Protocol Title: PREVAIL VII: Persistence of Ebola Virus in Ocular Tissues and Outcomes of Cataract Surgery in Survivors of Ebola Virus Disease

Abbreviated Title: PREVAIL VII: Cataract Surgery in Ebola Survivors

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Human Research Protections Program Investigator and Staff Training:

For this protocol, the following "Just in time" human subjects protection training courses are required for investigators and staff:

- Biomedical – Vulnerable Subjects – Research with Children
- International Studies – ICH Overview and ICH – Comparison Between ICH GCP E6 and US FDA Regulations, available to those who complete the CITI GCP course

Total Requested Accrual:

120 Participants

0 Healthy Volunteers

Project Uses Ionizing Radiation: ☒ No ☐ Yes

IND/IDE: ☒ No ☐ Yes

Durable Power of Attorney: ☒ No ☐ Yes

Multi-institutional Project*: ☐ No ☒ Yes

Site	FWA
National Eye Institute – Coordinating Site	FWA00005897
Johns Hopkins University **Date of IRB approval:** September 15, 2017	FWA00005834
Emory University **Date of IRB approval:** September 14, 2017	FWA00005792
PREVAIL JFK Hospital	FWA00024151

Data and Safety Monitoring Board: ☒ No ☐ Yes

Technology Transfer Agreement: ☒ No ☐ Yes

Samples Being Stored for Future Research: ☐ No ☒ Yes

Covered Protocol Requiring DEC Clearance (per SOP 21): ☒ No ☐ Yes

Approved for Short Form Consent Process for Non-English Speakers: ☒ No ☐ Yes

Consent and Assent

- **Flesch-Kincaid Reading Level of Consent:** 8.1
- **Flesch-Kincaid Reading Level of Assent:** 6.0

*The PREVAIL clinic at JFK and ELWA hospital receive oversight and are covered by the Liberian National Research Ethics Board. The Liberian NREB assumes oversight of the staff at the Liberian sites who might interact with subjects. The NIH CNS IRB assumes oversight of the NIH, Emory, and Johns Hopkins investigators.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
EVD	Ebola Virus Disease
NEI	National Eye Institute
NIH	National Institutes of Health
PTMS	[NIH] Protocol Tracking Management System
RT-PCR	Reverse Transcriptase-polymerase Chain Reaction
SAE	Serious Adverse Event
UP	Unanticipated Problem

PRÉCIS

Objective: *Zaire ebolavirus* is a single-stranded RNA virus associated with high morbidity and mortality. The most recent epidemic of Ebola virus disease (EVD) in West Africa resulted in over 11,000 deaths and disabling sequelae among survivors, among which eye complications are highly represented. Chronic intraocular inflammation and viral persistence may result in posterior synechiae and cataract formation, resulting in loss of visual acuity and requiring surgical intervention to resolve. Approximately one out of ten Ebola survivors present with cataract, most of whom will require intraocular surgery during their lifetime, and many of whom require intervention in the near future to regain quality of life. For survivors who are blind from cataract, cataract extraction is necessary to restore visual function, allow reintegration into society and facilitate performance of activities of daily living.

However, surgical parameters among Ebola survivors are unknown, including whether Ebola viral RNA persists in aqueous humor, whether additional anti-inflammatory medication is needed, and the expected degree of improvement in visual function. Moreover, sites of viral persistence are unknown, and it is unclear if lens tissues removed during cataract surgery may harbor virus in Ebola-affected eyes. We propose following EVD survivors and control subjects undergoing cataract surgery to determine visual outcomes among Ebola survivors and explore detection of the presence of virus in lens tissues. The data will inform both future surgical intervention and aid in the understanding of the pathophysiology of Ebola-associated eye disease.

Study Population: Up to 60 Ebola survivors and up to 60 controls will be enrolled. The accrual ceiling is 120 participants.

Design: This is a prospective, natural history study to evaluate the persistence of Ebola viral RNA in the eyes of Ebola survivors and assess the response to cataract surgery in survivors as compared to controls. EVD survivors will first undergo assessment of aqueous humor for the presence of viral RNA. Survivors testing negative for viral RNA and control subjects will undergo clinically indicated cataract surgery. Subjects will be evaluated 1 day, 1 week, 1 month, and 3, 6, 9, and 12 months after surgery for safety and visual outcome assessments, and more often as clinically indicated.

