigation belongs to; it's determination may be appealed, but will be final once a determination is reached by the Executive Committee.

Publication of the results of FLAME Trial will be governed by the policies and procedures developed by the Executive Committee. The Executive Committee reviews and must approve all primary, secondary and ancillary written reports prepared for publication before submission. Likewise abstracts submitted to conferences must be approved by the Executive Committee before presentation; if approval is not given and an abstract has been submitted, it must be withdrawn, unless the Executive Committee approves it retroactively.

The Chair's Office and NEI Project Officer(s) ensure that the preparation of the results for abstract presentation or publication complies with NIH policies and guidelines. The Executive Committee review ensures that appropriate analysis and conclusions are reached.

ii. Authorship

All **primary** and **secondary reports** from the FLAME Trial Research Group will list named authors "for the **FLuorometholone as Adjunctive MEdical Therapy for TT Surgery** (**FLAME**) **Trial Research Group**," and will include the appropriate credit roster. All professional participants of the Group are listed in a published or cited credit roster (usually an online supplement) and are considered as contributors. In addition, all FLAME personnel, past and present, may be listed with the approval of the Resource Center Director for whom they have worked.

Authorship plans for **ancillary studies** will be reviewed and approved by the Executive Committee at the time of approval of the ancillary study.

Authorship of **related studies** is at the discretion of the researchers and does not require Executive Committee approval.

The Chair's Office will keep a credit roster of all present and past members of the Research Group, which will be published or referenced in association with each primary and secondary publication. Each Resource Center Director is responsible for updating the list of current and past members, and supplying it to the Chair's Office to generate this credit roster. In general, all members of the Executive Committee will be named in all publications of the Research Group, along with additional individuals appointed by the Executive Committee to take part in a given publication. Publications will acknowledge the FLAME Trial Research Group, typically using a Modified Conventional Format (e.g., Named Author 1, Named Author 2,….. for the FLAME Trial Research Group). Exceptions will be allowed to accommodate and comply with all NIH policy requirements.

iii. Manuscript Writing Teams

The FLAME Executive Committee will determine potential manuscript topics based on hypotheses and analyses. Primarily Research Group members, and potentially others, are invited to volunteer for writing assignments and to suggest additional topics where appropriate. The Chair's Office solicits members for the writing committees for FLAME papers from among the FLAME Research Group. **Writing Committee** Chairs will be designated by the Executive Committee. For Primary Manuscripts, the study Chair will be the Writing Committee chair. Final designation of the writing committee membership will be proposed by the chair of the writing committee and approved by the Executive Committee. The Executive Committee may recommend particular members of the Research Group for inclusion in the writing committee of specific papers. Along with the Executive Committee, each writing team will select the journal to receive the submission. In this process, the general principle will be to include major academic contributors to the research effort as named coauthors as much as possible, including those pioneering the study and entering data. For this reason, in general the Executive Committee members (who have primary responsibility for creating, funding and implementing the study) will be included in Writing Committees and named as authors.

iv. Manuscript Pre-Submission Review

Papers prepared for publication must be sent to the FLAME Chair for review and advance approval by the Executive Committee. If approved by the Executive Committee, primary manuscripts are then sent to the Data and Safety Monitoring Committee (DSMC) for review and approval. If desired by the DSMC, secondary manuscripts will be submitted to them as well. Ancillary studies will not be submitted to the DSMC, but a list of approved ancillary studies will be reviewed at DSMC meetings. Related papers are not under the authority of the DSMC.

Oral presentations of more than local scope, or ones where press coverage is expected, must be approved in advance by the Executive Committee. Abstracts to be published must be approved by the Executive Committee. The DSMC also may expand mandatory advance DSMC review of oral presentations and abstracts or other scientific communications, or of certain subsets thereof (such as presentations of primary results), at their discretion. No unpublished study results may be used for oral presentations, local or otherwise, unless the Executive Committee grants a specific exception. The above restrictions do not apply to local presentations on the design of the FLAME Trial, provided

these presentations contain no unpublished Study results. Such presentations are encouraged to stimulate interest in the study.

Copies of published papers are electronically mailed to members of the DSMC and to the entire Research Group by the Chair's Office.

Manuscripts emanating from ancillary studies must be sent to the study Chair's Office for presentation to the Executive Committee for review before submission for publication; the ancillary study chair must submit a copy of the final publication to the FLAME Chair's Office for filing.

v. Acknowledgements

Each primary and secondary publication must acknowledge primary support from the National Eye Institute (NEI), naming the specific grants provided to support the study. Ancillary studies must acknowledge the contribution of the FLAME Trial Research Group, and acknowledge that FLAME is funded by the National Eye Institute, naming the grants. Allergan also must be acknowledged as donating the fluorometholone 0.1% study drug for publications related to the alternative treatments. Sources of additional funding or support also should be acknowledged, in a manner subordinate to the primary support obtained from the National Eye Institute.

mm. Data Sharing

NIH released "Final NIH Statement on Sharing Research Data" (NOT-OD-03-032) on February 26, 2003 which modified "NIH Announces Draft Statement on Sharing Research Data" (NOTOD-02-035). In accord with NIH guidelines, a summary, de-identified data set will be made kept available by the Data Center at the time of publication, which may be accessed through direct inquiries to the Study Chair or Data Center with approval by the Executive Committee. All the data collection forms will be embedded with variable names of FLAME datasets from each data collection forms. In addition, key derived variables will also be contained in the data sets. Release of data must be approved by the Executive Committee as long as it continues to meet. After the Executive Committee officially has ceased FLAME Trial operations, data may be accessed from the data repository established by the study (see below).

The rights and privacy of people who participated in the FLAME Trial will be protected at all times by stripping the data from all identifiers that could lead to disclosing the identity of individual research participants. As also mentioned elsewhere, this commitment to privacy-protected data sharing will be incorporated in all levels of database design.

By the time the Executive Committee officially has ceased FLAME Trial operations, de-identified SAS data sets and form images corresponding to all data collection forms used, as well as key derived variables, will be put on file with a data repository such as the National Technical Information Service (NTIS). The full SAS databases associated with the FLAME Trial will be kept on secured computer systems maintained by the Study Chair and by the Director of the Data Center. Researchers may request limited access data sets and will need to enter into a data sharing agreement with the Data Center before obtaining data. After approval by the Executive Committee and completion of the agreement, the Data Center will share the data. NIH guidelines for the process of requesting such

data sets and their content will be implemented to provide access to the FLAME Trial database. Researchers requesting limited access data sets will bear the cost of their preparation, and will be responsible for following FLAME and NEI policy in their use.

nn. Ancillary Studies

Individual investigators who wish to carry out ancillary studies are encouraged to do so. It is believed that such ancillary studies may enhance the value of the FLAME Trial and ensure the continued interest of many capable investigators. However, to protect the integrity of the FLAME Trial initiative, such ancillary studies must be reviewed and approved by the Executive Committee (and, if and only if desired by the Data and Safety Monitoring Committee, the DSMC) before their execution, whether or not they involve the need for supplementary funds.'

i. Definition of a FLAME Ancillary Study

An ancillary study is a research study that requires either
• Supplementary observations or procedures to be performed upon all or a subgroup of FLAME patients according to a set protocol, or,
• Additional effort or activity by either the FLAME Research Group beyond the current scope of FLAME, but is not primarily led by the FLAME Research Group (it may be led mostly independently by FLAME members).

ii. Reasons for Requirement of Approval

Everyone concerned with the FLAME Trial is entitled to prior assurance that no ancillary study will:
• Complicate the interpretation of the FLAME Trial results;
• Adversely affect patient cooperation;
• Jeopardize the public image of the FLAME Trial;
• Create a serious diversion of FLAME Trial resources locally or at Resource Centers.

iii. Preparation of Request for Approval of a FLAME Ancillary Study

The request for approval of an ancillary study should be in narrative form. It should contain a brief description of the objectives, methods, and significance of the study. Full details should be given concerning any procedures to be carried out on any FLAME Trial subjects, such as visual function tests, psychiatric interviews, psychological testing, radiological procedures, venipuncture, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be performed on a patient other than according to the FLAME Trial protocol by the Field Teams should be described. Mention should be made of the extent to which the ancillary study will require extra visits by the patient or will lengthen the patient's usual clinic visits. The Chair's Office may create a form to facilitate acquisition of such information.

iv. Procedures for Obtaining Ancillary Study Approval

The investigator concerned should send the ancillary study request to the Chair's Office for distribution to all members of the Executive Committee. Within a reasonable time, the study Chair or his designee will summarize any questions and/or objections raised by members of the Executive Committee and send this summary to the applicant so that (s)he may amplify, clarify, and/or withdraw the request. The members of the Executive Committee then will have another opportunity to review

the request. The Chair's Office then prepares a statement of the Executive Committee consensus, including any remaining reservations or objections. This statement is forwarded to the investigator who requested approval for the ancillary study. If and only if the DSMC decides it must approve such requests, after Executive Committee approval is obtained, the information will then be forwarded to the DSMC for its approval.

v. Funding of Ancillary Studies

If no additional funds are required, the investigator may proceed with the ancillary study as soon as the Executive Committee and Data and Safety Monitoring Committee approve it. If additional funds are needed, the investigator may prepare and submit a new research grant application to the Division of Research Grants, National Institutes of Health, or any other potential sponsor, for review in the same manner as any other new research grant application. It is understood that the investigator is not to activate the ancillary study until approval has been received from the FLAME Trial Executive Committee and DSMC.

vi. Publication of Ancillary FLAME Results

All manuscripts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the FLAME Trial Executive Committee before publication or presentation. Such review will pertain to the expected impact on FLAME Trial objectives and not to scientific merit alone. Appropriate acknowledgment of use of FLAME Trial resources used—whether data, patients, or investigators—must be included.

vii. Progress Reports to Executive Committee

The investigator of each approved ancillary study is required to provide a written progress report for review by the Executive Committee semi-annually (or more frequently if requested by the Executive Committee. The Chair's Office reminds the investigators of the deadline and collects progress reports for distribution to the Executive Committee.

oo. Related Studies

Individual FLAME investigators who carry out studies related to trachoma should be aware that their conclusions and interpretations might be viewed by non-FLAME investigators as reflecting the position of the FLAME Research Group. The study may be related because of types of patients included, types of treatment evaluated, or similarity of methods to those used in the FLAME Trial. If in doubt, investigators are encouraged to submit reports from related studies to the Executive Committee for review and comment prior to presentation or submission for publication in order to assure that the goals of the FLAME Trial are not jeopardized. However, because the FLAME Trial does not have jurisdiction over related studies, the Executive Committee does not have authority to prevent publication or force a change in the scientific content of such studies; nor to insist on acknowledgments.

pp. Interactions with Sponsors

Additional sponsorship of the FLAME Trial initiative with money or in-kind contributions—including but not limited to funding of ancillary studies—is encouraged, as additional investment may leverage the investment already made in the research initiative. However, such funding must not provide the

sponsor authority to influence the publications and presentations resulting from the FLAME Trial initiative. Funds or in-kind donations from sponsors that wish to have such influence may not be accepted.

4. STUDY STAFF RESPONSIBILITIES AND CERTIFICATION REQUIREMENTS

1. Chair's Office

Study Staff	Responsibilities (see Study Organization, MOP Section O for more details)	Certification Requirements
Study Chair	Oversight of the whole project, including on-site activities in Boston, Addis Ababa, and (during site visits) at field sites; recruiting and training Chair's Office staff; leading Executive Committee in implementing all aspects of the study; paper-writing	Human Subjects in Research Good Clinical Practice
Study Vice-Chair	Senior co-investigator advising Chair; Exec. Committee Service; paper-writing	Human Subjects in Research Good Clinical Practice
Study Coordinator Boston	Obtaining Chair's Office IRB approval and tracking IRB approvals for all centers; assist with maintenance of study documents; www.clinicaltrials.gov registration and maintenance; organizing meetings of the Research Group; support and monitor manuscript submission and review	Human Subjects in Research Good Clinical Practice
Postdoctoral Assistant	To assist the Study Chair and Study Coordinator with their responsibilities	Human Subjects in Research Good Clinical Practice
Health Economist	Oversee and advise regarding health economic outcomes	Human Subjects in Research

qq. Field Coordinating Center

Study Staff	Responsibilities	Certification Requirements

Field Coordinating Center Director	Oversight of the whole implementation of the Field Coordinating Center; recruiting and training staff, supervising field activities and reporting adverse events to collaborators; paper-writing	Human Subjects in Research Good Clinical Practice
Senior Study Coordinator	Oversight of the whole project, lead the hiring and training staff process, liaise with various stakeholders (investigators, partners, study staff), update operating manual, supervise field activities, prepare study reports, update master file regularly, handle IRB processes, prepare report, assist in manuscript preparation	Human Subjects in Research Good Clinical Practice
Internal Monitors	Ensure that project procedures are followed and comply with GCP guidelines, review all consent and eligibility forms, check the master file regularly, ensure adverse events are reported on time	Human Subjects in Research
Field Coordinator	Coordinate the work of the study teams collaborating with the Zonal and district health offices, plan and oversee the recruitment, enrollment and follow-up activities of the teams and prepare and send summary reports of activities and adverse event reports to the base office.	Human Subjects in Research Eye Health Care
Team Supervisor	Responsible for supervision of the field teams	Human Subjects in Research Good Clinical Practices
Study Team- Study Nurses	Responsible for screening, enrollment and follow-up of study participants. The Ophthalmic nurse will examine participants during enrollment and study visits	Human Subjects in Research Eye Health Care Good Clinical Practices
Study Team– Data Recorders	Responsible for screening, enrollment and follow-up of study	Human Subjects in Research

	participants. The recorder will complete study questionnaires on androids and paper and complete logbook information	Good Clinical Practices
Field Office Administrator/ Logistics	Responsible for financial, equipment, and scheduling logistics	Human Subjects in Research

rr. Surgical Team

Study Staff	Responsibilities	Certification Requirements
Principal Investigator	Oversight of the whole implementation of the Surgical Team; administrative duties; paper-writing	Human Subjects in Research Good Clinical Practice
Co-investigator and Safety Officer	Oversight of clinically oriented details of the Surgical Team; This investigator will have a lot of input into the protocol and science of trachoma; paper writing. Carrying out review and reporting of adverse events.	Human Subjects in Research Good Clinical Practice
Co-investigator	Oversight of clinically and programmatically oriented details of the Surgical Team; paper writing	Human Subjects in Research

ss. Data Center

Study Staff	Responsibilities	Certification Requirements
Data Center Director	Oversight of the whole implementation of the Data Center; Exec. Committee Service; recruiting and training staff; supervising training activities, etc; paper-writing	Human Subjects in Research Good Clinical Practice
Co-investigator	Senior co-investigator advising Director; Exec. Committee Service; paper-writing	Human Subjects in Research Good Clinical Practice

Clinical Co-Investigator	Receive and be responsible for details related to Allergan grant of fluorometholone; paper writing	Human Subjects in Research Good Clinical Practice
Biostatistician	Statistical Analysis (under supervision of PI), data checking for outliers and completeness	Human Subjects in Research Good Clinical Practice
Project Coordinator	Administrative, IRB management, Logistics Management, schedule and preparation of DSMC meetings/calls Quality Assurance, Field Coordinating Center Liaison	Human Subjects in Research Good Clinical Practice
Clinical Research Computing Unit	Develop, test, implement and maintain the RedCap data System. Provide webinar training with the field team for data collection, perform data quality assurance.	Human Subjects in Research Good Clinical Practice

5. ORGANIZATIONAL STRUCTURE OF THE STUDY

The FLAME Trial is a clinical trial implemented in a field setting in rural Ethiopia, assessing the efficacy, safety and cost-effectiveness of fluorometholone 0.1% as an adjunctive treatment to Trachomatous Trichiasis Surgery. The Research Group for the FLAME Trial is funded by two UG1 Cooperative Agreement Grants from the National Eye Institute to Massachusetts Eye and Ear (Chairman's Office) and to the University of Pennsylvania (Data Center).

