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

Version 1.4

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STUDY FLOW CHART (TABLE 1):

Table 1: 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 26-35	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)					

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 one year -Number and location of lashes touching the globe within ≤1yr -Entropion (presence and extent) within ≤1yr
Safety/adverse outcomes:	-Corneal opacity (Δ proportion 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

Additional variables:	-cosmetic outcome over 1 year postoperatively -health utility over 1 year postoperatively -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 Ethiopia Food and Drug Administration (EFDA; formerly 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.

PROTOCOL ADHERENCE AND REGULATORY COMPLIANCE STATEMENT

This study will be conducted in accordance with the protocol and all applicable regulatory requirements. The protocol will be registered on www.clinicaltrials.gov before initiating enrollment.

1 INTRODUCTION

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. Approximately 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]

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. In a comprehensive review summarizing reports through 2012, the median for the currently WHO-recommended procedures (bilamellar tarsal rotation and posterior lamellar tarsal rotation) appears to be in the 20-30% range, with programmatic results tending 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).[5] Reports based on selection and intensive training of TT surgeons would not be expected to be representative of typical programmatic conditions. Post-operative TT is a difficult problem, with worse outcomes of surgical repair than primary TT.[6] According to WHO, repeat TT surgery should be performed by an ophthalmologist, 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, ongoing pain, and limited management options—and the impact on community observations of such cases in reducing interest in sight-saving TT surgery, prevention of postoperative TT is of paramount importance.

Reported risk factors for postoperative TT include surgeon skill, severity of preoperative disease, patient age, and ongoing inflammation during the perioperative period.[5,7-10] Optimization of surgical quality is acknowledged as critical for obtaining good results of surgery, and a subject of considerable programmatic effort, but such efforts do not completely eliminate recurrence.

Ongoing inflammation in the setting of trachoma is associated with progressive conjunctival scarring,[11] and often is seen in persons with trachomatous trichiasis.[9,12-18] Such inflammation is only rarely associated with Chlamydia trachomatis infection,[13,19] and the specific causes thereof are incompletely understood. In the 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 by which benefit may have occurred.[8]

2 BACKGROUND

2.1 RATIONALE FOR FLUOROMETHOLONE 0.1% AS ANCILLARY 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. As discussed above, inflammation—whether induced by the trachoma disease process or surgery itself—most likely contributes to progressive cicatrization leading to failure of lid rotation surgery in a clinically important proportion of TT cases. 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,[20] with correspondingly smaller IOP-raising effect, but still has favorable effects on conjunctival inflammation[21,22] such as episcleritis, and therefore is likely to suppress the perioperative inflammation 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 in some settings (https://www.medindia.net/drug-price/fluorometholone/flomex-0-1percentw-v.htm , accessed on 3-September-2018). 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. Thus, we hypothesize that fluorometholone will be safe enough for widespread perioperative programmatic use.

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. 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) and an approximate 30% lower risk of TT recurrence in each of the active treatment groups than in the placebo group or in contraleral eyes (which received neither active treatment nor placebo). All three active treatment groups had similar efficacy results, with the twice daily having the lowest TT recurrence rate by a slight margin at one year as well as the best safety profile in the preliminary study and based on theoretical considerations. As per the phase 2-like safety-oriented design, the differences were not statistically significant (p=0.10 for the aggregated

active treatments vs. placebo plus contralateral eyes). However, the incidence of repeat surgery was significantly reduced in the placebo group compared with the aggregated active treatment groups (18% vs. 5.7%, p=0.018).

Following up on these favorable results, we aim to conduct a full-scale double-masked clinical trial comparing one drop of flurometholone 0.1% given twice daily vs. placebo twice daily in order to definitively confirm (or refute) efficacy and safety, in order to evaluate whether this intervention should be recommended as part of the TT element of global trachoma blindness alleviation programs.

2.2 SELECTION OF DOSE

Selection of doses for the proposed efficacy study with fluorometholone 0.1% is based on:

- The observation that fluorometholone 0.1% typically is effective for the treatment of episcleritis,[23] which represents inflammation at a roughly similar level of the ocular surface. In our preliminary study, doses of two and four drops daily had similar recurrence outcomes at 12 months.
- While side effects were few in all groups, no intraocular pressure elevation was observed in the twice daily dose group whereas efficacy results were similar. Theoretically, a lower dose of topical corticosteroids should have less risk, as well as potentially less cost and is a regimen that is more easy for patients to adhere to.
- While postoperative management with topical corticosteroids often involves gradual reduction of the dosage ("tapering"), a constantly changing dose may be difficult for poorly educated patients to follow at a programmatic level. Therefore, we decided to study a single fixed dose for a fixed duration of time instead of attempting a complicated "tapering" schedule.

For these reasons, and bearing in mind logistical constraints that not every possible dose can be studied, we selected one drop two times daily as the active treatment for this trial. We intend to use artificial tears as the placebo comparator at the same frequency. It was possible to double mask these treatments in the preliminary trial.

2.3 STUDY RATIONALE

This study is designed to assess the effectiveness and safety, when added to an extant trachoma control program, of:

- Fluorometholone 0.1% one drop two times daily for four weeks

for the treatment of eyes of patients with trachomatous trichiasis undergoing lid rotation surgery. The goals are to determine whether fluorometholone 0.1% improves the outcome of TT surgery, whether it is safe, and whether it is cost-effective. These goals fit within the overarching agenda of developing an improved approach to alleviating blinding trachoma by improving outcomes of trichiasis surgery suitable for widespread programmatic use for the surgical piece of the "SAFE" strategy of trachoma mitigation endorsed by the World Health Organization and the Ethiopian Federal Ministry of Health.

As demonstrated by the 2012-2015 Global Trachoma Mapping Project, Ethiopia is the country most severely affected by TT in the world. Ethiopia also has been the site of at least five completed randomized clinical trials of 1000 or more subjects which assessed alternative approaches to TT surgery, each of which have been successfully completed with outstanding follow-up (>93%).[8,14,18,24,25] Each of these was carried out in part by members of the current study team, four with the current study's Vice-Chair as principal investigator.

A positive result potentially would benefit trachoma programs worldwide. A negative result would provide guidance that ancillary corticosteroid therapy is unlikely to be beneficial.

While presently there are great efforts underway to reduce the burden of trachomatous trichiasis, and good progress is being seen, residual trachoma in remote areas and ongoing incidence of TT from pre-existing trachomatous disease can be expected to generate ongoing need for large-scale TT surgery for many years to come.