Outcome Measures: The primary outcomes are: 1) the proportion of EVD survivors with evidence of persistence of Ebola viral RNA in ocular tissue and 2) the comparison of amount of intraocular inflammation, as measured by average grade of anterior chamber cell by SUN criteria, between EVD survivors and controls at 1 month and 3 months following cataract surgery. Secondary outcomes include: 1) the proportion of survivors with at least 20/40 best corrected visual acuity (BCVA) after cataract surgery, relative to controls; 2) impact of the covariates age and gender on viral persistence and cataract outcomes; 3) post-operative optical coherence tomography results in EVD survivors.

1.0 INTRODUCTION/SCIENTIFIC RATIONALE

1.1 Background

Zaire ebolavirus is a single-stranded RNA virus associated with high morbidity and mortality. Its case-fatality rate over three decades of outbreaks averages 83% and up to 94% in a sample of individuals over 45 years old.[1] Among the almost 20,000 survivors from the most recent outbreak, complaints of frequent eye complications arose in early survivor surveys in late 2014.[2] However, due to limited ophthalmic capacity in the countries most affected by the Ebola outbreak, a significant burden of eye problems requiring surgery have yet to be addressed.

Ebola virus persists in the eye during the convalescent stage of disease after clearance from serum, although the length of such persistence is unclear. Of four survivors with uveitis reported from the 1995 epidemic in Congo, one case developed one month after discharge from treatment.[3] In a more recent case, viable Ebola virus was acquired from the aqueous humor nine weeks after viremia resolved.[4] PCR testing of tear samples detects virus during active infection[5] but not at three months,[4] consistent with the immune-privileged state of the intraocular space, and its ability to serve as a viral reservoir. The pathophysiology of viral persistence in the eye is unknown, although virus has been collected from aqueous paracentesis.

To characterize and understand the spectrum of ocular pathology among EVD survivors, an eye substudy was developed within the PREVAIL III Natural History Study of Ebola survivors, a partnership between the NIH and the Ministry of Health of Liberia (MOH). The eye substudy seeks to identify demographic, timing, and clinical factors associated with vision loss. To date, approximately 3000 comprehensive eye examinations have been performed of Ebola survivors and close contacts, which is combined with ophthalmic imaging to identify specific pathological changes occurring in this disease. The PREVAIL III study defines close contacts as household members at the time of Ebola diagnosis and sexual partners after recover from EVD. Treatment is facilitated with local Liberian ophthalmologists who, as study investigators, treat inflammation and monitor patients to ensure resolution of symptoms.

In the first year of presentation, approximately 1 in 10 survivors and close contacts presented with cataract (unpublished data). Such cataracts may be due directly to either intraocular inflammation or long-term steroid use, often needed to address the severe panuveitis present in disease, but may

also develop naturally. Cataract surgery is cost-effective and clearly indicated to help vision, but without knowledge of whether viral persistence exists, it is not known what infection control practices are necessary for surgery to be performed safely.

A similar proportion of patients have developed post-inflammatory epiretinal membrane (which requires more complex vitreoretinal surgery to address). Therefore, a need exists for the long-term development of surgical capacity in addition to short-term knowledge regarding intraocular persistence of virus. Although the mainstay of EVD treatment is largely medical, it is clear that a significant proportion of ophthalmic sequelae will require surgical intervention.

For survivors who are blind, cataract surgery is necessary to restore visual function, allowing re-integration into society, and for personal safety, to avoid falls and collisions. However, surgical outcomes among Ebola survivors are unknown. Ebola-associated ocular comorbidities such as hypotony must be accounted for post surgically. Given that cataracts associated with the rubella virus are characterized by severe postoperative inflammation due to viral persistence within the lens, requiring aggressive postoperative anti-inflammatory treatment with steroids, we must monitor intraocular inflammation in the postoperative period. Intraocular surgery among young individuals is also often marked by a robust inflammatory response. Both factors may influence outcomes in Ebola-associated cataract. We propose the study of surgical outcomes that will inform care in other affected countries and for future Ebola-affected patients.