The study group will consist of four resource centers. The resource centers are the Chairman's Office, the Field Coordinating Center, the Surgical Team and the Data Center. An Investigational Pharmacy will be funded by the Data Center. The Field Coordinating Center will employ Field Teams which enroll, follow, and collect data from patients.

1. Chairman's Office (CO).

The Chairman's Office funds the Study Chair—John H. Kempen, MD, PhD, a faculty member of Harvard Medical School's and Massachusetts Eye and Ear's Department of Ophthalmology who is highly experienced with the implementation of complex clinical trials and epidemiological studies—and his staff located in Boston, Massachusetts. In addition, the Chairman's Office Funds the Vice-Chair of the Trial (Prof. Matthew Burton) via a subcontract and the Health Economist (Prof. K. D. Frick), and the study Safety Officer (Dr. Wondu Alemayehu, MD, MPH) via consulting agreements. The Study Chair himself will divide his time between Boston and Ethiopia. Because of Dr. Kempen's frequent presence in Ethiopia, the Chairman's Office also funds via subcontracts the Field Coordinating Center and the Surgical Team. The Field Coordinating Center is located at Berhan Public Health and Eye Care Consultancy in Addis Ababa, Ethiopia, led by Berhan's Director of Programs, Dr. Aida Abashawl. The Field Coordinating Center will perform typical coordinating center functions within Ethiopia, with direct, regular involvement of the Study Chair, and supported by the Data Center's form and data system. The Field Teams interacting directly with patients to carry out enrollment and data collection will be employed by the Field Coordinating Center. The Surgical Team is derived from an extant trachoma control program in the Oromia Region of Ethiopia implemented by the Fred Hollows Foundation in partnership with the Ethiopia Federal Ministry of Health Oromia Regional Health Bureau, with offices in Addis Ababa, and field operations throughout the Oromia Region of Ethiopia. The Surgical Team will be directed by Sarity Dodson (Melbourne, Australia), and co-led by co-investigators Wondu Alemayehu, MD, MPH and the FHF TT surgery manager based in Addis Ababa, Ethiopia.

The CO provides overall leadership to the FLAME Trial Research Group. The specific responsibilities of the CO for the FLAME Trial are:

1) To provide overall scientific, executive leadership, and governance for the study;
2) To provide clinical, epidemiological, and biostatistical expertise in issues surround trachoma and clinical trials;
3) To be responsible for developing and maintaining study documentation, including updated protocol, study handbook, and other study materials (and assist the Data Center in developing and maintaining electronic data collection forms);

4) To organize, coordinate, provide logistical support for, and be financially responsible for all study meetings, including in-person meetings and weekly operation conference calls, except the DSMC meetings (organized by the DC);

5) To provide leadership and administrative support for the preparation of study manuscripts and scientific meeting presentations; to support correspondence about them;

6) To implement NIH-mandated activities including listing and maintaining the trial registration on www.clinicaltrials.gov and ensuring manuscripts are posted on PubMed Central;

7) To appoint and administer *ad hoc* study committees;

8) To administer financial issues of the CO;

9) To oversee the Ethiopian FCC in its activities of managing study data collection; hiring, training and certification of Field Team members; implementing quality assurance and monitoring procedures; and providing study data to the Data Center;

10) To oversee the Surgical Team in its efforts to obtain buy-in amongst the complicated, multilevel governmental and administrative web of overseers so that the outreach to identify study patients can be carried forward, and the TT surgery itself implemented within the context of a field program. In order to assure success of the Trial, the program in the study communities will be funded, organized and implemented by the FLAME Trial's Surgical Team;

11) The **Vice Chair**, Prof. Matthew Burton, has carried out more field trials about trachomatous trichiasis than anyone in the world, primarily in Ethiopia. Prof. Burton primarily will provide scientific input into the design and implementation of the study based on his extensive experience in successfully implementing multiple field trials about trachomatous trichiasis in Ethiopia,[19,22,36,50] making available materials and strategies he has developed in his previous extensive successful work carrying out studies of this nature;

12) The **Health Economist**, Prof. K. D. Frick, will oversee the protocol design and maintenance regarding health economic issues, will oversee the cost-effectiveness analysis of the study, and participate in paper-writing regarding health economic issues;

13) The **Safety Officer**, Dr. Aemero Abateneh, will oversee patient safety in the study, including designing and implementing the adverse event reporting system based on this study protocol, responding to safety events under the supervision of the FCC Director, and advising the study regarding safety issues.

14) Dr. Kempen and Prof. Burton will serve as Chair and member of the Executive Committee (study officers).

tt. Field Coordinating Center (FCC).

Directed by the Coordinating Center Director, Dr. Aida Abashawl, the Coordinating Center—based at Berhan Public Health and Eye Care Consultancy, Addis Ababa, Ethiopia—will oversee operational aspects of the study in a manner typical for a clinical trial coordinating center, except that the data system, data management and statistical aspects of the study will be managed by the Data Center (see below). Dr. Aida Abashawl, Director of Programs for Berhan Public Health and Eye Care Consultancy, has extensive experience leading field trials of health care interventions in Ethiopia and globally. Her experience includes having conducted trachoma field studies as part of the Global Trachoma Mapping Project in some of the most remote parts of Ethiopia. While she also has an appointment at Johns Hopkins University, because it will be necessary based on regulatory idiosyncracies in the Ethiopia context for the Coordinating Center rather than the Fred Hollows

Foundation to directly employ the study team, the study is being implemented through her Ethiopian employer (Berhan), which has the right to employ Ethiopian employees.

The FCC oversees field implementation of the trial in Ethiopia, employing and supervising all Ethiopian team members except those involved in programmatic services under the Surgical Team. The roles and activities of the FCC include:

1) implementing study data collection, including employing, overseeing, training/certifying, and supervising the Field Teams (which will have primary responsibility for enrolling, following and collecting data from study subjects;

2) implementing an Ethiopian investigational pharmacy to receive Study Drug from the investigational pharmacy at the University of Pennsylvania, clearing customs, and maintaining Study Drug accountability and distribution in Ethiopia;

3) implementing in Ethiopia the financial logistics for the study, such as vehicle and office rental and purchasing/maintaining office equipment (which has to be done by a registered Ethiopian entity);

4) assisting the Surgical Team liaison with Ethiopian authorities regarding the study implementation including village, kebele, regional and federal leaders and oversight bodies;

5) leading the effort to obtain Ethiopian institutional review board-like approvals at the Oromia Regional and Ethiopian Federal levels;

6) implementing and maintaining quality assurance and monitoring procedures for the field teams; and

7) contracting with the Chairman's Office to receiving funding to cover these expenses.

8) Dr. Aida Abashawl will serve as a member of the Executive Committee (study officer).

The FCC will conduct regular phone and in-person meetings with the Field Teams to review progress, troubleshoot problems, and conduct quality assurance exercises. (The Study Chair will participate in many of these meetings). The FCC, through its Field Teams, will consent and enroll patients brought as candidates by the Surgical Team, provide randomized treatment assignments to study participants, distribute the Study Drug to patients, and then conduct all follow-up visit activities themselves.

uu. Surgical Team.

The Surgical Team is derived from an extant trachoma control program in the Oromia Region of Ethiopia dedicated to the accomplishment of the FLAME Trial's objectives. The Fred Hollows Foundation, with offices in Addis Ababa, and field operations throughout the Oromia Region of Ethiopia, will implement the study Surgical Team, which will be directed by Sarity Dodson (Melbourne, Australia), and co-led by co-investigators Wondu Alemayehu, MD, MPH and Anne Heggen based in Addis Ababa, Ethiopia, and funded by a CO subcontract.

Specific responsibilities of the Surgical Team will be to carry out patient mobilization and implementation of trachomatous trichiasis surgery program for the study, including:

1) liaison with Ethiopian authorities to obtain approvals and support for TT surgery mobilization and implementation at the village, kebele, zonal, regional and federal levels;

2) mobilization of patients from communities to present themselves for TT surgery, including the conduct of an extensive publicity campaign to make the details of the opportunity known;

3) organizing and being financially responsible for the TT surgery programs in which trial subjects will be treated using standard surgical care, including obtaining permissions from local leaders;

4) employing TT surgeons from amongst Integrated Eye Care Workers—who typically perform TT surgery in extant Ministry of Health facilities—to carry out the surgeries;

5) providing the consumables on site needed to conduct the surgical program;

6) providing routine postoperative care of these patients, including post-operative medications other than the study drug.

7) Drs Sarity Dodson and Wondu Alemayehu will be members of the Executive Committee (Study Officers).

For ethical and logistical reasons, the Surgical Team will provide surgery for all those who respond to the outreach, whether they ultimately are randomized into the study or not; even those who are not ultimately randomized make up the screening population and are part of the study in that sense.

vv. Data Center (DC).

Directed by Data Center Director, Dr. Gui-shuang Ying, the Data Center—based at the Center for Preventive Ophthalmology and Biostatistics (CPOB), Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA—will oversee construction and management of the data system, and data analysis for the study. Dr. Maureen G. Maguire, Director of the CPOB, will serve as Co-Director. This team brings well-known expertise as one of the world's leading ophthalmology clinical trial coordinating centers to the design of the data system, statistical monitoring of the data stream, and statistical analysis. Because implementation of the study will be done in Ethiopia, which requires employment of the study team by a registered entity, coordination work will be done in Ethiopia by the Field Coordinating Center as described above.

The specific responsibilities of Data Center for the FLAME Trial are:

1. Providing biostatistical and epidemiological expertise in the analysis of trial data;
2. Development of the data collection forms: The DC will help develop the data collection forms based on the forms used for Phase II trial and input from the Study Chair.
3. Development of the study database: The DC will develop the REDCap database based on the data collection forms, and train the Field Coordinating Center and Field Teams on how to properly use the REDCap database for data collection.
4. Develop the statistical analysis plan: DC will develop and implement the detailed statistical analysis plan for the analysis of primary outcome and secondary outcomes.
5. Implement the surgeon-stratified randomization sequence and provide the randomization list to each field area for treatment assignment.
6. Monitor the progress of the study: the DC will receive the study database from the Field Teams in Ethiopia continuously (the data will upload whenever the data entry androids are online). The DC biostatistician will manage the study data, perform the analysis and

generate monthly reports for patients enrollment and follow-up for the study leadership. The DC will attend and present the report in the monthly operation call with Study Officers.

7. Monitor the data quality and completeness of data, conducting surveillance for exceptional values and generating data quality queries to the field team: Every month, the DC will run the data checking for completeness and accuracy, create data edit queries and communicate with study coordinators in Ethiopia for data cleaning and data correction to ensure high quality of data.
8. Maintain the data files: the DC will maintain the accumulating data in a secure manner (with backups) to assure the integrity and adherence with the HIPAA requirements.
9. Perform statistical analysis for the DSMC meetings: the DC will run the statistical analyses of the interim data and final data, and generate results tables for the DSMC meetings (5 in-person meetings expected: 1 meeting before trial started and 4 after trial started; also potentially phone call meetings at midpoints between in-person meetings).
10. Prepare, host, and be financially responsible for DSMC meetings held in Philadelphia: The DC will help prepare and distribute DSMC notebooks, arrange and host DSMB meetings.
11. Analyze final data for primary and secondary papers: the DC will perform the statistical analysis of final data for the primary paper and secondary papers from the trial.
12. Participate/lead the study papers: the DC will help with or lead the development of manuscripts for publication and presentation.
13. Drs. Ying and Maguire will serve as members of the Executive Committee (study officers).

The **Investigational Pharmacy**, directed by Vivian Leung, Pharm.D., is located at the University of Pennsylvania's Investigational Drug Service, funded by the DC. The Investigational Pharmacy will prepare the study test articles (packaged fluorometholone and identically packaged placebo) and ship them to Ethiopia, where they will be cleared and distributed by the Field Coordinating Center. Fluorometholone 0.1% will be donated to the study by Allergan.

ww. FLAME Trial Committee Structure.

The FLAME Trial has two primary standing committees attending to critical tasks: the Executive Committee (EC), and the Data and Safety Monitoring Committee (DSMC). See also MOP Section O for additional details.