3 STUDY SPECIFIC AIMS

- 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 assess whether such treatment is sufficiently safe for wide-scale implementation in TT programs.
- To estimate the costs of adding fluorometholone 0.1% treatment to TT surgery per case of postoperative TT averted, and to characterize the value of such treatment under a range of plausible health economic circumstances

4 STUDY DESIGN

This is a 1:1 randomized, double-masked, placebo controlled clinical trial in which a total of up to 2,500 subjects will be enrolled within locations in the Oromia Region of Ethiopia (Jimma and East Wollega zones) wherein the SAFE strategy for trachoma blindness mitigation is being implemented (including the conduct of lid rotation surgery for a large volume of patients) by the Fred Hollows Foundation in cooperation with the Ethiopian Federal Ministry of Health/Oromia Regional Health Bureau. The Oromia Region surrounds Addis Ababa, the national capital, and is the most populous region of Ethiopia, with a 2017 population estimated by the Central Statistical Agency of Ethiopia of 32,815,995 (reported on Wikipedia based on data retried on 4-June-2018). Based on Global Trachoma Mapping Project data, the prevalence of TT requiring surgery was approximately 0.82% in the 15+ year-old population,[26] translating to approximately 0.41% in the whole population. The Fred Hollows Foundation Program conducts surgery with the integrated eye care workers who perform TT surgery as part of the permanent public health system, as well as with dedicated mobile teams intended to clear the backlog of TT quickly. Given that mobile teams will not be widely used in the future, this study will assess surgery conducted by integrated eye care workers participating in the FHF program at the time of the study, so that results will be more generalizable to future programs. Patients with trachomatous trichiasis identified by the study's Surgical Team (within the FHF program), and undergoing

upper lid rotation surgery conducted by a participating surgeon who potentially are interested in participating in the study will undergo Screening Procedures to determine eligibility. Those who are eligible will be invited to participate in the study and will provide informed consent if they agree. Because the goal of the study is to assess the impact of adding fluorometholone treatment to the existing programmatic system, the study will not seek to alter the practices of the participating surgeons or of the program. In the Fred Hollows Foundation Program in this region, surgeons primarily perform posterior lamellar ("Trabut"), which was found superior to Bilamellar Tarsal Rotation surgery in a randomized trial reported during the conduct of our preliminary trial,[24] which led to the WHO endorsing it as an approved procedure for TT surgery as part of the SAFE program. However, the WHO still recommends Bilamellar Tarsal Rotation for surgeons who are more familiar with that procedure, and the minority of participating surgeons preferring Bilamellar Tarsal Rotation will be permitted to use that procedure. Dissolvable sutures are used exclusively. The Fred Hollows Foundation is committed to carrying forward TT surgery programs for longer than the proposed duration of the proposed trial.

After obtaining informed consent, baseline procedures will be conducted, including conduct of a medical/ophthalmic history, review of current medications, review of ocular symptoms, visual acuity measurement, assessment of clinical signs of trachoma using +2.5 diopter loupes (including trichiasis/entropion grading), and intraocular pressure measurement. These procedures should be performed no more than 7 days before randomization/initiation of treatment, and can (and typically will) be performed on the same day.

This study will evaluate both treatment arms concurrently, with subjects randomized between the active fluorometholone 0.1% or placebo treatment throughout the study.

Eligible subjects will be enrolled in the study. These subjects will be randomized 1:1 to: 1) fluorometholone 0.1% one drop two times daily for four weeks; 2) Placebo (artificial tears) one drop two times daily for four weeks. If both eyes are undergoing upper lid rotation surgery, both eyes will be treated using the same treatment, so as to avoid accidental crossovers of eyes of the same patient by using the wrong bottles.

Data on efficacy will be evaluated based on the proportion developing postoperative TT defined as one or more of the following in an eye previously operated for TT:

-one or more lashes touching the globe; *and/or*
-history of repeat TT surgery; *and/or*
-evidence of epilation on clinical examination

An important secondary analysis will be based on the proportion for whom reoperation (as opposed to epilation of minimal trichiasis) is performed or recommended but refused for recurrent TT, based on the judgment of the masked study team member trained to assess postoperative TT. Additional outcomes studied are listed in Section 11 below.

Subjects will be scheduled for follow-up evaluation approximately four weeks (primarily to assess adherence to therapy and side effect incidence; and six and 12 months (corresponding to the follow-up interval used in prior TT trials; 4-6 months after surgery also is the time point

recommended by the Ethiopian Federal Ministry of Health for TT surgery outcome audits[27]). A special effort will be made to make the four-week visit as close to 28 days as possible to assess potential IOP elevation and to weigh bottles for compliance assessment. Upon completing the one year follow-up visit, subjects will exit the study.

5 STUDY POPULATION

5.1 LOCATION OF THE STUDY

Areas of the Oromia Region determined by the Global Trachoma Mapping Program to have high levels of TT and which have not yet been programmatically addressed with high volume TT surgery programmatic outreaches have been identified in the Jimma and East Wollega zones, which will be the site of the study.

5.2 SCREENING POPULATION

Surgical Team members (mobilizers) will implement publicity and key informant strategies in these areas, to identify likely candidates for TT surgery. Those who are interested enough to travel to the location where a participating integrated eye care worker/TT surgery is operating will be transported at study expense to (and from) the site and evaluated regarding whether TT surgery is indicated for them. Those selected for TT surgery will make up the population to be screened for eligibility in the study (the Screening pool for the CONSORT Diagram). Research subjects will be recruited by the Field Coordinating Center Team (see Study Organization, Section 20), from among this group.

5.3 STUDY POPULATION

To be enrolled in this study, subjects must meet all inclusion criteria and none of the exclusion criteria for at least one eye. If only one eye meets eligibility criteria, only that eye will be studied, and the other eye will receive routine management. (Patients who need TT surgery but are ineligible for the study or unwilling to enroll will be operated under the auspices of the parent TT surgery program as per programmatic routine).

5.4 ELIGIBILITY CRITERIA

Subjects will be eligible for the study if they have been selected to have TT surgery by the Surgical Team, all of the Inclusion Criteria are met and none of the Exclusion Criteria are met.

5.4.1 Inclusion Criteria:

1. Age 15 years or more, corresponding to the age of patients treated in the Fred Hollows Foundation/Federal Ministry of Health Program at field sites without general anesthesia.

2. One or both eyes with upper lid trachomatous trichiasis (TT)—with one or more eyelashes touching the eye or evidence of epilation—for whom a decision already has been made to undergo TT surgery on at least one upper eyelid.

3. Collection of all baseline data prior to randomization

4. Signed, informed consent (and assent, when applicable)

5.4.2 Exclusion Criteria:

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

2. Subjects known to be pregnant

3. IOP≥22 mmHg and/or currently taking ocular anti-hypertensive medications in the study eye (prior IOP-lowering surgery is acceptable)

4. A known 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 of a degree to which where an intraocular pressure spike would be vision-threatening).

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

6. Any significant illness or condition (e.g., hypertension with systolic blood pressure≥170 mmHg and/or diastolic blood pressure≥110 mmHg) that could, in the study team's opinion, be expected to interfere with the study parameters or study conduct; or put the subject at significant risk.

7. Previous upper lid TT surgery on all eyes with upper lid TT. (If one eye has previously undergone upper lid TT surgery but another eye with upper lid TT has not, the patient may be enrolled, and only the latter eye will be counted for the primary analyses).

Note: Safety considerations regarding fitness for surgery will be addressed by the Surgical Team in its selection of persons for surgery, prior to a person entering the Screening Population pool of persons.

6 STUDY MEDICATION/TREATMENTS

1) Fluorometholone 0.1% one drop two times daily for four weeks;

2) Placebo (artificial tears) one drop two times daily for four weeks;

The study test articles will be prepared by the Penn Investigational Drug Service in Philadelphia, repackaging active treatment or placebo into identical bottles. Fluorometholone 0.1% suspension will be donated by Allergan (FML® Ophthalmic Suspension, USP 0.1%). Artificial tears will be purchased. Shelf-life of the repackaged drug will be assessed by testing a sample of bottles at six and 12 months after preparation, and is anticipated to be at least six months based on the preliminary study, in which six month shelf life was documented and 12 months' shelf life was not assessed. The packaging will contain a drug box code corresponding to the masked contents of the bottle, on a peel-off label. Each box code corresponding to treatment group will be unique to prevent unmasking of a large segment of the study population should unmasking be required. (No unmasking was required in the preliminary trial of 154 subjects).