1.2 Rationale

At present, the safety and optimal execution of cataract surgery in Ebola survivors is unknown. Specifically, it is unknown whether survivors experience extended periods of inflammation post-operatively and require adjusted management guidelines, and whether Ebola virus persists in the anterior chamber and lens, requiring special precautions by the surgical team. Currently, the pathophysiology of viral persistence in the eye is not understood.

Analysis of anterior chamber fluid and lens material will help answer these unknowns, as will close surgical follow-up management and monitoring. Since lenticular tissue is normally disposed of during cataract surgery, the collection and analyses of this material will provide a unique opportunity to assess a potential location for virus in Ebola-affected eyes, to further elucidate the pathophysiology underlying viral persistence. Following EVD survivors during the post-surgical

period will allow us to evaluate surgical outcomes and the effect of post-surgical comorbidities in this population, which are currently unknown.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives for this study are to 1) determine the proportion of EVD survivors with evidence of persistence of Ebola virus in ocular tissue and 2) compare the amount of intraocular inflammation, as measured by average grade of anterior chamber cell by SUN criteria, between EVD survivors and controls at 1 month and 3 months following cataract surgery.

2.2 Secondary Objectives

The secondary objectives are to: 1) assess visual outcomes of cataract surgery in EVD survivors, 2) assess the effect of age and gender on Ebola virus persistence and cataract outcomes in EVD survivors, and 3) assess postoperative structural changes after intraocular surgery in EVD survivors.

2.3 Exploratory Objectives

The exploratory objective is to validate the use of the GeneXpert for the detection of Ebola viral RNA in aqueous humor.

3.0 PARTICIPANTS

This study involves recruiting EVD survivors and controls who have a clinical need for cataract surgery, which will be performed using the small incision cataract surgery technique which is standard practice in Liberia. Therefore, we will enroll all individuals who meet study eligibility criteria and would otherwise be eligible (clinically) to undergo cataract surgery.

The accrual ceiling is 120 people, with up to 60 EVD survivors and up to 60 controls. Current estimates of numbers of survivors and controls meeting eligibility criteria is lower, at about 35-45 survivors and 35 controls.

3.1 Participant Eligibility Criteria

3.1.1 Inclusion Criteria

To be eligible, the following inclusion criteria must be met, where applicable.

1. Participant must be 14 years of age or older.
2. Participant must be able to understand and sign an informed consent or have a parent/legal guardian do so if they are minor children or a legally authorized representative to provide consent for adults without consent capacity.
3. Participant must be either:
   a. an Ebola virus disease (EVD) seropositive survivor or seropositive control OR
   b. an EVD seronegative survivor or seronegative control (Serology confirmation is available for PREVAIL participants and will be conducted for non-PREVAIL participants.).
4. Participant must have visually significant cataract(s) consistent with level of visual deficit.
5. Participant must have corrected visual acuity worse than 20/40 in affected eye and vision loss believed to be primarily the result of the cataract.
6. Any women and persons of childbearing age must have a negative pregnancy test at screening and must be willing to undergo pregnancy testing prior to the cataract surgery.

3.1.2 Exclusion Criteria

A participant is not eligible if any of the following exclusion criteria are present.

1. Concurrent life-threatening illness or other condition that compromises a participant's ability to safely undergo surgery, as determined by the surgical and medical team, including any condition that prevents the participant from lying down supine or remaining still, such as severe lung disease, or a known life-threatening, untreated or unstable cardiac or pulmonary condition.
2. Active uveitis at time of surgery or within the past three months, if documented.
3. Participant is pregnant, as surgery is elective and no adequate data regarding the use of postoperative topical antibiotic-steroid combination drops exists in pregnant women.
4. Any condition that poses a risk to the participant having a safe surgical or post-operative experience, including known inability or unwillingness to follow up for the full duration of the protocol.