The EC coordinates operations amongst the resource centers to implement the day to day operations of the Trial, monthly. A subset of the EC, the "Operations Committee," will meet weekly during the startup phase of the study, and generally twice weekly thereafter. Members of the EC (Study Officers) include the study Chairman (who chairs the EC), the Study Vice-Chairman, the Directors (and Co-Directors when applicable) of the DC, FCC, and PT, and the NEI Representative. The EC acts as the administrative arm of the FLAME Trial, making decisions on policies, procedures, and operational issues that affect the study; implementing recommendations of the DSMC; reviewing data collection and results; and addressing problems that arise. It also acts as the publication committee

for the study, commissions manuscripts/manuscript committees and reviews progress. EC meetings occur via conference call, annually in person in conjunction with the DSMC meeting (with Prof. Burton by phone from the UK), and additionally as needed for specific issues. Initial members of the EC include: Drs. John H. Kempen (Chair); Matthew Burton; Aida Abashawl; Gui-shuang Ying; Maureen Maguire; Sarity Dodson; and Wondu Alemayehu. The NEI also will appoint Project Officer to be a member of the EC.

The DSMC is an independent board, appointed as advisory to the EC and the NEI, which is responsible for ongoing review of the efficacy and safety data, policy and ethical issues, and study performance. The DSMC, appointed by NEI, is composed of members including the disciplines of: ophthalmology, biostatistics, epidemiology, and ethics. The DSMC will meet annually in person in either the United States or Ethiopia; additional phone meetings may be called by the DSMC itself, the NEI, and/or the EC as needed.

The EC and DSMC are engaged in governance of the study organization. In addition, specific study committees can be organized to address specific issues that come up in the study, such as ancillary publication committees (the EC will serve as the paper writing committee for primary results reports).

6. STUDY OVERSIGHT

1. Executive Committee

The Executive Committee is a group of the study officers of the FLAME Trial, Chaired by the Study Chair, with the Directors and important co-directors or investigators as voting members by role.

i. Membership

The membership (with initial incumbent) includes:

Study Chair (Kempen)
Study Vice-Chair (Burton)
Field Coordinating Center Director (Abashawl)
Surgical Team Director (Dodson)
Surgical Team Co-investigator (Alemayehu)
Data Center Director (Ying)
Data Center Co-investigator (Maguire)
NEI Project Officer (Bhargava and Le)

Members Burton, Alemayehu and Maguire are included because of their especially deep knowledge about trachoma and/or about clinical trial implementation and science, and are included in the Executive Committee because of the added value they provide with their depth of wisdom and experience, to assist the Resource Center Directors.

ii. Role in Study Oversight

The Executive Committee largely runs the study, and functions like the Senior Leadership Team of the FLAME Organization. It exists to coordinate operations amongst the resource centers to implement the day to day operations of the Trial, meeting (usually be phone) at least weekly during the startup period, and twice weekly thereafter. The EC makes decisions on nearly all major policies, procedures, and operational issues that affect the study. It also acts as the publication committee for the study, commissions manuscripts/manuscript committees and reviews progress. EC meetings occur via conference call, or annually in person in conjunction with the DSMC meeting

xx. Data Safety and Monitoring Committee (DSMC)

The DSMC is an independent board, appointed by the National Eye Institute as advisory to both the Executive Committee and the National Eye Institute, which is responsible for ongoing review of the efficacy and safety data, policy and ethical issues, and study performance. It functions like the Board of Directors of the Study, although it supervises the Executive Committee rather than just the Study Chair, given that grant funding comes in through more than the Chair's grant. The DSMC will meet annually in person in either the United States or Ethiopia; additional phone meetings may be called by the DSMC itself, the NEI, and/or the EC as needed. Urgent safety reports will be provided to the DSMC per the policy they select at their meetings, most likely with reports flowing from the FLAME Trial Safety Officer (under the Executive Committee's policy) reporting to the DSMC Safety Officer or Chair (per the DSMC's policy).

The DSMC has the authority to recommend termination or modification of the study, and typically makes recommendations to improve the effectiveness of the study on a regular basis. See also MOP Sections G (last heading), I10, L4, L8, N5 which discuss roles of the DSMC.

yy. Institutional Review Boards/Oversight Bodies

Institutional Review Boards will provide oversight to the FLAME Trial in the usual manner. The FLAME Trial will carefully consider and typically implement the input of all Review Boards and their determinations regarding the Trial. The protocol and consent forms (written in English, translated and back-translated into Amharic and Afaan Oromoo), will be submitted to and approved by each before initiation of the Trial. Protocol modifications and consent form modifications will be submitted for review and approval as well.

Academic IRBs from the institutions employing the Study Chair and Vice Chair will form the first level of review. As per NIH's "single IRB" policy, the US institutions will be under a single IRB, that of Partners Healthcare (the parent organization of Massachusetts Eye and Ear); thus the Data Center Director's institution will cede review to the Partners Healthcare IRB. In 2020 Partners Healthcare began a process of changing its name to Mass General Brigham.

After or in parallel with Academic IRB review and approval, the next step is to obtain approval from the Oromia Regional Health Bureau (ORHB). Once ORHB has granted its support for the project (which also leads to cooperation from the health facilities in the study), approval will be sought and gained from National Research Ethics and Review Committee (NRERC) of the Ministry of Science and Technology, which functions something like a national IRB for clinical trials. Approval also will be

sought and gained simultaneously from the Food, Medicine, and Health Care Administration and Control Authority (FMHACA) [now known as the Ethiopian Food and Drug Administration (EFDA)], which functions somewhat like the United States Food and Drug Administration in this regard, and strictly regulates clinical trials even of approved drugs as in this case. The Ethiopian review groups can be expected to carefully review the Amharic and Afaan Oromoo versions of the consent forms, as a plurality of Ethiopians speak these languages, and these are the languages used in the study sites.

Renewal of approval will be obtained regularly from the IRBs as per their policies, typically annually.

The FMHACA is highly likely to conduct at least one site visit during the conduct of the FLAME Trial based on past experience. The Research Group will make every effort to cooperate with such a visit and respond to any advice or deficiencies found. If at all possible, the Field Coordinating Center Director and Study Chair will be present for such a site visit.

zz. National Eye Institute Project Officer

Following NIH policy for a cooperative agreement (UG 1) such as those funding the FLAME Trial, representative(s) of the funding agency (National Eye Institute) will join the FLAME Research Group and serve as study officer/Executive Committee member(s). This individual(s) will be involved in all the critical decision-making for the Trial, subject to the restrictions on her/him by the National Institutes of Health (see https://oir.nih.gov/sourcebook/ethical-conduct/research-ethics/nih-policies/intramural-extramural-collaborations/nih-staff-involvement-extramural-awards-cooperative).

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8. Annexes

i. Annex A:

SOP for Visual Acuity Measurement with Peek Acuity

1. **Purpose:**
   To describe the standard operating procedure for measuring visual acuity (VA)

2. **Scope:**
   All study participants will take a visual acuity test using the Peek Acuity application on the data collection smartphone (Samsung Galaxy S8 +). The visual acuity measurement procedure needs to be followed precisely and is done at every visit (baseline, 4 weeks, 6 months, and 1 year).

3. **Responsible staff:**
   3.1. Data recorder (Mainly)
   3.2. Study nurse or study supervisor (Occasionally, if necessary)

4. **Materials required:**
   4.1. Smartphone (Samsung Galaxy S8 +)
   4.2. Peek Acuity application
   4.3. A measuring tape or pre-measured rope of 1 meter and 2 meters long
   4.4. Duct tape
   4.5. A chair
   4.6. Eye examination form

5. **Procedure:**
   5.1. Visual acuity is measured using the Peek Acuity application on the study data collection smartphone
   5.2. Place a chair then measure and mark with a piece of duct tape the 1 meter and 2 meters distance from the back of the chair
   5.3. Make sure the phone screen is clear and there is no glare on the phone when evaluating the study participant
   5.4. Assist the participant to sit on the testing chair
   5.5. Explain the procedure to the patient and show them how to point fingers/hand in the direction of the E on the display while covering one eye at a time with the other hand
   5.6. Follow instructions on the screen and hold the device at the patient's eye level (often below chest, over belly) while standing at the 2 meters mark
   5.7. Ask the study participant to cover their left eye with their left hand and start measuring the visual acuity of the right eye
   5.8. Start measuring the visual acuity by swiping in the direction the participant indicates the E is pointing, without you looking at the screen

5.9. If the participant cannot see, shake the phone for the next E position and size
5.10. If the participant cannot see or gets several wrong answers, the application will instruct you to get closer to the participant. Follow instructions.
5.11. When the test is over, the phone will vibrate and the visual acuity score will be listed in LogMAR
5.12. Record the score
5.13. Repeat the procedure above for the left eye
5.14. Repeat visual acuity measurement at all study participant visits (baseline, four weeks, six months, and one year)

6. **References:**
Peek Vision Ltd (n.d.). *Peek Acuity.* Retrieved on September 6, 2022, from https://peekvision.org/en_GB/peek-solutions/peek-acuity/
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ii. Annex AA:

SOP for Height and Weight Measurement

1. **Purpose:**
To describe the standard operating procedure for measuring the height and weight of study participants

2. **Scope:**
Each enrolled study participants height and weight is measured at baseline visit

3. **Responsible staff:**
3.1. Data recorder (Mainly)
3.2. Study nurse or study supervisor (Occasionally, if necessary)

4. **Materials required:**
4.1. A weight scale
4.2. A measuring tape for height measurement
4.3. A clipboard
4.4. Baseline information form

5. **Procedure:**
5.1. Set up the height and weight station, away from the crowd. Place the scale against a wall.
5.2. Measure the weight
5.2.1. Ask study participant to empty their pockets or remove any heavy material or excess clothing to get accurate weight measure
5.2.2. Ask participant to stand on scale facing straight

5.2.3. Record the weight in kilograms

5.3. Measure the height

5.3.1. Ask the participant to stand straight against the wall, with their heels, back, and shoulder touching the wall, and looking straight out

5.3.2. Put the clipboard on the study participants head to get a straight horizontal line, then using the measuring tape, measure the height of the study participant starting from the floor to the clipboard on their head

5.3.3. Record the height in centimeters

iii. Annex B

SOP for capturing a full face and/or ocular pictures.

Purpose: To describe the standard operating procedure for capturing full face and ocular pictures

Introduction: Full face, straight gaze, up gaze, cornea, and palpebral photos are taken at each visit provided both eyes are intact (no shrunken eye).

Material Required: Smart phone

Responsible: Study data recorder

Procedure:

1. Take all photos in a well-lit area except for corneal pictures. Corneal photo is captured in a dark area.

2. Hold the phone vertically.

3. Open the camera app and make sure the rear-facing (back) camera is selected. Turn the flash on and adjust the zoom as necessary.

4. Move the phone's rear-facing camera as close to the face or eye as possible while still maintaining sharp focus (usually about 10 – 15 cm away from the eye). It is very important to assure that the image is crisp and clear.

5. The entire face or eye should be visible and centered in the photo. The eyelids should be opened as wide as possible. No shadows should cover the eye.

6. Hold the phone steady while capturing the photo.

7. Keep the head and eye still.

8. Tap on the phone screen over the area of interest to adjust the camera focus and brightness to this area.

9. Take multiple photos while the subject is looking in different directions:
- Full face
- Straight gaze
- Up gaze
- Cornea
- Palpebral photos

10. Take as many photos as you need to obtain quality images of the area of interest.

11. Repeat the process to obtain photos of the other eye. Each eye should be photographed separately.

Reference:
Associated Eye Care, *Smart Phone Eye Photography,* Retrieved April 1, 2024, from https://www.associatedeyecare.com/wp-content/uploads/AEC-Smartphone-Eye-Photography.pdf

iv. **Annex C**:

SOP for Ocular Examination

Purpose
- To describe the standard operating procedure to conducting visual function assessment, intraocular pressure measurement and ocular examination then collecting examination data into data collecting form.
- This SOP will be used as a guide by the data collectors

Introduction
All study participants will undergo detailed visual function assessment, IOP measurement and ocular examination of trachoma including other eye problems.

Responsible staffs
- Study nurses to examine the study subjects
- Examination Assistant-assist the study nurses and recorders to smoothen the process
- Data recorder to collect data including photograph of study subject and enter to the data collecting application

Materials required
- Data collection Tablet with PEEK software installed.
- Examination loupes
- Examination torches
- IOP measuring instrument(Icare)

- Examination rack with other examination materials such as gloves, antiseptic swabs, different eye drops, clean epilation forceps with a bowl/dish of alcohol cotton swab, referral forms)
- Chairs and tables

Study participant Examination

- Open blank form the “Eye examination” form
- Enter ID and alpha code of the study participant
- Ask the photographer to take the full face of the participant before he/she sits on the examination chair.