Upon obtaining official approval of a trial by EFDA, permit for importation of study drugs will be obtained from the Authority. Study test articles will be shipped by air to a recipient investigational pharmacy in Ethiopia. The pharmacist will store the study drug at temperatures recommended by the manufacturer and distributed in batches to the Field Coordinating Center's field teams, which will distribute the assigned study drug to patients. One team member on each field team will be assigned to dispense the study drug, at which time the label will be peeled off and stuck on a log with the study number, so that drug dispensing accountability can be audited, but the patient and other members of the study team will not know even the letter corresponding to the treatment assignment, as a strategy to avoid unmasking. The first dose will be given prior to TT surgery (see also Section 7).

To minimize complexity in a population which will not be well educated and for a large scale undertaking, all eyes of the same patient undergoing TT surgery will receive the same randomized treatment: a fixed dose of two drops per day for a duration of four weeks. This approach will avoid potential crossovers between eyes that might occur if different treatment bottles were prescribed for different eyes.

Adherence to the study treatment will be assessed at the four week visit by questioning patients and by weighing bottles at the time of dispensing and at the four week visit. Subjects will be told that bottles will be weighed in order to encourage adherence.

7 STUDY METHODS AND PROCEDURES

7.1 APPROVALS PRIOR TO STUDY INITIATION

Before recruiting any subjects into the study, written approval of the protocol and of the informed consent form must be obtained from all governing Institutional Review Boards (IRB). These will include the IRB of the Study Chair's institution (currently Massachusetts Eye and Ear Infirmary), the Vice-Chair's institution (currently London School of Hygiene and Tropical Medicine), and the Data Center Director's institution (which delegates IRB approval to Massachusetts Eye and Ear Infirmary as per the National Institutes of Health "single IRB" policy). In addition, Ethiopian authorities are required by law to approve clinical trials—these include the National Research Ethics Review Committee of the Ministry of Science and Technology and the Ethiopia Food and Drug Administration, in addition to the Regional Health

Authority (for the Oromia Region in this case) or their successors if the names change. In the preliminary study, the Ethiopian agency approvals were obtained in approximately two months.

Because fluorometholone 0.1% is approved for ocular inflammation treatment by the US FDA, the European Medicines Agency, and Ethiopia's EFDA, US and EU investigational new drug exemptions will not be required. EFDA regulates all medication trials as if the drug were investigational; EFDA regulations will be followed.

The study also will be registered on www.clinicaltrials.gov prior to initiation of enrollment.

Finally, the study will not be launched until the study's Data and Safety Monitoring Committee (see below) has approved the protocol.

7.2 SUBJECT SCREENING

Study information will be provided to all individuals in the Screening Pool (see Section 5.2) and each person will be asked if they are interested in the study. For those who provide informed consent, eligibility screening will be conducted. Subjects who are not eligible will be informed that they are ineligible and will not be followed and will not be traceable after this stage.

7.3 SCREEN FAILURE

Study centers will document all screen failures on a Subject Screening Log with the reason for the failure to be enrolled. (This information is necessary for the ultimate reporting of the trial, as the information is required for the CONSORT diagram.[28]) For screen failure patients, no information other than failure of screening and the reason for failure will be entered (which in some cases would include unwillingness to consent to study participation as the reason for screen failure). Screen failure status and reason for failure will be entered along with the identification number on a Subject Screening Log.

7.4 SUBJECT ENROLLMENT AND RANDOMIZATION

Willing subjects who have provided informed consent to participate in the study will be issued a FLAME identification number (FID). As mentioned in 7.2, those who are eligible will be randomized. Randomized patients either (in most cases) immediately will undergo the Visit 2 procedures (which includes trichiasis surgery), or will be scheduled to return to the center for Visit 2 within seven days. Thus, Visit 1 (the screening/baseline visit) and Visit 2 (surgery visit) can occur on the same day if desired, which in our experience is typically the logistically simpler approach to avoid transporting the subject multiple times.

At the surgical location, the study team will enter the patient's name and date of enrollment on the study-supplied Enrollment Log for study patients of each participating surgeon (given that randomization is stratified simultaneously by surgeon and geographical area). A pre-selected Treatment Identification (RxID) number is associated with the FID on each line on the Log and this RxID is assigned to each sequential patient. A medication box will be assigned to each enrolled patient, and the medication box RxID label will be put on the enrollment form. At this point the patient will have a Screening Number (SN) (one of each of these is given to each subject screened) and FLAME Identification number (FID) and Treatment Identification Number

(RxID) associated with a Medication box number (one of each of these is given to each subject enrolled, more than one if the first Medication box is somehow inadequate). Identifying details other that the Medication box number FID, and RxiD will be kept only by the Field Team associated with each treating center, and will not be entered into the central study database. Subjects will be counted as enrolled in the study, and part of safety and efficacy analyses, from the moment the patient's name is entered in the Enrollment Log. Medication box number(s) will be used to link to the actual treatment assignment for the statistical analysis of efficacy and safety data.

After treatment assignment, the study Field Team then will proceed to implement the treatment protocol for Day 0, treating the study eye(s) with an eye drop from the pre-prepared treatment kit (which is pre-prepared according to the randomization schedule with the appropriate study medication). The treatment kit will contain a bottle with sufficient fluorometholone 0.1% or placebo for all eyes for four weeks' treatment, from which the medication box numbers will be peeled off at the time of dispensing to the subject. The subject will be carefully instructed how to apply eye drops, how often to apply them, and for how long (using the Ethiopian calendar) and practice using the eyedrops from the assigned medication bottle. Subjects will receive their first randomized eye drop treatment just prior to surgery, will undergo TT surgery, and then will resume their study treatment upon removal of any bandages.

Shelf life of the medication kit (anticipated to be at least six months based on the preliminary study) will be determined in advance by the investigational pharmacy; expired kits will be replaced. The medication kit key mapping medication box numbers to bottle contents (fluorometholone or placebo) will be kept both at the Data Center in Philadelphia, USA and the Field Coordinating Center in Addis Ababa, Ethiopia in a private, secure location, and also will be made available to the study pharmacy team preparing the kits.

Prior to initiating the study, the Data Center Director will prepare a computer-generated randomization schedule assigning study treatments in a 1:1 ratio for each participating surgeon (to accommodate stratification by surgeon/geographical area). Randomization will be carried out within varying block sizes of between 2 or 4, varying the sizes to prevent team members from predicting the treatment assignment, but keeping them small to avoid imbalance on the stratification variables should participating surgeons perform only small numbers of surgeries. Boxes of 20 treatment kits will be prepared; block sizes will be varied in such a way that every 20 bottles will have 10 fluorometholone and 10 placebo bottles, and each surgeon will work through one box at a time, and new treatment kits will be used by other surgeons in other geographical areas. Stratification will ensure that an approximately equal number of patients in each treatment group will be operated by each participating surgeon in each geographical area. Blocking will ensure that the treatment assignments are balanced within each surgeon and over time across each geographical area. Balance of treatment groups on other relevant factors will be assessed at the time of analysis, and statistical methods will be used to adjust for them when indicated (see Section 11).

7.5 MASKING

Certified masking will be implemented by an investigational pharmacy as described in Section 6, which will obtain 0.1% fluorometholone eye drops from the corporate donor, prepare a matching

placebo using purchased artificial tears, transfer both into matching sterile dropper bottles, and add masked peel off labeling. Through this approach, both the patient and the study field team will be kept unaware of what treatment the patient is receiving. The Study Officers will make provision for a procedure for emergency unmasking of an individual patient should such be required for clinical care. Use of several different letter codes for active and placebo treatment will facilitate operations, in case a treatment kit needs to be replaced by a backup kit if some problem is detected, while use of these medication box numbers supplemented by peel-off labels (to be attached to a study dispensing log) will minimize the risk of unmasking of large segment of the study population should a study participant or staff member discover whether a particular letter corresponds to active or placebo treatment or should unmasking be required for safety reasons.