4.0 STUDY DESIGN AND METHODS

This is a prospective, natural history study to evaluate the persistence of Ebola viral RNA in the eyes of Ebola survivors and assess the response to cataract surgery in survivors as compared to controls. For the purposes of the study procedures and analysis, EVD survivors and controls who are seropositive are considered cases with potential for persistence of Ebola viral RNA and will have an initial aqueous humor tap to assess for the presence of Ebola viral RNA by GeneXpert. All EVD survivors, defined as those who are seropositive for the Ebola virus, testing negative for Ebola viral RNA and control subjects will undergo clinically indicated cataract surgery. Subjects will be evaluated 1 day, 1 week, 1 month, and 3, 6, 9, and 12 months after surgery for inflammation, safety and visual outcome assessments, and more often as clinically indicated. Participant enrollment and all study visits, including cataract surgery, will be performed at various sites in Liberia.

Co-enrollment guidelines: Participants may be co-enrolled in the PREVAIL III Natural History Study and may be co-enrolled in other studies; however, study staff should be notified of co-enrollment on any other study.

4.1 Recruitment

Participants may be recruited from several sources. Ebola survivors and controls will be recruited from the ongoing PREVAIL III study using the PREVAIL Social Mobilization and Communications team and Participant Trackers who are assigned to follow individual subjects. Ebola survivors may also be recruited from other survivor care clinics, such as ELWA Hospital and their outreach clinics, research programs, or be self-referred. The accrual period will be one year.

4.2 Screening

Consent will be obtained before any procedures, including screening procedures, are performed. Study eligibility will be confirmed on all participants during a standardized baseline screening exam to occur within 30 days of the planned surgery. This evaluation will include the following assessments:

- focused history and physical
- presenting vision,

- pinhole vision,
- best-corrected vision,
- color vision,
- pupil exam,
- intraocular pressure,
- slit lamp examination,
- dilated fundus examination,
- eye measurements to determine needed intraocular lens power
- ultrasound biomicroscopy if needed to assess ocular structures in cases when visibility is impaired due to cataract.
- blood draw, as indicated
- additional testing, as clinically indicated

Screening procedures performed under the PREVAIL protocol may be used if performed within 30 days of the scheduled surgery date.

Note that throughout the study, the ETDRS tumbling E chart will be used for vision testing, and any acceptable method such as the iCare device, will be used for measurement of intraocular pressure.

Most participants will already have been previously assessed either as part of a PREVAIL III study visit or as part of an outreach ophthalmic or cataract screening effort, such as those organized by ELWA Hospital.

For those survivors who do not yet have serology confirmation, a blood sample will be collected and tested.

HIV/syphilis infection status will be collected from non-PREVAIL III participants (PREVAIL III participants will have had previous HIV/syphilis testing). Participants having HIV/syphilis testing will receive pre-test counseling at the screening visit and will receive their results and post-test counseling at the next study visit. Participants who test positive for HIV or syphilis will be referred for treatment according to local standards and, if otherwise eligible, may continue in the study.

For women and persons of childbearing age including minors and adults without consent capacity, a urine pregnancy test will be conducted at screening and one week prior to cataract surgery. Participants testing positive for pregnancy will not proceed to cataract surgery.

After screening, qualified EVD survivors will proceed to the aqueous humor sampling, and qualified control subjects will proceed to cataract surgery as described below.

4.3 Study Design and Procedures

In the case of Ebola survivors, if the participant has bilateral cataracts meeting inclusion criteria, the eye with worse vision will be selected for surgery. Surgery will not be performed on the second eye of seropositive survivors in the scope of this study, since optimal post-surgical management of cataract in Ebola survivors is still being established so this could pose increased risk to the participant. Surgery may be performed on the second eye of survivors confirmed via serological assessment to be seronegative. In the case of controls with bilateral cataracts meeting study criteria, the eye with worse vision will be selected as the first (and possibly only) eye to receive surgery. There is a possibility that surgical capacity will be adequate to accommodate surgery on the second eye of all control participants. If that is the case, then control participants will be offered the option of receiving surgery on their second affected eye. If the capacity does not exist to provide surgery to all control participants in that category, then it shall not be offered to any participants, in order to ensure equity of access to this potential option.