VISION TEST PROCEDURE

- Assist the participant to sit on the test chair
- Explain that you will be measuring participant’s vision and its purpose.
- Open the PEEK application by clicking on the PEEK sign. Tap lightly and gently on the application using one of your fingers
- Train the participant how to point with fingers/hand in direction of E, with large E close to the eye.
- Educate the participants not to cheat.
- Follow all the instructions displayed on the smart phone screen during the tests
- **Measure distance visual acuity** Tap on the “Test eyesight” tab, and read and follow the instruction.
- Make sure you are holding the device at the patient’s eye level with one hand. This is usually in front of your belly. Please do not tilt the phone.
- If the person is sitting on the floor for some reason you need also to sit on the floor to make the smart phone level to the person’s eye.
- Ask the person to cover one eye with the PALM of their respective hand.
- Start measurement always form the right eye.
- Click done to go to the measurement.
- Ask the participants to point the direction of the “E” by looking on to the smart phone screen using his/her right eye while his/her left eye is still covered
- Swipe in the direction the participants indicates the E is pointing
- If the participants cannot see, shake the device for anew letter. The devise will automatically show a letter one line above to the letter that the participant is not able to see
- You do not have to see the direction of the letter on the screen while swiping
- When the test is completed a dialog box with a sound will appear on the screen of the smart phone to tell you the visual acuity score of the participant in logMAR
- Document the score into the record form of the participant in the right eye
- If the participant is not able to see the first letter shown at the start of the test, shake the smart phone horizontally until he/she is able to see the next letter shown on the screen
- If the participant is not still able to see the letter, keep shaking until a dialog box with a sound appears on the screen of the smart phone
- Read the message and then stand 1 meter away with the participant’s left eye covered
- Go through steps above

- If the participant is still not able to see the first letter at 1 meters distance, shake the smart phone again until you hear a sound and instruction box appears
- This time hold the phone 30cm from the participant eye and ask them to identify how many bars are displayed.
- If the participant answers correctly, tap the “can see” box on the right hand side of the screen and record the answer in the form.
- If the participant is not able to count the bars, tap the “can’t see” box on the left hand side of the screen
- A message which instructs you to hold the phone close to the participant’s eye will appear on the screen. This is to see of the participant can see the movement of the bar.
- Tap done and then a black bar moving from left to right will appear on the screen
- If the participant identifies the movement of the bar, tap the “can see” box on the right hand side of the screen and record the visual acuity score as “2.5” (which is equivalent to Hand Movement)
- If the participant is not able to identify the movement of the bar, tap the “can’t see” box on the left hand side of the screen
- A message which instructs you to shine the camera’s flash into the participant’s eye will appear on the screen.
- Press done on the instruction box. During this time the camera flash will open with light; shine it into the participant’s eye.
- If the participant is able to detect the flash light, tap the “can see” box on the right hand side of the screen and record the visual acuity score as “3.0” (which is equivalent to Perception of Light)
- If the participant is not able to detect the flash light, tap the “can’t see” box on the left-hand side of the screen and record the visual acuity score as “3.5” (which is equivalent to No Perception of Light)
- Once you have completed the test for the right eye, enter the result immediately before measuring the left eye.
- To do this minimize the Peek application by clicking smartphone’s circle sign at the central lower end of the phone.
- Then click on the rectangle sign on the bottom right hand side of the phone. This will bring both the ODK and the Peek applications. Choose the ODK by clicking on it and then enter the VA score for the right eye
- Repeat the procedures above to measure VA for the left eye
- Once finished distance VA measurement, make sure you completed the necessary boxes in the data collecting form.

INTRAOCULAR PRESSURE MEASUREMENT PROCEDURE

TURNING THE TONOMETER ON AND LOADING THE PROBE

- Place the wrist strap into the wrist strap attachment.
- Place the wrist strap around your wrist and secure it.
- The wrist strap protects the tonometer from dropping onto the floor accidentally.
- Press the measurement button to turn the tonometer ON.

- The tonometer display will display all of the LCD segments (see the figure beside).
- Check that all of the segments are functional in the four-digit, seven segment LCD display.
- Following a brief pause, the display will show “LoAd,” reminding the user to load the single use probe into the tonometer prior to measurement

LOAD THE PROBE IN THE FOLLOWING WAY:

- Open the probe tube by removing the cap and insert the probe into probe base as shown in the image.
- After the probe has been inserted, be careful not to point it down before activating the tonometer in order to prevent the probe from falling out.
- Activate by pressing the measurement button once and the tonometer will be ready for measurement when 00 appears on the display.
- After activating the probe is magnetized and will not fall out.
- To obtain firm support for the patient’s forehead, in order to obtain an accurate measurement at the right distance, you can adjust the forehead support by turning the forehead support adjusting wheel.

MEASUREMENT

- Ask the patient to relax and look straight ahead at a specific point.
- Bring the tonometer near the patient’s eye.
- The central groove should be in a horizontal position, and the distance from the eye to the front part of the collar should be the length of the collar. In other words, the distance from the tip of the probe to the patient’s cornea (see picture) should be 4-8 mm (1/6-1/3 inch).
- If necessary, adjust the distance by turning the forehead support adjusting wheel.
- Press the measurement button lightly to perform the measurement, taking care not to shake the tonometer.
- The tip of the probe should make contact with the central cornea.
- Six measurements are made consecutively.
- After each successful measurement, you will hear a short beep.
- Once the six measurements have been performed, the IOP will be shown on the display after the ‘P’, three such different measurement will be taken for single eye and record on the study subject form.
- If there is an erroneous measurement, the tonometer will beep twice and display an error message.
- Press the measurement button to clear the error message.
- To obtain the most accurate reading, six measurements are required, but the result is also displayed after the first measurement, which can usually be considered valid.
- The measurement values displayed are average values for all previous measurements.
- Following the performance of the entire measurement, a new measurement series can be begun by pressing the measurement button.

- The tonometer will then be ready for the next measurement series (00 will show on the display).
- If the user doubts the validity of the measurement (for example, if the probe made contact with the eyelid, or missed the central cornea etc.), it is recommend that take a new measurement.
- In addition, when encountering unusual values (for example over 22mmHg or below 8 mmHg) it is recommended to take of a new measurement to verify the result

TURNING THE TONOMETER OFF

- Press either selector button until the display shows 'End'.
- Press the measurement button for two seconds - the display will show 'byE' and the tonometer will switch off.
- The used probe will be partially ejected. Use the used package to remove it from the tonometer.
- Ensure that you dispose of the probe properly

EYE LID EXAMINATION

- Use bright light to examine(torch light or sun light)
- Use magnifying loupe to examine the lid margin.
- Examine the eye lid margin for ocular discharge, misdirected eye lash, inward rotation of the eye lid margin and eye lid couture abnormality.
- Examine both eyes upper and lower eye lids.

Assess the presence of ocular discharge and if present characterize as serous/purulent or foamy and document on the space provided. The following definition will be used to classify the ocular discharge.

- Serous = Watery discharge,
- Purulent = yellowish relatively thick discharge,
- Foamy = Foam like discharge

Assess trichiasis

- Assess the eye for the presence of one or more lashes touching the eyeball on both eyes upper and lower eyelid. In addition, assess eyelash position, number and grading with the eye in primary position (looking straight ahead) and document in the space provided
  1. Number of lashes whose point touches globe medial to cornea
  2. Number of lashes whose point touches globe lateral to cornea
  3. Number of lashes whose point touches cornea
- Determine grade of trichiasis using the following grading definition
  1. T 0 No trichiasis
  2. T 1 Lashes deviated (pointing) towards the eye, but not touching the globe
  3. T 2 Lashes touching the globe but not rubbing the cornea.

4. T 3 Lashes constantly rubbing the cornea.

- Count and document the different types of lashes for only lashes touching the eyeball. Please note that often mixed type of lashes exist in one trichiatic eye
- Count number of trichiatic lashes in the right and left eye and both upper and lower eye lids.

Assess epilation and document if there is clinical evidence of epilation

- Clinical evidence of epilation is defined as presence of broken or regrown eyelashes or presence of part of the eyelid margin with no lashes

Asses and document the amount of epilation

- Examine if evidence of epilation is present in <1/3rd or 1/3rd-2/3rd or >2/3rd of the lash margin

Assess entropion

- Assess orientation of the lid margin of the eye in the primary position
- If necessary, gently raise any excess folds of upper lid skin, *without*, disturbing the position of the upper lid.
- Please note that to say that there is entropion at least more than half of the eyelid margin (grey line) should not be visible when the person looks straight ahead. Please give the participant a point to fix on a straight gaze.
- If there is a mixed picture, classify as the worse grade.
- Use the following grading

	Area of entropion	
Degree of severity	**<50% of lid margin**	**>50% of lid margin**
None	E0 (none)	
Without globe-lash base contact	E1 (mild)	E2 (moderate)
With globe-lash base contact	E3 (severe)	E4 (total)

The grading system is defined as follows:

1. None = 'normal' lid margin (see picture below) visible
2. Without globe-lash base contact = Definite inwards rotation of the lid margin, without any lash bases touching the globe
3. With globe-lash base contact = Inward rotation of lid margin, with some or all of the lash bases touch the globe.

Figure: Normal eye lid margin (Eyelid margin between the eyelash bases and the eyeball is visible across the eyelid)

Assess the contour of the eye lid for any abnormality like notching and other abnormality.
If there is contour abnormality document either central, lateral or medial on the eye lid and the severity of the abnormality either it is mild, moderate, sever.

The severity is defined as follow

- Mild-vertical deviation from the natural couture less than 1mm in height (less than half pupil height in day light) or affecting less than 1/3rd horizontal eyelid length(figure a).
- Moderate- vertical deviation from the natural couture 1-2mm in height (about the pupil height in day light) or affecting 1/3rd – 2/3rd of horizontal eyelid length (figure b).
- Sever- vertical deviation from the natural couture more than 2mm in height (more than the pupil height in day light) or affecting more than 2/3rd of horizontal eyelid length (figure c).

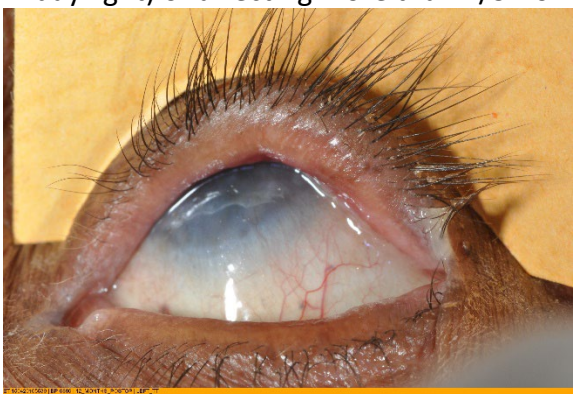


Figure a-mild notching

Figure b-moderate notching

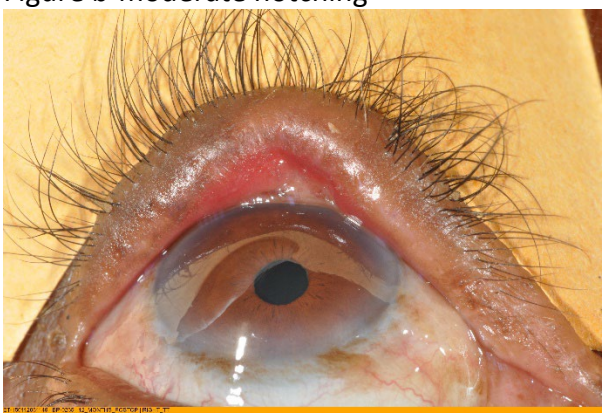


Figure c- sever notching

Examine corneal scarring

- Ask the patient to look straight, and make all grading while the patient is looking in a straight gaze
- Shine the torch light on to the cornea without creating glare on the cornea surface – usually best to do this from below or the sides.
- Please start examining the cornea from the centre to the periphery. Do not be destructed with easily visible scars on the periphery – look for more scars around the central visual axis.
- If there are more than one corneal scars, grade as for worst/most central scar
- See card below for diagrammatic representations of corneal scar grade
- Definitions of grading (see the figure below)
    - C1 Opacity not entering central 4mm
    - C2a Opacity within central 4mm but not entering within the central 1mm of the cornea. The pupil margin is visible through the opacity.
    - C2b Opacity within central 4mm but not entering within the central 1mm of the cornea. The pupil margin is not visible through the opacity.
    - C2c Opacity within central 4mm and entering the central 1mm of the cornea. The pupil margin is visible through the opacity.
    - C2d Opacity within central 4mm and entering within the central 1mm of the cornea. The pupil margin is not visible through the opacity.

C3 Opacity large enough and dense enough to make whole pupil margin invisible.

C4 Phthisis

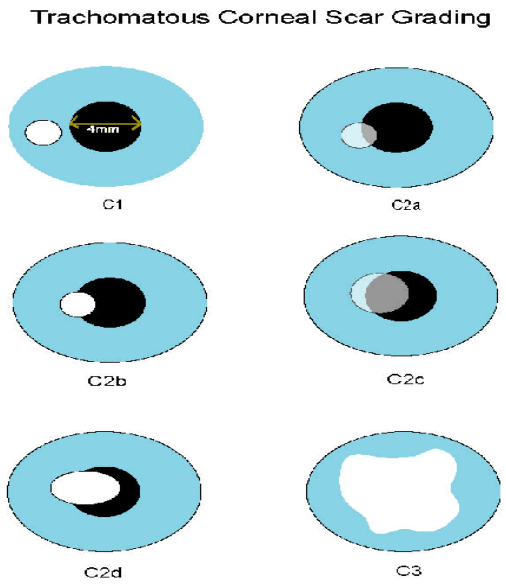


Figure: trachomatous corneal scar grading

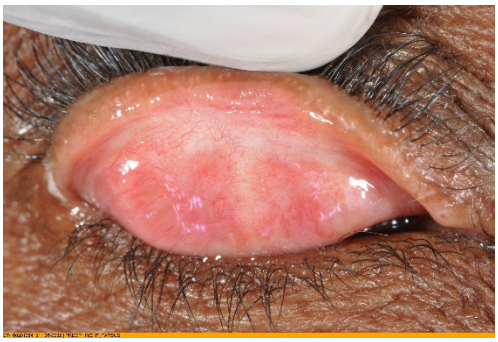
Assess the upper tarsal conjunctiva

- Evert the eye lid and examine for the following signs and take tarsus photograph**.**
- Ask the patient to look down
- Gently pull and evert the upper eyelid, at the same time by applying a slight pressure at approximately the centre of the eyelid externally

Assess the presence of conjunctivalisation of the both upper and lower lid margin of both eyes

Use the following grading and definition

- CM 0 No conjunctivalisation of the lid margin
- CM 1 The muco-cutaneous junction is located anterior to its normal position, but the whole line is still posterior to the line of Meibomian gland orifices.
- CM 2 The muco-cutaneous junction is located anterior to the line of the Meibomian gland orifices for less than 50% of the lid.
- CM 3 The muco-cutaneous junction is located anterior to the line of the Meibomian gland orifices for greater than 50% of the lid.