7.6 STUDY ASSESSMENTS

Subjects will be scheduled to return for follow-up at four weeks (day 26-35), 6 months (+/- 60 days), and one year (+/- 90 days) after enrollment/trichiasis surgery. After completing the one year visit, subjects will exit the study.

Visit 1 (Day -7 to 0): Screening/Baseline

Subjects who fulfill all the inclusion and none of the exclusion criteria will be accepted for participation in the study, and written informed consent will be obtained before randomization to treatment. 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 will be detailed in the Subject Informed Consent Form. A witness who is not a member of the study team also will sign if the patient is unable to read. Documentation of the subject's fulfillment of the entry criteria for all subjects is to be completed by the study team on the Eligibility Form prior to enrollment in the study.

Baseline evaluation will be performed within 7 days before trichiasis surgery/initiation of treatment, typically on the same day as surgery at the surgical location where the participating TT surgeon (an integrated eye care worker based at a Ethiopia Federal Ministry of Health health center). Baseline procedures will include:

- Collection of demographic and other patient level data including age and sex
- Detailed medical and ophthalmic history
- Assessment of the presenting visual acuity and penlight eye examination
- Grading of clinical signs of trachoma (including trichiasis) by masked, study-certified team members, by comparison with standard photos.
- Intraocular pressure measurement using a study-supplied portable electronic tonometer (the median of three measurements in each study eye)
- Review of medications subject currently is taking
- (Randomized) treatment assignment

Visit 2 (Day 0): Trichiasis surgery and initiation of treatment

Subjects will undergo trichiasis surgery by a participating TT surgeon performing the procedure typically used by that surgeon in the programmatic context (either posterior lamellar tarsal

rotation ("Trabut") surgery or bilamellar tarsal rotation surgery). In addition, they will be given a study medication box, and instructed on its proper use by a study staff member, including administration of the first drop under the study team's supervision prior to the surgery.

The following data will be collected at this visit:

- Surgical details, in order to obtain any data about variances in surgical technique (for assessment as to their possible relationship to relapse of trichiasis or adverse events)
- Medication review
- Adverse event review (for the brief period since randomization; see Section 10)

Visit 3 (Day 26-35 days): Study Procedures/Assessments at Postoperative Follow-up Visits.

Upon reporting to the study location, subjects will undergo the following procedures:

- Medication review
- Adverse event review (see Section 10)
- Assessment of adherence to therapy by questioning subjects and weighing study treatment bottle
- Assessment of the presenting visual acuity and penlight eye examination
- Ophthalmic examination:
    - Trichiasis assessment (no eyelid eversion during the early postoperative period)
    - Measurement of intraocular pressure

Note: the Field Team will aim to make the visit as close to 28 days as possible to properly assess bottle weight and during the period where subjects will be able to recall their adherence to therapy as well as possible. Should protocol violations occur where bottles are weighed before 28 days, the weight will be adjusted according to the number of days of therapy remaining.

Visits 4 (Day 180 +/- 60 days) and 5 (Day 365 +/- 90 days): Study Procedures/Assessments at Follow-up Visits After Completion of All Study Treatment:

Upon reporting to the study facility, subjects will undergo the following procedures:

- Detailed medical and ophthalmic history
- Adverse event review (see Section 10)
- Assessment of the presenting visual acuity and penlight eye examination
- Intraocular pressure measurement using a study-supplied portable electronic tonometer (the median of three measurements in each study eye)
- Grading of clinical signs of trachoma (including trichiasis) by masked, study-certified team members, by comparison with standard photos
- Review of medications subject currently is taking

After completion of Visit 5, subjects will exit the study, and resume usual medical care.

7.7 CONCOMITANT THERAPY

For ethical reasons, patients will not be restricted from taking medications that are indicated for their health. Rather, the eligibility criteria are designed to prevent medications that potentially

could distort study results from being widely used in the study. However, use of systemic and topical medications will be tracked during the study on study forms at each visit.

7.8 COMPLETED SUBJECTS

A completed subject is one who completed the last (Visit 5) follow-up visit. After Visit 5 procedures, subjects will exit the study.

8 WITHDRAWAL FROM STUDY

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. The following are the criteria for considering withdrawal from this study:

- Withdrawal of subject consent; or
- Intercurrent illness including death that prevents continuation of regular follow-up visits.
- Administrative withdrawal (see Safety Monitoring below).

All subjects will be followed through their final visit unless withdrawn from the study. The Field Coordinating Center will be informed of any subjects who have withdrawn consent or have been administratively withdrawn from the study, to instruct the field teams not to attempt to collect further data from those subjects.

The Study Officers, treating clinicians, and governing IRB(s) also have the right to withdraw subjects from the study for the following reasons: when study continuation may jeopardize the health of the subject, protocol violations, AEs or concurrent conditions posing a threat to subjects, administrative or other reasons. As a general principle, absent compelling other circumstances (like patient refusal), follow-up should be continued through one year unless the study is being terminated or continued follow-up would pose a threat to the participant.

Subjects who withdraw from the study following randomization for any reason will not be replaced. Subjects who wish to voluntarily withdraw from the study will be asked to complete at least the final study visit's assessments (where the primary outcome is assessed). Subjects who have treatment discontinued because of suspected adverse outcomes of treatment will be followed through resolution, stabilization, or until the next study visit after treatment, whichever comes first. Serious Adverse Events (SAEs; see below) will be followed until resolution or stabilization. An ophthalmologist study Safety Officer will oversee adverse event reports and make recommendations to the study leadership as to whether adverse events require actions in response, as well as being responsible for meeting urgent reporting obligations.

9 OUTCOME ASSESSMENTS

9.1 EFFICACY ASSESSMENTS

Efficacy assessments will be made by masked, trained and study-certified Field Team personnel (employed by the Field Coordinating Center), using +2.50 diopter magnifying loupes.

9.1.1 Trichiasis/Entropion Grading

9.1.1.1 Trichiasis

Assess eyelash position with eye in primary position (looking straight ahead)

- Number of lashes whose point touches globe medial to cornea
- Number of lashes whose point touches globe lateral to cornea
- Number of lashes whose point touches cornea
- Evidence of epilation-broken/regrowing lashes or sections of eyelid denuded of lashes

Then determine grade of trichiasis:

Trichiasis Grade	**Definition**
T 0	No trichiasis
T 1	Lashes deviated towards the eye, but not touching the globe
T 2	Lashes touching the globe but not rubbing the cornea
T 3	Lashes constantly rubbing the cornea

Primary Outcome: Recurrent TT: Post-operative trichiasis is defined as:
-one or more lashes touching the globe in an eye operated for TT); and/or
-history of repeat TT surgery prior to the study visit; *and/or*
-evidence of epilation on clinical examination (see Section 9.1.2.1)

Whether there was lash-touch at the end of TT surgery (primary failed TT surgery) also will be assessed at Visit 2 (the surgical visit).

9.1.1.2 Entropion

a) 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.

If there is a mixed presentation, classify as the worse grade.