Scheduled study visits will take place at either ELWA hospital, the PREVAIL JFK eye clinic, or a mobile eye clinic staffed by study investigators to serve outlying locations. The location of any particular participant's study visit will depend on the participant's geographic location. In addition, participants requiring clinical eye care at any other time than study-directed eye visits may receive that care at additional locations to include the New Sight Eye Center in Monrovia, the L.V. Prasad Eye Clinic in Monrovia, and the eye clinic in Lofa. These additional sites are resources for the study and study participants, and the data gathered from these sites can be accessed for study purposes. All of the study and clinical care sites meet minimum requirements for performance of eye exams and are staffed by qualified eye care providers.

Aqueous humor sampling

Prior to being scheduled for cataract surgery, participants in the EVD survivor group and controls who are seropositive will undergo aqueous fluid (aqueous humor) sampling to assess for the presence or absence of Ebola virus RNA via RT-PCR using the GeneXpert assay. GeneXpert is a system that uses real-time polymerase chain reaction (PCR) to detect target sequences in

biological samples. It automates the process and includes sample preparation, nucleic acid amplification, and in addition to detection, provides both summary and test results. The GeneXpert has undergone validation for use of detection of Ebola Zaire in blood and has an EUA from the US FDA for detection of Ebola viral RNA from the blood. The validation has also been done for male semen. One of the exploratory objectives of the protocol is to provide verification of the use of the GeneXpert for Ebola viral RNA in aqueous humor. The NIAID Integrated Research Facility will be working on this with the Liberian Institute of Biomedical Research with is now part of the Liberian Public Health Institute.

Subjects with negative RT-PCR results in aqueous will proceed with cataract surgery within three months. Participants whose aqueous humor has detectable Ebola viral RNA will not proceed to cataract surgery. They might be considered for cataract surgery at a future date, likely requiring that they be re-tested for persistence of Ebola viral RNA in the aqueous prior to time of surgery. However, this would not be part of this current study. Currently, there are no clear guidelines about how to proceed for participants who test for Ebola viral RNA in the aqueous. Because the aqueous is internal ocular fluid, these participants do not require additional infection control procedures in daily activities and routine medical care.

For aqueous humor sampling, a sample of approximately 100 microliters of aqueous humor will be extracted by 30G needle or cannula under an operating microscope. Only trained cataract surgeons, who have undergone formal, multiyear, dedicated cataract surgery training, will be performing aqueous humor sampling. The surgeons may be AI's on the protocol (i.e., Dr. Yeh, Dr. Shantha, Dr. Hayek) or other qualified available eye surgeons with appropriate credentials at ELWA hospital. Personal protective equipment will be utilized by the staff performing the procedure. This will be conveyed according to applicable laws and guidelines for the transport of hazardous biomaterials to the Liberian Institute for Biomedical Research for analysis. RT-PCR will be performed to assess for the presence or absence of Ebola viral RNA. The collection of aqueous humor is a standard ophthalmic procedure. In this case, it is being performed for research purposes and to inform the safety of both participants and surgeons surrounding the cataract surgery.

In the unlikely event that aqueous fluid is not successfully collected and/or analyzed, a second attempt at fluid collection and analysis may be made at the discretion of the surgeon and participant. Failure to obtain aqueous fluid will be treated similarly to subjects who test positive, with completion of study participation and counseling about options to receive cataract surgery following completion of the study.

Should there be a surgical complication during the AC tap procedure, such as penetration of the anterior lens capsule, the participant will be managed according to the best judgment of the surgeon and study investigators, using anti-inflammatory medication, and/or surgery as needed.

Aqueous humor will be collected from control participants at the time of cataract surgery and will be used to verify study assays.

Cataract surgery visit

All survivors who have tested negative for Ebola viral RNA in the aqueous humor, as well as controls, will proceed with cataract surgery within 30 days of the screening visit. It is expected that most if not all surgeries will take place the second week of the protocol. If the surgery does not occur within 30 days of the screening visit, the screening visit procedures will be repeated prior to surgery. For Ebola survivors, the aqueous humor tap must be performed within three months of cataract surgery. If cataract surgery has been delayed beyond the three-month window following the aqueous tap, then the surgery can no longer be performed under this protocol as the resources to perform the AC taps on Ebola survivors are available in country for only a limited period of time.