Fig; CM0

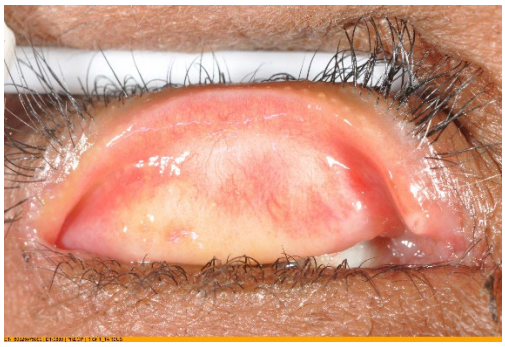


Fig: CM1

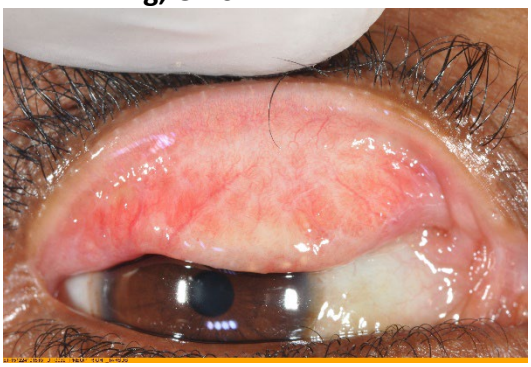


Fig: CM2

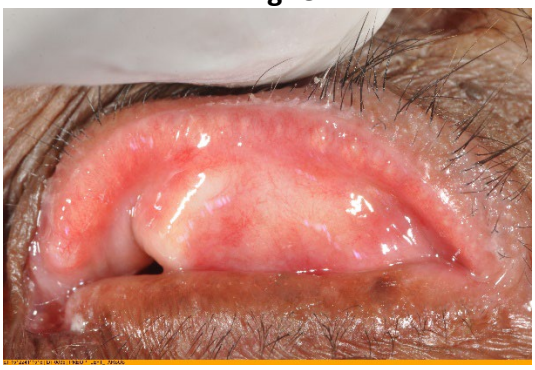


fig: CM3

WHO trachoma grading- Examine the upper eyelid tarsal conjunctiva of upper eyelid for trachoma and grade according WHO trachoma Grading. Use the following grading and definition

1. TF- The presence of five or more follicles, each at least 0.5 mm in diameter, in the central part of the upper tarsal conjunctiva. Follicles are round lumps or spots that lie beneath more superficial epithelium and are paler than the surrounding conjunctiva.
2. TI- Pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels
3. TS- The presence of easily visible scarring in the upper tarsal conjunctiva. Scars are white lines, bands, or sheets in the upper tarsal conjunctiva
4. TT- At least one eyelash from the upper eyelid touches the eyeball, or evidence of recent epilation of in-turned eyelashes from the upper eyelid(check the findings in the trichiasis part)
5. CO- Easily visible corneal opacity that is so dense that at least part of the pupil margin is blurred when viewed through the opacity

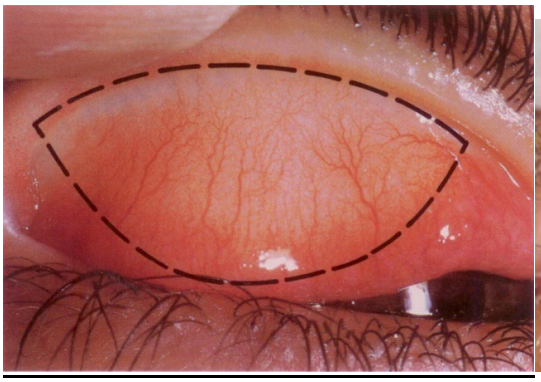


Fig: Normal tarsal conjunctiva

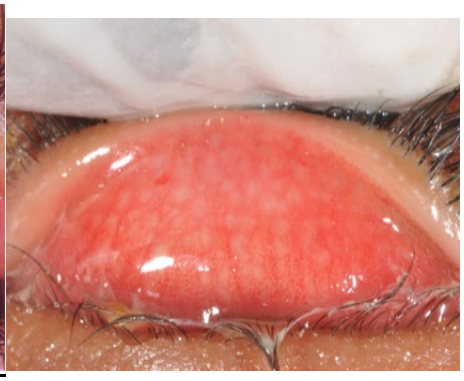


Fig: Trachomatous follicular

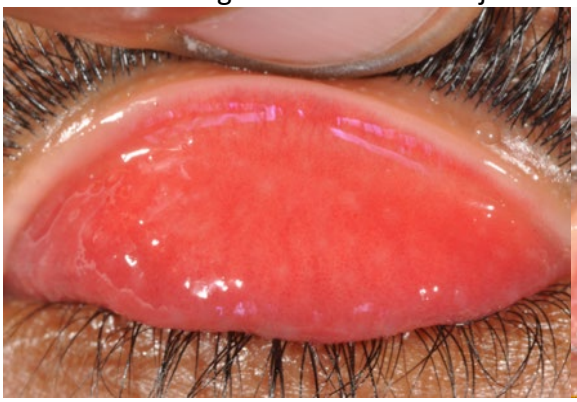


Fig: Trachomatous inflammation – intense

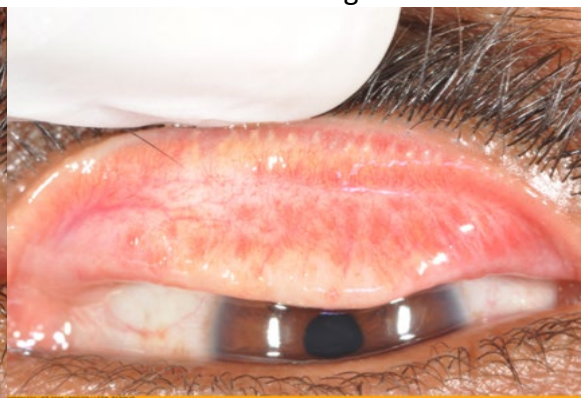


Fig: Trachomatous scarring (TS)

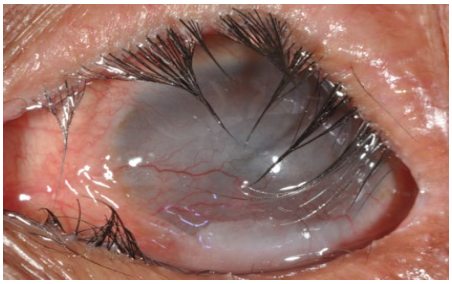
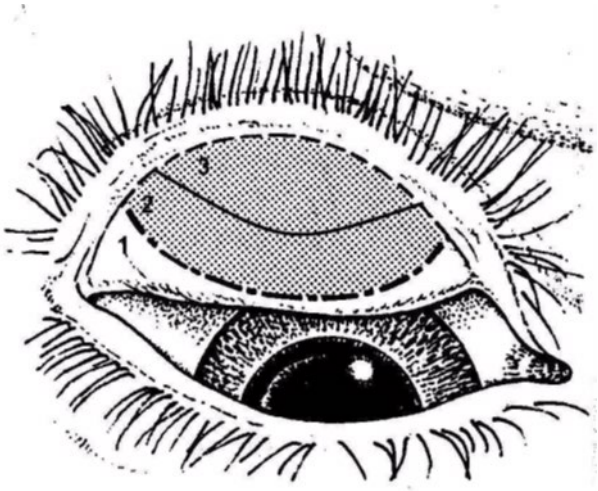


Fig: Trachomatous trichiasis and trachomatous corneal opacity

Examine the upper eyelid for Follicles using the following (FPC) grading and definition

F0 Absent
F1 Follicles present, but no more than 5 in zones 2 and 3 together (Figure below)
F2 More than 5 follicles in zones 2 and 3 together, but less than 5 in zone 3 (Figure below)
F3 Five or more follicles in each of the three zones (Figure below).



Examine upper lid papillary hypertrophy and grade severity of papillary hypertrophy using the following definitions

1. P 0-absent: normal appearance
2. P1- Minimal: individual vascular tufts (papillae) prominent, but deep subconjunctival vessels on the tarsus are not obscured.
3. P2- Moderate: more prominent papillae and normal vessels appear hazy, even when seen by the naked eye.
4. P3- Pronounced: conjunctiva thickened and opaque, normal vessels on the tarsus are hidden over more than half of the surface

Assess conjunctival scarring using the following grading and definition if there is no previous lid surgery

-If for some reason you are not able to grade the tarsus, select the "ungradable" tab from the choices

1. C0 No scarring on the conjunctiva
2. C1 Mild: fine scattered scars on the upper tarsal conjunctiva, or scars on the other parts of the conjunctiva
3. C2 Moderate: more severe scarring but without shortening or distortion of the upper tarsus.
4. C3 Severe: scarring with distortion of the upper tarsus.
5. C6 Not applicable

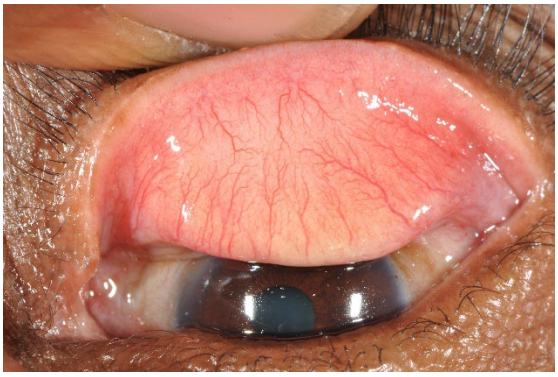


Fig: C0

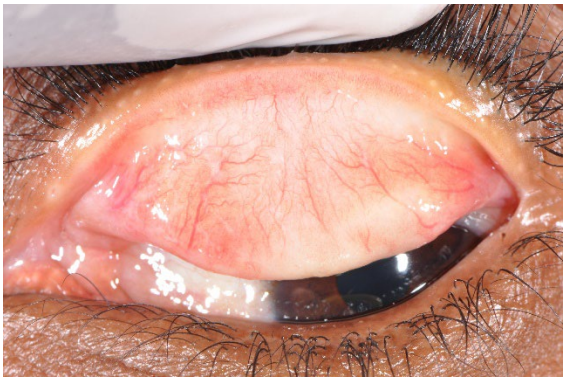


Fig:C1

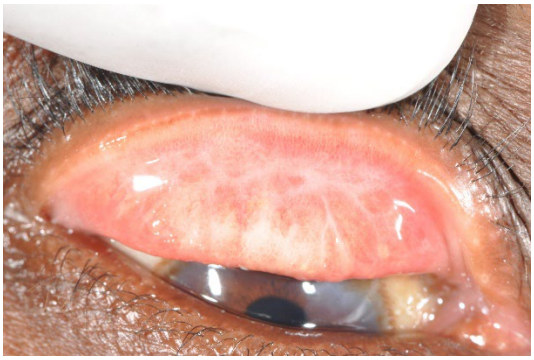


Fig: C2

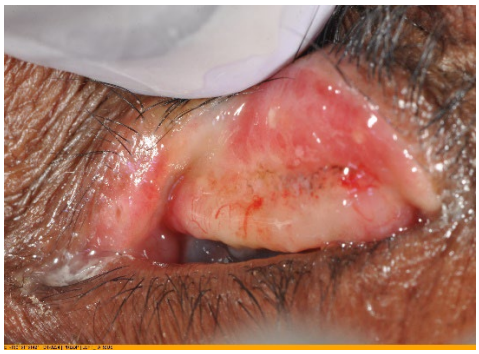


Fig: C3

Assess conjunctival scarring using the following grading and definition if there is previous lid surgery

1. SCO No scarring on the conjunctiva
2. SC1 Surgical line only.
3. SC2 Surgical line and occasional scattered scars
4. SC3 Surgical scar with widespread trachomatous scarring but no distortion
5. SC4 Surgical scar with distortion immediately around the incision line.
6. SC5 Surgical scar with additional distortion secondary to widespread trachomatous scarring.
7. SC6 Not applicable

- **Ask the photographer to take tarsal conjunctival photo, prior to realising the version.**
- **Examine the person for other eyelid conditions that may relate with trichiasis**
- ***Document if you noticed other conditions during the examination. This may include, cataract, glaucoma, eyelid infections, lacrimal duct infections, symblepharon, overcorrection, granuloma, eyelid closure defect, conjunctival and corneal infections or any other blinding and painful eye conditions.***
- ***Document the trichiasis management offered to the participant***
- ***Please ensure you examined both the right eye and the left eye using the same procedure as above.***

Complete ocular examination

- Check the examination data completeness before the participant leaves the room
- Ask the photographer to check that he has all the photographs with the quality needed
- Go through all to check if you entered the correct data. Make sure you entered the name of the person who did the examination and the certification number. This marks the completion of this section of data collection for this person.
- Thank and tell the participant that the examination is completed
- Provide the necessary management for the participant such as eye drops, eye ointment, referral … etc
- Keep the consent form with you as this marks the end of the data collection for that particular participant.