	Area of entropion

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

None='Normal' lid margin visible; Without corneal-lash base contact: Definite inwards rotation of the lid margin, without any lash bases touching the cornea; With corneal-lash base contact: Inward rotation of lid margin, with some or all of the lash bases touch the cornea.

b) Cases with corneal touch also will be evaluated as: mild (1-5 lashes touching the cornea), moderate (6-9 lashes touching the cornea) or severe (10 or more lashes touching the cornea).

9.1.2 Assessing Clinical Signs of Trachoma

9.1.2.1 Assess epilation

9.1.2.1.1 Assess and document if there is clinical evidence of epilation

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

9.1.2.1.3 Assess and document the amount of epilation

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

9.1.2.2 Assess the eye for presence and type ocular discharge and document:

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

9.1.2.3 Assess the upper tarsal conjunctiva for the following signs (Visits 1,4,5 only)

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 center of the eyelid externally

9.1.2.3.1 Assess the presence of conjunctivalisation of the lid margin. 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.

9.1.2.3.2 Examine upper lid papillary hypertrophy. Determine the grade of severity of papillary hypertrophy using the following definitions

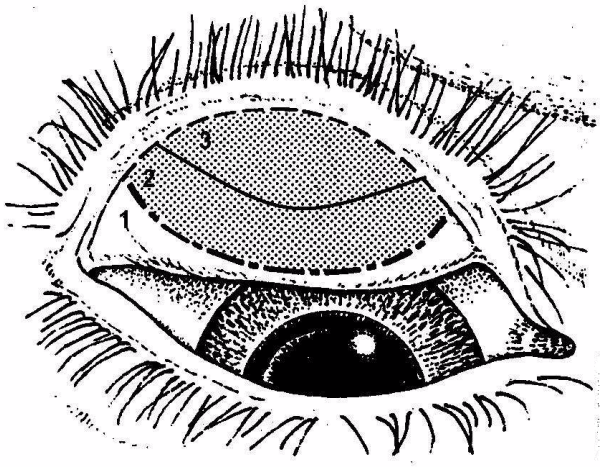
- P 0 Absent: normal appearance
- P1 Minimal: individual vascular tufts (papillae) prominent, but deep subconjunctival vessels on the tarsus are not obscured.
- P2 Moderate: more prominent papillae and normal vessels appear hazy, even when seen by the naked eye.

P3 Pronounced: conjunctiva thickened and opaque, normal vessels on the tarsus are hidden over more than half of the surface.

9.1.2.3.3 Examine the upper eyelid for Follicles. Use the following grading and definition (see Figure 2)

F0 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.

Figure 2: Superior Palpebral Conjunctival Zones



9.1.2.3.4 Assess conjunctival scarring.

9.1.2.3.4.1 Use the following grading and definition if there is no previous lid surgery

C0 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

9.1.2.3.4.2 Use the following grading if there is previous lid surgery

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

9.1.3 Visual Acuity

Presenting Visual Acuity measurement will be conducted at baseline, the 4 week visit, the month 4-6 visit, and the one year (final) follow-up visit). Because many subjects will be non-literate,

the "Peek" application in outdoor lighting will be used to perform visual acuity testing in a manner that is not dependent on familiarity with symbols or letters commonly used in the English language, and allows translation of results onto a logMAR scale with validity within 0.033 logMAR units.[29]

9.1.4 Patient-Reported Outcomes and Costs

9.1.4.1 Patient-Reported Outcomes

-patient overall satisfaction with surgery at one year: Likert Scale
-cosmetic outcome at one year: Likert Scale
-symptom inventory at baseline, during surgery, at each follow-up visit (pain, foreign body sensation, watering, photophobia, discharge, vision problem, itching): Likert Scale
- Health utility at baseline and follow-up visits: EQ5D 5-level and thermometer versions in the three study languages (Amharic, Afaan Oromoo, and English). Existing English and Amharic versions will be used; for Afaan Oromoo, the EQ5D instrument will be translated and backtranslated, and validated.
-Vision-related quality of life as measured by the World Health Organization/Prevention of Blindness and Disability Visual Functioning Questionnaire (available at: https://apps.who.int/iris/handle/10665/68601, accessed on 31 December 2019) at baseline and follow-up visits. Unless extant translations can be found, this instrument will be translated and backtranslated into Amharic and Ofaan Oromoo, and validated.

9.1.4.2 Costs

The focus of cost data collection is to conduct health economic analyses regarding the costs from the programmatic and patient perspective. Data on costs will be modeled or based on the actual experience of patients as appropriate.
-Fluorometholone 0.1%: Programmatic cost
    -Acquisition cost
    -Importation cost in various country scenarios
    -Duty (when applicable)
    -Storage and distribution
    -Wastage
-Costs of additional medications: medications started by at least 1% of subjects are potentially related to study treatments. Such medications will be discovered by medication review at each visit. The study team will determine whether each such cost would be required as part of the program (programmatic cost; primarily for frequent medications) or would be an occasional cost to patient cost.
-Costs of reoperation. Unit costs will be based on the Surgical Team's actual costs in providing such services throughout the program (not just the cases operated as part of the study). This value will be multiplied by the estimate of the proportion requiring reoperation as per the judgment of masked clinicians. Assumed to be a programmatic cost, though reoperation may not be offered by all programs.
-Costs of epilation. Epilating patients will be queried regarding the costs the experience with epilation.

9.2 ADVERSE OUTCOME ASSESSMENTS

9.2.1 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 the side.

9.2.1.1 If there are more than one corneal scars, grade as for worst/most central scar, based on the diagrammatic representations of corneal scar grade (see Figure 1)

9.2.1.1.1 Definitions for grading

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.

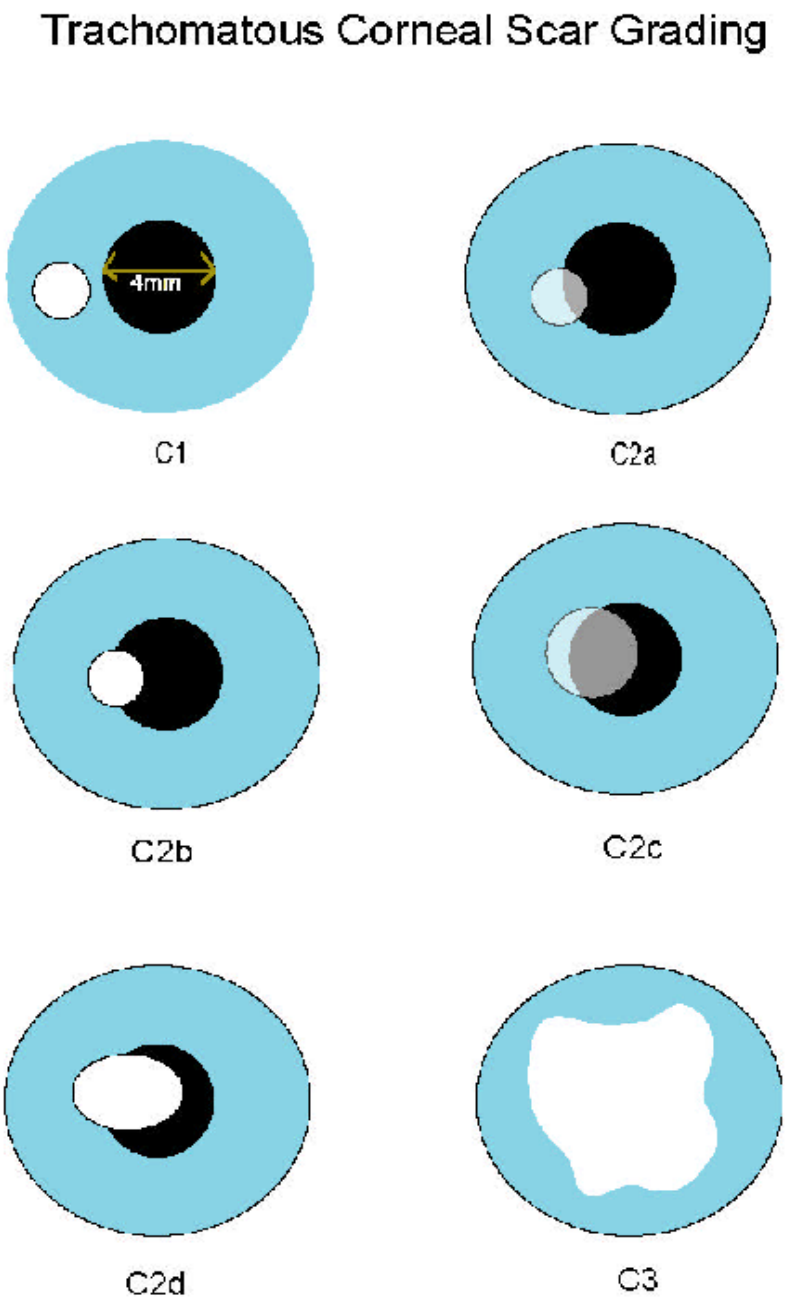
C2c Opacity within central 4mm and entering the central 1mm of the cornea. The pupil margin is visible through the opacity.

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

Figure 1:



9.2.2 Assess and document the presence of lagophthalmos

Ask the patient to close his/her eyes gently, like he/she is sleeping. Look for the closure of the lids

9.2.2.1.1 Lagophthalmos is defined as "the inability to close the eyelids completely".
9.2.2.1.2 Measure the amount of lagophthalmos in mm using a transparent plastic ruler held in front of the widest area of lagophthalmos

9.2.3 Other adverse outcomes

Adverse outcomes related to surgical correction of trachomatous trichiasis which will be studied at each visit include:
-Overcorrection
-Lid margin notching
-granuloma
-blepharitis
-necrosis of eyelid margin

Adverse outcomes potentially related to corticosteroid eye drops as a class were minimal in the pilot study, with one elevation of intraocular pressure (IOP) and one instance of possible infection that the masked investigator thought was unrelated to treatment, but no cataract-related adverse events for any kind of cataract. As mentioned previously, fluorometholone was developed to minimize such effects, based on less ocular penetration and less potency. Adverse outcomes possibly related to the study treatment which will be studied here include:
-IOP elevation (rise in IOP from baseline of 10 mmHg or more; rise in IOP to a level of ≥30 mmHg
-Occurrence of cataract surgery (within the study period); also, planned cataract surgery at the time of the last visit.
-Infectious keratitis
-Other observed adverse events attributed to study treatment. Given the wide variety of typically rare other potential side effects, we plan to study any other conditions in aggregate under the rubric of other dose-limiting toxicity. It is difficult to pre-specify what events may be encountered that would indicate a lack of safety. However, examples of events that would meet this definition include: 1) SAEs (see below) judged as likely related to the treatment by the investigators; 2) allergy to the study test article; or 3) 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 (>30%)), also would be considered a dose-limiting toxicity.

10 ADVERSE EVENTS

All adverse events (AEs) will be described in detail in the source documents and documented in the case report forms (CRFs). AE's requiring urgent reporting will be reviewed promptly by an 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 also will establish, with the aid of the Study Officers, a reporting protocol to

ensure the Field Team promptly reports required events, including training in response to any errors in such reporting.

10.1 DEFINITION OF ADVERSE EVENTS

An adverse event (or adverse experience) is any untoward medical occurrence in a clinical investigation subject administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Protocol deviations or errors will also be treated in the same manner as adverse events. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), 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. An AE is considered serious if it meets any of the serious criteria listed below.

10.2 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 Investigator or 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 does not require reporting as an AE.

10.3 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.

10.4 RELATIONSHIP TO STUDY TREATMENT

All AEs will be evaluated by the Investigator 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

For AEs that are assessed to be related to the study treatment, the Investigator must determine whether to continue or discontinue the study treatment.

10.5 ELICITING ADVERSE EVENTS

At each study visit, the subject will be questioned about AEs in a non-leading manner. 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).

10.6 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

All AEs should be followed until they are resolved or until a stable clinical endpoint is reached.

10.7 SERIOUS ADVERSE EVENTS

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS.

10.7.1 Definition of a serious adverse event (or serious adverse experience)

Although this is not an FDA regulated study, we will follow 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
- 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.

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 subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.7.2 Hospitalization

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.

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.

10.7.3 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 ascertainment of the SAE. This will be facilitated by having an Ethiopia-based ophthalmologist serve as the Safety Officer. 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. If the internet and mail services are disrupted, the Study 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 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, notification of an SAE or clinically significant AE must also be submitted in accordance with the overseeing body's requirements. Per the Ethiopian Food and Drug Authority (formerly FMHACA) requirements, SAEs including measures taken will be reported in writing to the Authority within 48 hours of the ascertainment of the SAE in the format provided by the Authority. In addition, per agreement with Allergan (as a condition for donating the fluorometholone 0.1% for the study), serious adverse events, and occurrence of pregnancy and breastfeeding during the study will be reported to Allergan.

10.8 REPORTING PERIOD FOR ADVERSE EVENTS

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

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.

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 4 week visit, which is in place largely to detect such events.

A summary of non-serious adverse events will be reported to the National Authority (EFDA) every six months.

10.9 PREGNANCY

Following SAFE programmatic practice in the study area, self-reported pregnancy is a contraindication to enrollment in the study because we desire to assess outcomes in patients given azithromycin, and azithromycin is not administered to pregnant patients, which is possibly dangerous in pregnancy. However, because azithromycin is not administered as part of the study, surveillance for pregnancy is not required as part of the study. This approach is the same as that used and approved in the preliminary trial.

Because corticosteroids are permitted in pregnancy, should a study subject becomes pregnant, pregnancy will not entail any adverse event reporting, unless the outcome of the pregnancy or some other issue related to pregnancy constitutes an adverse event under the guidelines described above.

10.10 DATA AND SAFETY MONITORING COMMITTEE

A Data and Safety Monitoring Committee (DSMC) convened by the National Eye Institute 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 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.

11 STATISTICAL ANALYSIS AND SAMPLE SIZE CONSIDERATIONS:

11.1 OVERVIEW OF THE STUDY DESIGN

The **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 TT undergoing lid rotation surgery. The trial is designed with fixed sample size and 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 treatment 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/geographical area. Because surgeons operate only in one geographical area, this stratification variable in effect stratifies for geographical area as well.
- 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 postoperative recurrence of TT by one year as determined by the trained study 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; (2) history of repeat TT surgery; (3) evidence of epilation on clinical examination.

- Secondary efficacy outcome measures (after TT surgery) are:
  - Reoperation for TT
  - Number and location of lashes touching the globe and cornea
  - Entropion (presence and extent)
  - Corneal opacity
  - Overcorrection
  - Eyelid notching/eyelid contour abnormalities
  - Lid closure defect
  - Granuloma
- Safety outcome measures are:
  - Intraocular pressure (IOP) elevation
  - Cataract
  - Adverse events attributed to study treatment
- Patient-reported outcomes:
  - Overall patient satisfaction
  - Cosmetic outcome
  - Impact on quality of life
  - Ocular Surface Disease Index[30]
  - EuroQol Questionnaire[31]
- Health economic analysis

11.2 STATISTICAL HYPOTHESES

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.