References

1. The simplified trachoma grading system, amended Anthony W Solomon,a Amir B Kello,b Mathieu Bangert,a Sheila K West,c Hugh R Taylor,d Rabebe Tekeraoie & Allen Foste. *Bull World Health Organ 2020;98:698–705 | doi: http://dx.doi.org/10.2471/BLT.19.248708*

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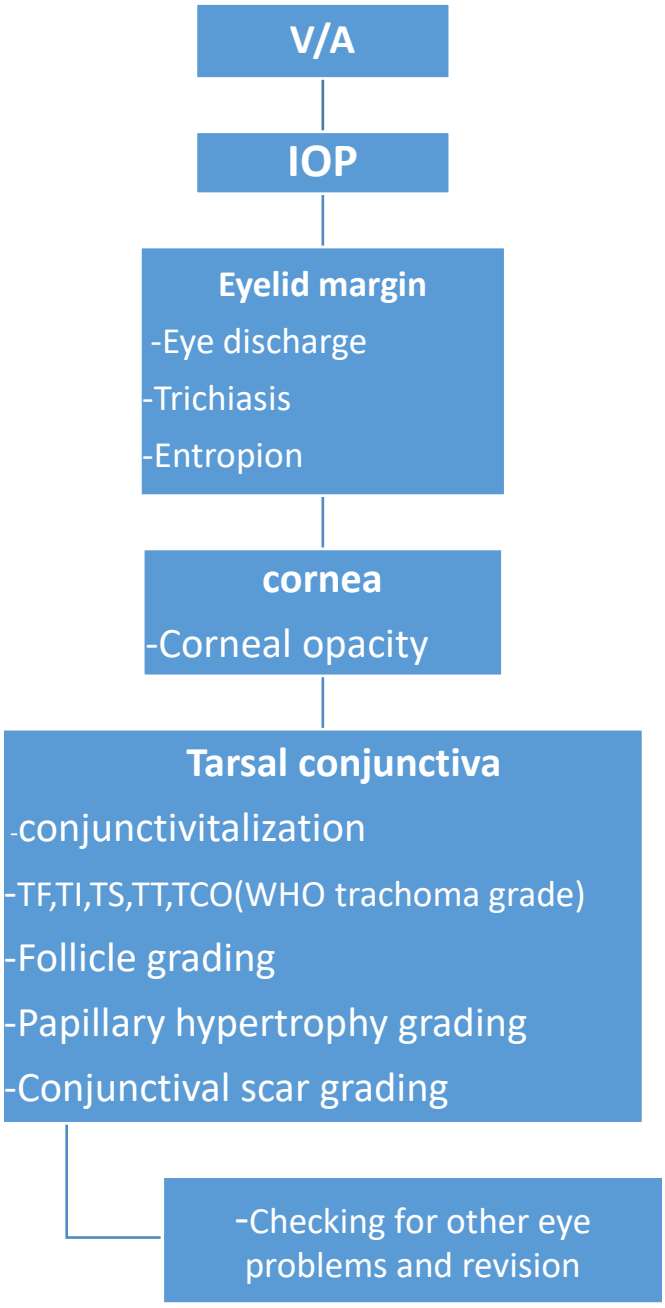
. https://nhsforthvalley.com/wp- accessed on September 13, 2022.

3. Peek acuty home vision test guide content/uploads/2020/04/Peek-Acuity-Pro_for-Android_Guide_NHSFV_v1.pdf accessed on September 13, 2022.

4. FLuorometholone as Adjunctive MEdical Therapy for TT Surgery (FLAME) Trial Version 1.3 Version Date: 08 March 2022,Version 1.3

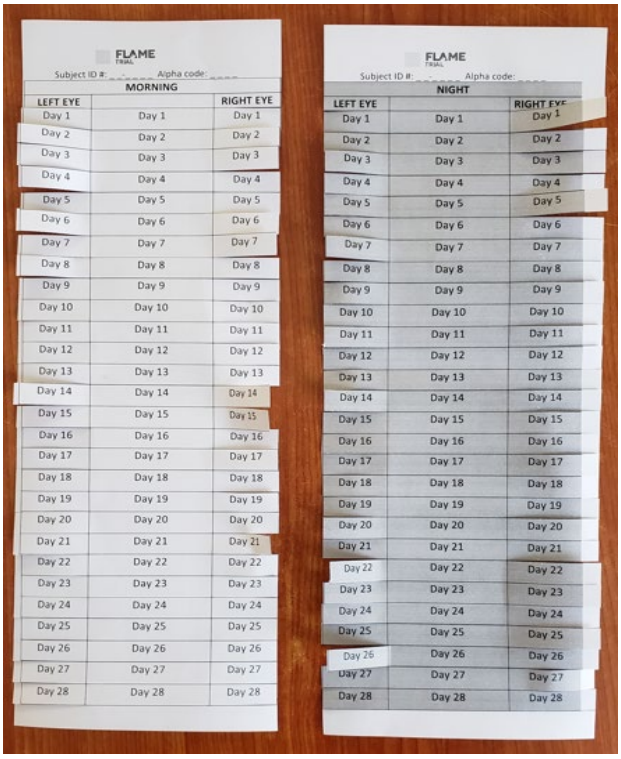
5. Eyelid conture abnormality. https://www.researchgate.net/figure/Eyelid-contour-abnormality-definitions_ accessed on September 13, 2022.


V/A
IOP
Eyelid margin
-Eye discharge
-Trichiasis
-Entropion
cornea
-Corneal opacity
Tarsal conjunctiva
-conjunctivitalization
-TF,TI,TS,TT,TCO(WHO trachoma grade)
-Follicle grading
-Papillary hypertrophy grading
-Conjunctival scar grading
-Checking for other eye problems and revision

v. Annex D:

SOP for Eyedrop Diary Use

1. **Purpose:**
   To describe the standard operating procedure for using the eyedrop diary
2. **Scope:**
   The eyedrop diary is given to each study participants at the baseline visit after the study participant is randomized and collected at the four weeks follow-up visit. The number of torn papers for morning and night use from the eyedrop diary is one of the approaches used to determine patients' adherence to medication.
3. **Responsible staff:**
   3.1. Study nurse
4. **Materials required:**
   4.1. Treatment adherence form (at four-week follow-up visit)
   4.2. Eyedrop diaries for morning and night (at baseline visit)



5. **Procedure:**
   5.1. After practicing the eyedrop administration procedure with the study participant, give out the morning and night medication diaries

5.2. Depending on which eye was enrolled in the trial, which side of the diary they will be using throughout the 28 days of eyedrop use
5.3. Explain the use of the tearing off process as eyedrops are administered
5.3.1. Tear off the piece of paper on the morning diary for Day 1
5.3.2. Instruct the study participant to skip tearing Day 1 from the night diary since the eye will be patches after surgery until their post-op follow-up the following day
5.3.3. Instruct the study participant how to continue tearing off the pieces of paper from the morning and night diaries each day after eyedrop administration
5.3.4. Explain to the study participant that if they forget to administer the eyedrop, the piece of paper for that time and day should not be torn off
5.4. Remind patient to bring back the eyedrop diaries at the four-week follow-up visit
5.5. At the four-week follow-up visit, record on the treatment adherence form, the total number of days the medication was used based on the total number of days the pieces of papers from the eyedrop diaries were torn off.

vi. Annex E:

SOP for Study Medication Weight Measurement

1. **Purpose:**
   To describe the standard operating procedure for measuring the weight of the study medication

2. **Scope:**
   The weight of the study medication is measured at the baseline visit after the study participant is randomized and at the four weeks follow-up visit. The change in medication bottle weight is one of the approaches used to determine patients' adherence to medication.

3. **Responsible staff:**
   3.1. Study nurse

4. **Materials required:**
   4.1. A medication scale
   4.2. 4 x C batteries for the scale or a power outlet
   4.3. Randomization form (for the baseline visit) or treatment adherence form (for the four-week follow-up visit)

5. **Procedure:**
   5.1. Set the medication scale on a flat surface and fix the scale legs until the little water bubble on the scale is in the center of the circle
   5.2. Unlock the scale spring and put the plate cover on top of the scale
   5.3. Turn on and Tare/ zero the scale until you see the 0.00 g
   5.4. Put the medication bottle on the scale

5.4.1. The bottle is weighed after applying the first drops into the study participants eye at the baseline visit, and when the bottle is returned at the four-week follow-up visit

5.5. Record the weight of the bottle in grams

5.5.1. At baseline, the medication bottle weight is recorded on the randomization form

5.5.2. At four-weeks, the weight is recorded on the treatment adherence form

5.7. If at baseline visit, remind the study participant to bring the study medication at the four-week follow-up. If at the four-week follow-up visit, discard the study medication at the health center or health post after weighing and if the study participant has completed 28 days of medication use.

5.8. Turn off the scale to save the batteries in between study participants evaluation

vii. VII. Annex F Study Form Completion Guidelines

Here are the instructions for completing study forms.

1. Baseline Eye Examination Form

SOP for Baseline Eye Examination Form

Purpose:

To describe the standard operating procedure for completing the Baseline Eye Examination Form.

Introduction: Study participants undergo detailed ophthalmic examination during the visit number one /or the baseline visit/. This form is used to capture those examination results.

Materials required:

CRF and other Forms	
1. Baseline Eye Examination Form	To record observations
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse

Procedure:

A. The patient ID label is affixed at the top of the Baseline Eye Examination Form.

B. Provide the required answers to the listed questions as appropriate. For the relevant form filling out instructions, also, please refer to the sections of the *SOP for CRF Completion and Correction*.

C. The Study nurse will collect and record the following information on the form.

1. Date of examination
2. Visual Acuity
   Refer to instructions for Visual Acuity measurements with Peek Acuity.
   [See Annex A]

For questions below please refer to the SOP of the ophthalmic examination as applicable. *[See Annex C]*

3. Ocular Surface Discharge OD
4. Ocular Surface Discharge OS
5. Assessment of Trichiasis
6. Trichiasis Grading
7. Evidence/extent of epilation
8. Entropion
9. Is there any Eyelid Contour Abnormality
10. Corneal Opacity/Scar Grading
11. Conjunctivalization of the Lid Margin Grade
12. Trachoma Grading
13. Upper Eyelid Follicles
14. Upper Eyelid Papillary Hypertrophy
15. Upper eyelid conjunctival scarring If prior lid surgery at the time of grading
16. Conjunctivalization of the Lid Margin Grade
17. Trachoma Grading
18. Upper Eyelid Follicles
19. Upper Eyelid Papillary Hypertrophy
20. Upper eyelid conjunctival scarring If prior lid surgery at the time of grading
21. Are any of the following present in the Eye?
22. If vision in either eye is worse than logMAR 0.48, please indicate the most likely cause
23. Were all exams/questions completed for both eyes?
24. Were ocular photographs taken?
25. Name & certification number of person performing examination
    i. Print Name
    ii. Certification #

2. Baseline Information Form

SOP for Baseline Information Form

Purpose: To describe the standard operating procedure for completing the *BASELINE INFORMATION FORM*.

Introduction:

To fully evaluate the treatment effect, in addition to the primary analysis, secondary analysis of the Primary Outcome will be done.

In the equation used in the final analysis, to check the consistency of results over subgroups, selected factors will be included to assess possible *predictors for postoperative TT* & *effect modification of the study intervention* on the primary outcome.

To that end, this form is utilized for gathering applicable baseline data.

It is one of the group of forms that are filled out before surgery.

Materials required:

CRF and other Forms	
1. Baseline Information Form	To record the required baseline information
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible:

Person	Responsibility
Study nurse or Study data recorder	Ensures the Baseline Information Form is properly labeled. Complete the Baseline Information Form Checks the form for completion. Enters the data on the form into RedCap

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. The study nurse or study data recorder will collect and record the following information.
   1. Did the patient sign the consent form?
   2. Enrollment location
   3. What is your age?
   4. Patient's height
      Refer to instructions of the height & weight measurement. *[See Annex AA]*
   5. Patient's weight
      Refer to instructions of the height & weight measurement. *[See Annex AA]*
   6. Is the patient male or female?

7. Race: Is the patient African?
8. What is your marital status?
9. Which language do you speak best?
10. Are you able to read?
11. What is your highest level of education?
12. What is your occupation?
13. Are you taking any medication for treating systemic or ocular (eye) diseases?
14. Do you use health care for something other than trichiasis?
15. Have you ever been diagnosed with cataracts?
16. Have you ever been diagnosed with glaucoma?
17. Have you ever had eye surgery?
18. Have you ever had an eye injury?
19. Is the patient currently breastfeeding?

20. Name & Certification number of person completing form.
    i. Print Name
    ii. Certification Number
21. Date form completed.

3. CRF Completion and Correction

SOP for CRF Completion and Correction

Purpose: The aim of this SOP is to describe how CRFs should be completed and corrected.

Introduction: The Case Report Forms (CRFs) contain nearly all of the data collected during the study.

Responsibilities: This SOP applies to all personnel involved with the on-site completion and verification of the CRFs.

Procedures:

1. Subject privacy:
   The CRF is an anonymous document. The only identifiers present on the CRF are the participant's ID Number and the ALPHA Code.
   - Do not file the Informed Consent in the CRF.

2. Completing the CRF
   - Use a blue pen to fill the CRF.
   - Only enter results in the fields provided. Do not create additional fields on the CRFs.
   - Do not leave questions unanswered, unless an instruction allowing to do so is provided specifically in the questionnaire.
   - Mark/enter the following as appropriate.

- For selection options, please make X mark in the check boxes.
- If an answer is not known, mark “NK” (Not Known).
- If a procedure is not done, enter ND (Not Done).
- If a question is not applicable, mark “NA” (Not Applicable).
- Sign and date the CRFs each time a form is completed. By doing so you take responsibility for the correctness and accuracy of the data.

3. Correcting the CRF
   - Do not use any correction fluid to erase the entry you wish to modify.
   - Each correction in the CRF must be dated and initialed (or signed).
   - For selection options, using a red pen draw through the incorrectly marked box with a single line, and then using a blue pen make X mark in the correct check box. The original entry should remain legible.
   - For a fill in the blank questions, using a red pen draw through the error with a single line. Then using a blue pen, write the correct answer next to the original entry. The original entry should remain legible.

4. Institute quality assurance measures such as “double checking” entries, to maximize efficiency and eliminate unnecessary data clarifications.
5. Storage and access
   - CRFs must be kept in a locked and safe place. The access should be strictly restricted to the study staff.
   - The CRF must be retained with regard to local legislation and for at least 5 (five) years [as per NRERC’s guideline] after the end of the study.

Reference:

1. No. 32 – Data management SOP: Completing case report forms (CRFs) http://journals.plos.org/plosntds/article/asset?unique&id=info:doi/10.1371/journal.pntd.0004818.s032 Accessed Aug. 2022

4. Eligibility Form

SOP for Eligibility Form

Purpose: To describe the standard operating procedure for completing the *ELIGIBILITY FORM*.

Introduction: The aim of this SOP is to describe how subject eligibility confirmation will be documented by the field team. Eligibility Confirmation must be determined before a subject can be enrolled into a clinical trial.
It is the responsibility of the study nurse to perform all assessments required to determine eligibility. Enrolling ineligible subjects is considered to be a compliance violation of the currently approved IRB protocol (investigational plan), GCP guidance and local regulations.

Materials required:

CRF and other Forms	
1. Eligibility Form	To document subject's eligibility status
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Smart phone	For REDCap entry

Responsible: Study nurse

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. The Study nurse will collect and record the following information.
1. Visit Date
2 – 5. INCLUSION CRITERIA
6 – 17. EXCLUSION CRITERIA
For question number 16, refer to instructions of the ocular examination. *[See Annex C]*
18. Is the subject eligible for the study?
19. Name & Certification number of person completing form
    i. Print Name
    ii. Certification Number
20. Date form completed

5. Enrollment Log

SOP for the Enrollment Log

Purpose:
To standardize the **Enrollment Log** and fulfill regulatory requirements allowing for the identification of research subjects.

Introduction:
Study-specific Identification codes [*SCREENING ID number, SUBJECT ID number-ALPHA Code,* and *TREATMENT ID number*] serve to maintain research subject's confidentiality but need to be verifiable. In parallel, research logs serve to link the identity of research subjects to these assigned codes on the research forms.
All subjects screened for the study will be documented on the *SCREENING LOG*. Furthermore, after eligibility has been confirmed, the study team will enter the participant's name and date of enrollment on the study-supplied *ENROLLMENT LOG*.

Responsibility: Study nurse or Study data recorder

Procedure:
Unlike the Screening ID number, the use of *Subject ID* number along with an *Alpha Code* will not occur until after the confirmation of eligibility of the subject is received.
Willing subjects who have provided informed consent and are determined to be eligible will be issued a *Subject Identification number* and an *Alpha code*. At randomization a medication box will be assigned to each enrolled patient, and the *Treatment Identification Number* (*RxID*) label, too, will be put up on the **Enrollment Log**.
The participant will have a *Screening ID number* (one of each of these is given to each subject screened), *Subject Identification number* along with an *Alpha Code* and *Treatment Identification Number* (*RxID*) correlated with a Medication Box number.
A pre-selected Treatment Identification number (RxID) is associated with the *Subject ID number /and ALPHA Code/* on each line on the log and this RxID is assigned to each sequential patient.

9. The **Field Coordinating Center (or designee)** will coordinate with the **Field Study Supervisor (or designee)** in making the subject identification codes available for the field team.
10. Once eligibility is confirmed, the study team will enter the enrolled participant's name and date of enrollment on the study-supplied ***Enrollment Log***.

11. The Study nurse or Study data recorder will collect and record the following information on the Log.

- Subject Name
- Sex
- Age
- Height (cm)
  [Refer to instructions of the height & weight measurement]
- Weight (Kg)
  [Refer to instructions of the height & weight measurement]
- Address (Woreda, Kebele, Gere)
- Patient Phone Number
- Case Finder Name
- Case Finder Phone Number
- Consent (Face)
- Consent (Eye)
- Enrolled Eye
- Enrollment Date
- Surgery Date
- Follow-up Dates (28 days)
- Follow-up Dates (6 months)

- Follow-up Dates (1 year)
- Comments

12. Certain fields, such as: *Treatment ID number*, *Surgery Date* and *Follow-up Dates* will not be filled until after randomization & surgery.

13. The Study nurse or Study data recorder will transfer relevant data from the **ENROLLMENT LOG** to the **PATIENT INFORMATION SHEET &** the **PATIENT TRACKING SHEET.**

Reference:

1. Subject logs and codes **- Clinical, Standard Operating Procedures for Clinical Trials (SOPs),** https://globalhealth.duke.edu/standard-operating-procedures-clinical-trials-sops. Accessed Aug. 2022

6. EQ5D Form

SOP for EQ5D Form

Purpose:

To describe the standard operating procedure for completing the *EQ5D.*

Introduction:

One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "….to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."
Another aim is to try and characterize the value of adding such treatment to TT surgery under a range of plausible health economics circumstances.
Patient-reported outcomes /patients' perspectives/ are key aspects of the design and rationale of the trial that have major bearing on the approaches to data analysis, statistical issues, and data monitoring. A broad range of information is collected to inform the analysis for health economics and the overall outcome.
To that end, this form is employed as one of the tools adopted by FLAME to gather pertinent data.

Materials required:

CRF and other Forms	
1. ED5D form	To record patient reported outcomes
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or Study data recorder

Procedure:

A. The patient ID label is affixed at the top of the EQ5D Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. In Question # 6, indicate on the scale, as accurately as possible, the relevant patient response.

D. The study nurse or study data recorder will collect and record the following information.
   1. Mobility
   2. Self-Care
   3. Unusual Activities
   4. Pain/Discomfort
   5. Anxiety/Depression
   6. Scale (0-100) to gauge the opinion of the subject on how good or bad she/he believes her/his health is.
   7. Name & Certification number of person completing form.
      i. Print Name
      ii. Certification Number
   8. Date form completed.

7. Exit Form

SOP for Exit Form

Purpose: To describe the standard operating procedure for completing the *EXIT FORM*.

Introduction:

This form gets filled out whenever a subject exits the study, even before completing the study. A completed subject is one who completed the last (Visit 5) follow-up visit. After Visit 5 procedures, subjects will exit the study. During this last visit, the Exit Form is filled out by the study team.

Material Required:

CRF and other Forms	
Exit Form	To record the required Exit information
Other Materials	
Labels	To indicate the designated study ID & alpha code
Smart phone	For REDCap entry

Responsible: Study nurse or study data recorder

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Form Completion Guidelines.

C. The study nurse or study data recorder will collect and record the following information.

1. Date of study exit
2. Has the subject completed 12 month visit?
3. On the scale of 1 to 10 (10 is the highest level of satisfaction), how satisfied are you with the outcome of TT surgery?
4. What eye drops do you think you used in the first 4 weeks after TT surgery?
5. Name & Certification number of person completing form
    i. Print Name
    ii. Certification Number
6. Date form completed

8. Eye Pain Impact Questionnaire

SOP for Eye Pain Impact Questionnaire

Purpose:
To describe the standard operating procedure for completing the *Eye Pain Impact Questionnaire.*

Introduction:
One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "….to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."
Another aim is to try and characterize the value of adding such treatment to TT surgery under a range of plausible health economics circumstances.
Patient-reported outcomes /patients' perspectives/ are key aspects of the design and rationale of the trial that have major bearing on the approaches to data analysis, statistical issues, and data monitoring. A broad range of information is collected to inform the analysis for health economics and the overall outcome (including surgery satisfaction).
To that end, this form is employed as one of the tools adopted by FLAME to gather pertinent data.

Materials required:

CRF and other Forms	
1. Eye Pain Impact Questionnaire form	To record patient reported outcomes
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or study data recorder

Procedure:

A. The patient ID label is affixed at the top of the Eye Pain Impact Questionnaire Form.

B. Circle the number that represents the correct response. Also, please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. The study nurse or study data recorder will collect and record the following information.

1. In the last month, how often has eye pain interfered with your personal care such as bathing, eating, and dressing?
2. In the last month, how often has eye pain disturbed your sleep?
3. In the last month, how often has eye pain interfered with your household work such as cooking, house cleaning, washing cloth, fetching water, fetching firewood, caring to other family members?
4. In the last month, how often has eye pain affected your non-household work, such as agricultural or paid work?
5. In the last month, how often has eye pain affected your participation in social activities such as attending weddings, social meetings, and funerals?

6. Name & Certification number of person completing form
    i. Print Name
    ii. Certification Number
7. Date form completed

9. Follow-up Health Review Form

SOP for Follow-up Health Review Form

Purpose: To describe the standard operating procedure for completing the *Follow-up Health Review Form*.

Introduction:

One of the specific study aims of the study is to assess the efficacy of the interventional treatment. To be precise, it is, "…..to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."

To that end, this form is utilized during the follow up visits for the documentation of a range of applicable data.

Materials required:

CRF and other Forms	

1. Follow Up Health Review Form	To capture follow-up information
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse

Procedure:

A. The patient ID label is affixed at the top of the Follow-up Health Review Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. The study nurse will collect and record the following information.

1. Date of Visit:
2. Has the subject had surgery on the right eye since the last study visit?
3. Has the subject had surgery on the left eye since the last study visit?
4. Is cataract surgery recommended for either eye?
5. Has the subject started any new medications or had changes to existing medications since the last study visit?
6. Has the subject had any new adverse events since the last study visit?
7. Has the subject had any health event which required major medical intervention or hospitalization since the last visit?
8. Are there any events listed on the adverse event log that were unresolved as of the previous study visit?
9. Has the subject utilized health care beyond the usual care for TT surgery since the last study visit?
10. Are you pregnant or breastfeeding?
11. Name & certification number of person completing form
12. Date form completed

10. Missed Visit Form

SOP for Missed Visit Form

Purpose: To describe the standard operating procedure for completing the *Missed Visit Form.*

Introduction:
It is stated in the protocol that when available, the reasons for losses to follow-up, will be reviewed. This form ought to be filled out for all study participants who end up missing the surgery or any of the follow up visits.

Materials required:

CRF and other Forms	
1. Missed Visit Form	To track the reason and any additional information pertaining missed visits
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or study data recorder

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* in the Study Forms Completion Guidelines.

C. For question number two, there may exist more than one answer. If that is the case, then please indicate all that apply.

D. The Study nurse or study data recorder will collect and record the following information.
   1. Which visit was missed?
   2. Reason this visit was missed?
   3. Has a new appointment been scheduled?

   4. Name & Certification number of person completing form.
      i. Print Name
      ii. Certification Number
   5. Date form completed.

11. Month 6 & 12 Eye Examination Form

Purpose:
To describe the standard operating procedure for completing the Month 6 & 12 Eye Examination Form.

Introduction: Study participants undergo detailed ophthalmic examination during the Months 6 & 12 follow up visits. This form is used to capture those observations.

Materials required:

CRF and other Forms	
1. Month 6 & 12 Eye Examination Form	To record observations
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse

Procedure:

D. The patient ID label is affixed at the top of the Serious Adverse Event Initial Reporting Form.

E. Provide the required answers to the listed questions as appropriate. For relevant form filling out instructions, also, please refer to the sections of the *SOP for CRF Completion and Correction*. *[See Annex B]*

F. The Study nurse will collect and record the following information on the form.

1. Date of examination
2. Visual Acuity
   Refer to instructions for Visual Acuity measurements with Peek Acuity. *[See Annex A]*
3. Intraocular Pressure (IOP) Measurements

For questions below please refer to the SOP of the ophthalmic examination as applicable. *[See Annex C]*

4. Ocular Surface Discharge
5. Assessment of Trichiasis
6. Trichiasis Grading
7. Evidence/extent of epilation
8. Entropion
9. Is there any Eyelid Contour Abnormality
10. Corneal Opacity/Scar Grading
11. Conjunctivalization of the Lid Margin Grade
12. Trachoma Grading
13. Upper Eyelid Follicles
14. Upper Eyelid Papillary Hypertrophy
15. Upper eyelid conjunctival scarring If prior lid surgery at the time of grading
16. Conjunctivalization of the Lid Margin Grade
17. Trachoma Grading

18. Upper Eyelid Follicles
19. Upper Eyelid Papillary Hypertrophy
20. Upper eyelid conjunctival scarring If prior lid surgery at the time of grading
21. Are any of the following present in the Eye?
22. If vision in either eye is worse than logMAR 0.48, please indicate the most likely cause
23. Were all exams/questions completed for both eyes?
24. Were ocular photographs taken?
25. Name & certification number of person performing examination
    iii. Print Name
    iv. Certification #

12. Ocular Surface Disease Index

SOP for Ocular Surface Disease Index

Purpose: To describe the standard operating procedure for completing the *Ocular Surface Disease Index.*

Introduction: One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "….to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."
Another aim is to try and characterize the value of adding such treatment to TT surgery under a range of plausible health economics circumstances.
Patient-reported outcomes /patient's perspectives/ are key aspects of the design and rationale of the trial that have major bearing on the approaches to data analysis, statistical issues and data monitoring. This form is one of the tools used to capture such a class of data.

Material required:

CRF and other Forms	
Ocular Surface Disease Index form	To record patient reported outcomes
Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or study data recorder
Procedure:

A. The patient ID label is affixed at the top of the Ocular Surface Disease Index Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions.

C. The study nurse or study data recorder will collect and record the following information.

Have you experienced any of the following during the last week?

1. Eyes that are sensitive to light?
2. Eyes that feel gritty?
3. Painful or sore eyes?
4. Blurred vision?
5. Poor vision?

Have problems with your eyes limited you in performing any of the following during the last week:

6. Reading?
7. Driving at night?
8. Working with a computer or bank machine (ATM)?
9. Watching TV?

Have your eyes felt uncomfortable in any of the following situations during the last week:

10. Windy conditions?
11. Places or areas with low humidity (very dry)?
12. Areas that are air conditioned?

13. Name & certification number of study team member completing form
14. Date form completed

13. Poverty Questionnaire

SOP for Poverty Questionnaire.

Purpose: To describe the standard operating procedure for completing the *Poverty Questionnaire*

Introduction: This form is utilized during the first and last visit and focuses on the socio-economic status of the study participant.

Materials required:

CRF and other Forms	
1. Poverty Questionnaire Form	To record the required information
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For RedCap entry

Responsible: Study nurse and study data recorder

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the SOP for CRF Completion and Correction for relevant form filling out instructions.

C. The study nurse or study data recorder will collect and record the following information.

1. Determine if the Respondent Lives in an Urban or Rural Area

2. Does your household have electricity?
3. Does your household have a radio?
4. Does your household have a television?
5. Does your household have a refrigerator?
6. Does your household have an electric mitad?
7. Does your household have a table?
8. Does your household have a chair?
9. Does your household have a bed with cotton/sponge/spring mattress?
10. Does any member of this household have a bank account?
11. What is the main source of drinking water for members of your household?
12. What kind of toilet facility do members of your household usually use?
13. What type of fuel does your household mainly use for cooking?
14. What is the main material of the floor of your house?
15. What is the main material of the exterior walls in your household?
16. What is the main material of the roof in your household?

17. Name & certification number of study team member completing form

18. Date form completed:

14. Primary Endpoint Assessment Form

SOP for Primary Endpoint Assessment Form

Purpose: To describe the standard operating procedure for completing the *Primary Endpoint Assessment Form.*

Introduction:

One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "….to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."
Accordingly, the primary investigated outcome is characterized as *the postoperative recurrence of TT by one year* as determined at four weeks, six months and one year. Recurrence is defined as the presence of one of the following:

(1) One or more lashes touching the globe in an eye.