11.3 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.[5] 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,[24] 0.40 in the Doxycycline trial[25] (from personal communication), and 0.48 from the Clamp trial.[32] 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%).[14,18,24,25]

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

11.4 STATISTICAL ANALYSES

11.4.1 General Approaches to Statistical Analyses

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.[33-35]
- 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).[36] 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.

11.4.1.1 Baseline Descriptive Analyses

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.[33] 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.

11.4.2 Data Analyisis of the Primary Outcome Variable

11.4.2.1 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.[32] 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) [3-5]. 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.

11.4.2.2 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.

11.4.2.2.1 Effect modification for primary outcome

To check the consistency of results over subgroups, we will assess effect modification of the intervention on the primary outcome (postoperative TT within one year) with the following factors by including an interaction term with treatment arm in the 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 arm and their odds ratios will be reported for each effect modifying variable.

a. Operating surgeon (surgeons 1, 2, 3, etc.)

b. Preoperative upper eyelid trichiasis severity with six 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, total)

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)

11.4.2.2.2 Predictors for postoperative TT:

A multivariate repeated measures logistic regression model will be used to identify potential explanatory factors for postoperative trichiasis within one year. Predictors of recurrent trichiasis to be considered in the multivariate repeated measures logistic regression model will include:

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

b. Type of trichiasis lashes at baseline

c. Trichiatic lashes' location at baseline (touching cornea or not)

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)

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

Intention-to-treat analysis will be used to assess the effect of surgery on incidence of postoperative trichiasis at four weeks, four-to-six months and one year separately, using logistic regression. 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). Baseline imbalanced and important prognostic factors will be considered in this analysis to estimate the adjusted odds ratio for postoperative recurrence between fluorometholone 0.1% or placebo.

11.4.2.2.4 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.

11.4.2.2.5 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 [37,38] 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.[39]

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.

11.4.3 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 [36,40] 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.[33] 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.[41]

11.4.4 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.[37,42] 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.[42]

11.4.5 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. Identified outliers or potentially fraudulent data will be investigated by the Field Coordinating Center and Field Teams 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.

11.4.6 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/)[43], or Mplus (computer software, Los Angeles, CA) will be used.

12 DATA MONITORING

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. The first DSMC meeting(s) will be held prior to the start the trial to review and approve the trial protocol (with any needed revisions

implemented prior to approval). DSMC meetings will be held semi-annually after the start of the trial to review the accumulated safety and efficacy data.

There will be no formal statistical guidelines for stopping the trial early because of safety considerations. The magnitude of the difference in safety outcomes, as well as their severity will be considered in deciding whether the trial should be stopped.

13 QUALITY CONTROL AND QUALITY ASSURANCE

This study will be monitored by the Study Officers to assure protocol adherence. The protocol, Case Report Forms (CRFs), study drug supplies, and relevant procedures will be explained in detail to study staff during their training period. Subsequent to subject enrollment, the Field Coordinating Center Director and Study Chair will conduct periodic monitoring visits to ensure these aspects are being implemented correctly and review documents to ensure that the study is conducted according to the protocol. Additionally, monitoring officers from the Field Coordinating Center will review all field activities bi-monthly for protocol adherence and compliance with GCP. Due to the low risk nature of the trial, these measures together with reviews by DSMC and national regulatory visits are expected to provide adequate clinical monitoring of the study.

The study field teams will direct data enter onto paper forms, which then will be entered into a tablet-based eCRF system which will implement range checks and other intrinsic quality control mechanisms to allow for correction of data errors in real time. Because the staff often will be out of range of cellular data systems, a REDCap (Vanderbilt University, Nashville, TN) android-based system (see Section 15) 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 (see section 15), analogous to the approach Dr. Aida Abashawl used in implemented the Global Trachoma Mapping Program project in rural Ethiopia. The system will provide for e-signature, date and timing of each form. The data center will perform range checks and feedback data quality queries to the study team. Both of paper and electronic data entry will be done on site; the paper forms are done as a backup in case the tablets used for data entry are lost or malfunction while off line, and to fulfill expectations of the Ethiopian regulatory auditors that paper forms would be available for inspection. The Coordinating Center will check hard copy documents (those containing subject identifiers) which will be kept at the field office so as to avoid misdirection of protected health information.

In addition, photography will be used as a quality assurance check. Face photographs taken at baseline will allow proper identification of subjects during follow-up. Digital photographs will be taken of the eyelids, conjunctiva and cornea for independent grading of a random subset for quality control checking on coordinators gradings.

14 PROTOCOL AMENDMENT AND COMPLETION

14.1 CHANGES TO FINAL STUDY PROTOCOL

All protocol amendments will be submitted to the governing IRB(s). 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.

14.2 PROTOCOL 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. Reports required by the Ethiopian authorities will be submitted as required.

15 DATA HANDLING AND RECORDKEEPING

15.1 CASE REPORT FORMS

The Study Leadership, led by the Data Center, will provide electronic case report forms (CRFs), and visit-specific bundles of paper CRFs, to be completed for each visit. The study team will enter data electronically CRFs for each subject using an electronic database system (REDCap, Vanderbilt University, Nashville, TN). REDCap is a well established secure web application for building and managing online surveys and databases (https://www.project-redcap.org/). Each form for each subject will be identified by a FLAME identification number, as described above. The e-CRFs will not allow the subject to be identified by name. Paper CRFs also will be generated to accommodate screening and randomization logs containing patient identifiers; these must be maintained on site and available for inspection by site visitors. Paper CRFs corresponding to the e-CRFs also will be filled out so that there is a backup available in the event of loss of electronic data while off the internet grid. (The Field Team often will be out of internet range for a full week at a time). Subjects' medical records kept by the field team also must be made available to site visitors during scheduled monitoring visits, as well as during any inspections by the IRB(s) or a government agency should such occur. When a subject discontinues the study, all CRFs must be completed/entered in a timely manner under the appropriate member of the study team's login.

15.2 RECORD RETENTION

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 study team. The field office/Field Coordinating Center will maintain the records of test article accountability/disposition, signed consent forms, correspondences, monitoring visit dates, and records that support this information for a period of one year after completion of the protocol.

The Field Coordinating Center must be notified, in writing, when a study team member leaves the study site 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.

All study records are subject to inspection by governmental agencies (when legally mandated) or the Coordinating Center (or its designees) at any time. All study documents will be transferred to the keeping of the Coordinating Center upon completion of the study.

15.3 CONFIDENTIALITY

The Study Team will preserve the confidentiality of all subjects taking part in this study. In the event of subject names inadvertently appearing on any study documentation, this information will not be entered into the computer database for this study. The electronic data entry system will be designed to be unable to accommodate patient names. Any paper records linking identifiable patient information to study numbers will be kept at the field office site under lock and key. Electronic devices containing data will be password protected, with access limited to the study team. Two copies of such keys will be kept (one primary copy, and one backup copy), so as to avoid losing access to study data. As an additional precaution against data loss, de-identified data will be uploaded automatically to the Data Center in Philadelphia as soon as devices are online.

Representatives of the Study Officers will seek access only to clinical information 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 programmatic evaluations by the sponsor or other organizations with the Study Officers' approval. NIH policy regarding making de-identified information available also will be followed.

16 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 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."

17 STUDY SURGEON TERMINATION

The Study Officers 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.

18 PREMATURE STUDY TERMINATION

Premature termination of this clinical study may occur because of governmental action, safety problems, or upon the agreement of Study Officers, 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.

If a study is prematurely terminated or discontinued, the Study Officers will promptly notify the study Field Team. After notification, the study Field Team must contact all actively participating subjects within 4 weeks. All study materials must be collected and all CRFs completed to the greatest extent possible.

19 PUBLICATION POLICY

The Study Officers, under the leadership of the Study Chair, jointly have the ultimate responsibility and authority regarding the decision and responsibility to publish results of the study. Additional investigators also will participate in publications per the consensus of the Study Officers. The Data Center will keep a list of all present and past members of the Research Group, which will be published or referenced in association with each publication. In general, all members of the Study Leadership Team (Study Officers) will be named in all publications of the Research Group, along with additional individuals appointed by the Study Officers 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. The clinical trial will be registered at clinicaltrials.gov.

20 RESEARCH GROUP STRUCTURE

20.1 STUDY ORGANIZATION OVERVIEW

The FLAME Trial is a clinical trial implemented in a field setting in rural Ethiopia, assessing the efficacy, safety and health economics 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 4 resource centers and 3 study field teams that enroll/follow patients and collect data. The resource centers are the Chairman's Office, the Field Coordinating Center, the Surgical Team and the Data Center.

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); and the Health Economist (Prof. Kevin D. Frick), via consulting agreements. The Study Chair himself will divide his time between Boston and Ethiopia, spending several months per year in Ethiopia. Note: Because of Dr. Kempen's frequent presence in Ethiopia, the Chairman's Office also will fund 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, MD, PhD. 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 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, with offices in Addis Ababa, and field operations throughout the Oromia Region of Ethiopia. The Surgical Team will be directed by Wondu Alemayehu, MD, MPH (Addis Ababa, Ethiopia) and Co-Directed by Sarity Dodson (Melbourne, Australia/Fred Hollows Foundation Headquarters).

The Data Center is located at the University of Pennsylvania's Center for Preventive Ophthalmology and Biostatistics in Philadelphia, Pennsylvania, directed by Gui-shuang Ying, MD, PhD, and co-directed by Maureen Maguire, PhD. The Investigational Pharmacy, under Vivian Leung, Pharm.D. will be located at the University of Pennsylvania's Investigational Drug Service, funded by the DC grant.

20.2 CHAIRMAN'S OFFICE (CO)

The CO provides overall leadership to the FLAME Trial Research Group. The specific responsibilities of the Chairman's Office/ 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 serve as a liaison with relevant organizations and lead publicity efforts (in Ethiopia, primarily through the Surgical Team)
4. To Develop and maintain study documentation, including updated protocol, study handbook, and other study materials (and assist the Data Center in developing and maintaining electronic data entry forms); The Field Coordinating Center will assist with this activity.
5. To provide protocol, clinical and epidemiological expertise to the Data Center in its work preparing study forms
6. To organize, coordinate, provide logistical support for, and be financially responsible for all study meetings, including in-person meetings and weekly operation conference calls. Note that Data and Safety Monitoring Committee (DSMC) meetings are an exception that will be organized by the DC
7. To provide leadership and administrative support for the preparation of study manuscripts and scientific meeting presentations; to support correspondence regarding published/presented study findings
8. To monitor the manuscript review process, submissions and post-publication correspondence
9. To implement NIH-mandated activities including listing and maintaining the study listing on clinicaltrials.gov and ensuring manuscripts are posted on PubMed Central
10. To contract with, collaborate with, and oversee the Ethiopian Field Coordinating Center, Surgical Team (under the Fred Hollows Foundation) and the Consultants; to assist the Field Coordinating Center in supervising the Field Team

11. To appoint and administer study committees
12. To administer financial issues of the Chairman's Office including tracking of expenditures and payment of invoices.
13. To serve as a communication hub for the study.
14. To oversee the Ethiopia Coordinating Center in its activities of managing study data collection; hiring, training and certification of study team members; implementing quality assurance and monitoring procedures; and providing study data to the Data Center
15. 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 by the trial.
16. The Co-Chair, Prof. Matthew 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, making available materials and strategies he has developed in his previous extensive successful work carrying out studies of this nature. Prof. Burton has carried out more field trials about trachomatous trichiasis than anyone in the world, which have been done primarily in Ethiopia.
17. The Health Economist, Prof. Kevin Frick, will oversee the protocol design and maintenance regarding health economic issues, will oversee the analysis regarding health economic aspects of the study, and participate in paper-writing regarding health economic issues. Prof. Frick is a well-known health economist who has had extensive engagement in health economic studies about eye diseases, and is the best known health economist in the area of trachoma.
18. John Kempen and Matthew Burton will serve as Study Officers.

The Study Chair, John H. Kempen, MD, PhD, will lead these efforts from his bases in Boston, Massachusetts and Addis Ababa, Ethiopia. He will spend a minimum of six months per year on site in Ethiopia for hands-on oversight of the study activities. The Study Vice-Chairman, Prof. Matthew Burton, will draw upon his expertise as Study Chair for the implementing four prior completed field trials about trachomatous trichiasis surgery in advising and assisting Dr. Kempen in CO activities and overall study leadership. Prof. Burton will be funded under a consulting agreement because his institution as a matter of policy will not implement grants and contracts of value less than GBP 50,000.

20.3 FIELD COORDINATING CENTER (FCC).

Directed by the FCC 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 has extensive experience leading field trials of health care interventions in Ethiopia and globally, 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;
7. Assigning a local Ophthalmologist to be the Safety Officer who 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 Study Chair and FCC Director, and advising the study regarding safety issues. and
8. contracting with the Chairman's Office to receiving funding to cover these expenses.
9. Dr. Aida Abashawl will serve as a Study Officer.

The FCC will conduct regular phone and in-person meetings with the field team 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.

20.4 SURGICAL TEAM

Directed by Surgical Team Principal Investigator Dr. Sarity Dodson in Australia and Co-PI Dr. Wondu Alemayehu in Ethiopia, the Surgical Team will oversee implementation of TT surgery and present candidates to the Field Team for enrollment in the study. The Surgical Team is based within the programmatic context of the Trachoma Control Program of the Fred Hollows Foundation, overseeing trachomatous trichiasis surgery delivery for the Oromia Region of Ethiopia (over 30 million population) Administratively, the funds from the study will be distributed through the international office in Australia, due to Ethiopia governmental restrictions

on the activities of "charities" like the Fred Hollows Foundation, Ethiopia (which are required to spend no more than 30% of funds on administrative activities, whereas research has been ruled to be an administrative activity).

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

1. liaison with Ethiopian authorities regarding obtaining approvals and support 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 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. Wondu Alemayehu and Sarity Dodson will serve as 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 (see Section 5.2)

20.5 DATA CENTER (DC).

Directed by Data Center Director, Prof. 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. Prof. 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 FML 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 the input from PI.

3. Development 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/geographical area-stratified randomization sequence and provide the randomization list to the Investigational Pharmacy for preparation of medication boxes.
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 tablets 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 Study Officers.

The study Investigational Pharmacy, led by Vivian Leung, Pharm.D., will be at the University of Pennsylvania, as was done in the preliminary clinical trial. The Investigational

Pharmacy will prepare the study test articles and ship them to Ethiopia, where they will be cleared by the Coordinating Center.

20.6 FLAME 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).

The EC coordinates operations amongst the resource centers to implement the day to day operations of the Trial. 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 to write specific manuscripts and reviews progress thereon. Regular EC meetings may occur via conference call, in person or via other media.

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 is appointed by the NEI. The DSMC will meet approximately 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).

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