(2) History of repeated TT surgery.

(3) Evidence of epilation on clinical examination.

The sole focus of this form is the recording and presentation of the primary outcome.
This form is to be filled out at visits 3, 4, and 5.

Materials required:

CRF and other Forms	
1. Primary Endpoint Assessment Form	To record the Primary Outcome
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse

Procedure:

D. The patient ID label is affixed at the top of the Primary Endpoint Assessment Form.

E. Please refer to the *SOP for CRF Completion and Correction*.

F. The study nurse will collect and record the following information.

1. Has the subject met any of the following Primary Study Endpoint in the Right Upper Eyelid? Please refer to the relevant sections on assessment procedures in the SOP for Ophthalmic Examination. [*See Annex C*]
2. Has the subject met any of the following Primary Study Endpoint in the Left Upper Eyelid? Please refer to the relevant sections on assessment procedures in the SOP for Ophthalmic Examination. [*See Annex C*]
3. Name & certification number of person completing form
4. Date form completed

15. Protocol Deviation and Unanticipated Event Form

SOP for Protocol Deviation and Unanticipated Event Form

Purpose: To describe the standard operating procedure for completing the *Protocol Deviation and Unanticipated Event Form.*

Introduction: This document is used to document any departure from the study procedures or treatment plans as specified in the IRB-approved protocol, or unanticipated events that are not adverse events.[1]

Materials required:

CRF and other Forms	
1. Protocol Deviation and Unanticipated Event Form	To document protocol violations and unexpected problems
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Smart phone	For REDCap entry

Responsible: Study team

Procedure:

A. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions.

B. The study team will collect and record the following information

1. Are you reporting a Protocol Deviation or Unanticipated Event…?
2. Type of Deviation or Unanticipated Event:
3. Patient ID (if applicable):
4. Deviation or Unanticipated Event Summary:
5. Reason the deviation or unanticipated event occurred:
6. Action Taken:
7. Please provide a corrective action plan to prevent this from occurring in the future:
8. Was the study masking broken?
9. Deviation or Unanticipated Event Assessment: If any of these questions are answered Yes, the deviation or unanticipated event must be reported to the IRB.
10. Did the event meet IRB expedited reporting requirements (see #9 above)?
11. Person completing this form (please print):
12. Date form completed:

Reference:
1. https://www.unr.edu/research-integrity/human-research/human-research-protection-policy-manual/735-protocol-deviations, Accessed 16 January 2024.

16. Randomization and Initial Treatment Form

SOP for Randomization & Initial Treatment Form

Purpose: To describe the standard operating procedure for completing the *Randomization & Initial Treatment FORM*.
Introduction: This form is filled out as part of the enrollment process.

Materials required:

CRF and other Forms	
1. Randomization & Initial Treatment Form	To document the observations
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Smart phone	For REDCap entry

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions.

C. The Study nurse will collect and record the following information.

1. Which eye(s) are eligible for the study?
2. Was the subject randomized?
3. Was the subject instructed on the proper use of the study medication?
4. Did the subject practice instilling the assigned eyedrops?
5. Was a drop of the study medication administered in the eligible eyes prior to TT surgery?
6. Did the subject experience any adverse events from the study medication?
7. Weight of medication bottle after practice and initial drop(s) instillation: __ __.__ __ g
   [Refer to medication bottle weighing instructions: see *Annex E*]
8. Name & certification number of person completing form
    1. Print Name:
    2. Certification #:
9. Date form completed:

17. Satisfaction with TT Surgery

SOP for Satisfaction with TT Surgery

Purpose:
To describe the standard operating procedure for completing the *Satisfaction with TT Surgery form.*

Introduction:
One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "…..to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."
Another aim is to try and characterize the value of adding such treatment to TT surgery under a range of plausible health economics circumstances.
Patient-reported outcomes /patients' perspectives/ are one of the key aspects of the design and rationale of the trial that have major bearing on the approaches to data analysis, statistical issues and data monitoring. A broad range of information is collected to inform the analysis for health economics and the overall outcome (including surgery satisfaction).
To that end, this form is employed as one of the tools to gather pertinent data.

Materials required:

CRF and other Forms	
1. Satisfaction with TT Surgery form *[See Annex A]*	To record patient reported outcomes
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or study data recorder

Procedure:

A. The patient ID label is affixed at the top of the Satisfaction with TT Surgery form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions. *[See Annex B]*

C. The study nurse or study data recorder will collect and record the following information.
   1. How satisfied are you with the **Trichiasis Surgery Outcome** in your **Right Eye**?
   2. How satisfied are you with the **Cosmetic Outcome** in your **Right Eye**?
   3. How satisfied are you with the **Trichiasis Surgery Outcome** in your **Left Eye**?
   4. How satisfied are you with the **Cosmetic Outcome** in your **Left Eye**?

5. Name & Certification number of person completing form
    i. Print Name
    ii. Certification Number
6. Date form completed

18. Surgical Consent Form

SOP for Surgical Consent Form

Purpose: To describe the standard operating procedure for completing the Surgical Consent Form.

Introduction: All patients planned for TT surgery will be asked to sign a surgical consent form.

Responsible: TT surgeon and (study nurse or study data recorder)

Procedure:

A. The patient ID label is affixed at the top of form after the subject has provided informed consent and is determined to be eligible to participate in the study.
B. The TT surgeon will record the following information.
    1. Date
    2. Name of patient
    3. I consent to have eyelid rotation surgery performed on these eyelids:
    4. My questions about the reason for surgery and the risks of surgery have been answered to my satisfaction:
    5. Patient Signature or Thumbprint
    6. Name of patient
    7. Witness Signature
    8. Name of witness
    9. Person Obtaining Consent Signature
    10. Name of person obtaining consent

19. Surgical Site Verification Form

SOP for Surgical Site Verification Form

Purpose: To describe the standard operating procedure for Surgical Site Verification Form.

Introduction: This form is to be completed prior to surgery. The study team should fill out the form with the Integrated Eye Care Worker (IECW) in the presence of the patient.

Materials required:

CRF and other Forms	
Surgical Site Verification Form *[See Annex A]*	To document the verification of the surgical site

Responsible: Study nurse and Integrated Eye Care Worker

Procedure:

A. The patient ID label is affixed at the top of the Serious Adverse Event Initial Reporting Form.
B. The study nurse or the Integrated Eye Care Worker will record the following information on the form.
    1. The study participant has Trachomatous trichiasis (TT); in turned eyelashes or sign of epilation on:
    2. Surgery is planned on:
    3. Type of TT surgery:
    4. Surgical consent has already been administered, and patient is aware which eye is going to be operated on:
    5. Eyelid with TT is clearly labeled with tape and marker on the forehead.
    6. Name & certification number of study team member completing form:
    7. Name & certification number of IECW:
    8. Date form completed:

20. Treatment Adherence Form

SOP for Treatment Adherence Form

Purpose: To describe the standard operating procedure for completing the *Treatment Adherence Form*.

Introduction: This form is to be completed by the study nurse at the Week 4 Follow-up Visit by questioning the subjects about their use of the study eye drops.

Materials required:

CRF and other Forms	
1. Treatment Adherence Form	To document subject's report of study eye drop's use
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the study ID & alpha code
Smart phone	For REDCap entry

Procedure:

A. The patient ID label is affixed at the top of the Baseline Information Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions.

C. The Study nurse will collect and record the following information.
   1. Visit Date:
   2. "Did you use the study eye drops in your right eye?"
      2A. "On average, how often did you use the study eye drops in your right eye in the last 4 weeks?"
      2B. "How would you rate your compliance using the study drops in your right eye in the last 4 weeks?"
   3. "Did you use the study eye drops in your left eye?"
      3A. "On average, how often did you use the study eye drops in your left eye in the last 4 weeks?"
      3B. "How would you rate your compliance using the study drops in your right eye in the last 4 weeks?"
   4. "Who administered the eye drops for you most of time?"
   5. "Did you experience any problems from the study eye drops?"
   6. "When was the last day (not including today) that you used the study eyedrops?"
   7. "How many eye drops did you use that day in each eye?"
   8. Did the patient return the study medication bottle?
      8a. Weight of returned study medication bottle:
      [Refer to medication bottle weighing instructions: see *Annex E*]
   9. Can the number of drops used be determined from the study medication diary?
      9A. Count the number of times the eye drops were used in each eye (morning and night) and enter totals below:
   10. Name & certification number of person completing form
       1. Print Name:
       2. Certification #:
   11. Date form completed:

21. Visual Function Questionnaire

SOP for Visual Function Questionnaire

Purpose:
To describe the standard operating procedure for completing the *Visual Function Questionnaire.*

Introduction:
One of the study aims is to assess the efficacy of the interventional treatment. To be precise, it is, "….to assess the efficacy of fluorometholone 0.1% one drop twice daily for four weeks in reducing the incidence of post-operative TT when given as adjunctive therapy with TT surgery in the programmatic setting."

Another aim is to try and characterize the value of adding such treatment to TT surgery under a range of plausible health economics circumstances.
Patient-reported outcomes /patients' perspectives/ are one of the key aspects of the design and rationale of the trial that have major bearing on the approaches to data analysis, statistical issues and data monitoring.
To that end, this form is employed as one of the tools adopted by FLAME to gather pertinent data.

Materials required:

CRF and other Forms	
Visual Function Questionnaire form	To record patient reported outcomes
Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse or study data recorder
Procedure:

A. The patient ID label is affixed at the top of the Visual Function Questionnaire Form.

B. Please refer to the sections of the *SOP for CRF Completion and Correction* for relevant form filling out instructions.

C. For questions one to twenty, circle the number that represents the correct response.

   For questions twenty and twenty one, please mark X next to the relevant study participant's response to indicate *YES* or *NO*.

D. The study nurse or study data recorder will collect and record the following information.

   "The first two questions are about your overall eyesight. I will read out a choice of five answers and you will choose the one that describes you best."

   1. Overall, how would you rate your eyesight using both eyes – with glasses or contact lenses if you wear them?
   2. How much pain or discomfort do you have in your eyes (e.g. burning, itching, and aching)?

   "In the next section, I am going to ask you how much difficulty, if any, you have doing certain activities. I will read out choice of five answers and you will choose the one that describes you best."

   3. Because of your eyesight, how much difficulty do you have in going down steps/stairs/ steep slopes?
   4. How much difficulty do you have in noticing obstacles while you are walking alone (e.g. animals or vehicles)?
   5. How much difficulty do you have in seeing because of glare from bright lights

6. Because of your eyesight, how much difficulty do you have in searching for something on a crowded shelf?
7. How much difficulty do you have in seeing differences in colours?
8. Because of your eyesight, how much difficulty do you have in recognizing the face of a person standing near you?
9. How much difficulty do you have in seeing the level in a container when pouring?
10. Because of your eyesight, how much difficulty do you have in going to activities outside of the house on your own (e.g. sporting events, shopping, religious events)?
11. Because of your eyesight, how much difficulty do you have in recognizing people you know from a distance of 20 metres? (e.g. from that building/tree – give marker of 20 meters)
12. How much difficulty do you have in seeing close objects (e.g. making out differences in coins or notes, reading newsprint)?
13. How much difficulty do you have in seeing irregularities in the path when walking (e.g. potholes)?
14. How much difficulty do you have in seeing after a few moments when coming inside after being in bright sunlight?
15. How much difficulty do you have in doing activities that require you to see well close up (e.g. sewing – not including threading the needle, using hand tools)?
16. Because of your eyesight, how much difficulty do you have in carrying out your usual work?

"In the next section, I am going to ask you how you feel because of your vision problem. I will read out a choice of five answers and you will choose the one that describes you best."

17. Because of your eyesight, how often have you been hesitant to participate in social functions?
18. Because of your eyesight, how often have you found that you are ashamed or embarrassed?
19. Because of your eyesight, how often have you felt that you are a burden on others?
20. Because of your eyesight, how often do you worry that you may lose your remaining eyesight?
21. Does your vision problem affect your life in ways we have not mentioned?
22. Are there things you are unable to do because of your eye problem?
23. Name & certification number of study team member completing form
24. Date form completed

22. Week 4 Eye Examination Form

SOP for Week 4 Eye Examination Form

Purpose:

To describe the standard operating procedure for completing the Week 4 Eye Examination Form.

Introduction: Study participants undergo detailed ophthalmic examination during the week 4 follow up visit. This form is used to capture the observations.

Materials required:

CRF and other Forms	
1. Week 4 Eye Examination Form	To record observations
2. Referral form	As needed to refer patients for care
Other Materials	
Labels	To indicate the designated study ID & alpha code
Android phone	For REDCap entry

Responsible: Study nurse

Procedure:

- The patient ID label is affixed at the top of the Serious Adverse Event Initial Reporting Form.
- Provide the required answers to the listed questions as appropriate. For relevant form filling out instructions, please refer to the sections of the *SOP for CRF Completion and Correction*.
- The Study nurse will collect and record the following information on the form.
  1. Date of examination
  2. Visual Acuity
     Refer to instructions for Visual Acuity measurements. *[See Annex C]*
  3. Intraocular Pressure (IOP) Measurements
     Refer to instructions for IOP measurements. *[See Annex C]*
  4. Ocular Surface Discharge
     For questions below please refer to the SOP of the ophthalmic examination as applicable. *[See Annex C]*
  5. Assessment of Trichiasis
  6. Trichiasis Grading
  7. Evidence/extent of epilation
  8. Entropion
  9. Is there any Eyelid Contour Abnormality
  10. Corneal Opacity/Scar Grading
  11. Conjunctivalization of the Lid Margin Grade
  12. Are any of the following present?
  13. If vision in either eye is worse than logMAR 0.48, please indicate the most likely cause.
  14. Were all exams/questions completed for both eyes?
  15. Were ocular photographs taken?
  16. Name & certification number of person performing examination:
      i. Print Name

ii. Certification #