For control participants, aqueous fluid sampling will be performed during the cataract surgery and will be used in the GeneXpert verification.

Cataract surgery will be performed by qualified eye surgeons with formal cataract surgery training. The surgeons may be AI's on the protocol (i.e. Robert Dolo) or other qualified available eye surgeons with appropriate credentials at ELWA hospital. Surgeries will be performed at the ELWA hospital. Anesthesia for the surgery will consist of peribulbar block. Routine manual small incision cataract surgery, with use of biometry to assess for an appropriate intraocular lens to be implanted, will be performed for all participants. All subjects will receive standard postoperative topical

antibiotic and anti-inflammatory regimens. During surgery, the individual lens components (capsule, nucleus, and cortex), which would normally be discarded, will be placed into neutral-buffered formalin for immunohistochemistry for detection of Ebola virus protein.

Immediately after surgery, participants will be asked to rest in beds provided by ELWA and will stay overnight. It is expected that participants will be fully ambulatory the day after surgery. They will then receive their travel allowance to commute home. Those from distant locations will stay at ELWA through the Week 1 postoperative exam.

If a participant is having any medical problems or difficulty with ambulation after the surgery, they will be cared for at ELWA until they are able to safely travel home. If needed for complications with their eye, participants will be able to access medical care and be reimbursed for their commuting expenses.

Participants who test positive for Ebola in lens materials will be counseled about this fact, and informed that the significance of this finding is unknown. No additional infection precaution procedures will take place for those patients for the same reasoning offered regarding positive aqueous tap findings.

There may be Ebola survivors or PREVAIL control participants who meet the age requirement and have cataracts which meet study criteria but who do not qualify for another reason which is temporary, such as pregnancy or inability to meet study visit schedule, but which will resolve such that they would meet all study criteria within one year of when the study is initiated. There is a separate fund outside of the study which will support standard of care cataract surgery and post-operative management at L.V. Prasad Hospital for this potential group of people with cataracts. The limitation of this resource, however, is that anterior chamber fluid analysis to determine possible presence of Ebola virus RNA will not be able to be collected and tested as part of standard of care cataract surgery at L.V. Prasad. Therefore, for Ebola survivors to avail themselves of this option, safety guidelines which do not yet exist must be developed. It is the hope of this study team that the current protocol might generate such safety standards within one year of study initiation. However, there is no guarantee that this will be accomplished, and no guarantee that the determination will be made that cataract surgery is safe in Ebola survivors without the need of an anterior chamber fluid analysis testing negative for Ebola prior to surgery.

Post-operative visit #1: 1 day after surgery

All participants who have undergone surgery will return after one day for standard postoperative assessment, during which they will undergo vision assessment and slit-lamp biomicroscopy. The degree of intraocular inflammation will be recorded.

Post-operative visit #2: 1 week (±4 days) after surgery

All participants who have undergone surgery will return one week (±4 days) after surgery for continued evaluation and management. Vision and intraocular pressure will be assessed. Slit-lamp biomicroscopy and, when indicated, dilated eye examination will be performed to assess for inflammation in the anterior and, when indicated, posterior segments of the eye and any other ocular findings.

Post-operative visit #3: 1 month (±14 days) after surgery

All participants who have undergone surgery will return at 1 month (±14 days) after surgery to undergo manifest refraction (performed according to standard procedures) to assess for best-corrected visual acuity using the ETDRS Tumbling E chart, slit-lamp biomicroscopy and dilated eye examination to assess for recurrent or persistent inflammation and any other potential ocular changes. When available, optical coherence tomography will be conducted according to standard procedures to assess for the presence of macular edema.

Post-operative visits #4-7: 3, 6, 9, and 12 months (Visits 4 and 5 ±21 days, Visits 6 and 7 ±1.5 months) after surgery

All participants who have undergone surgery will return at 3 and 6 months (±21 days) and 9 and 12 months (±1.5 months) to undergo manifest refraction (performed according to standard procedures) to assess for best-corrected visual acuity, measurement of intraocular pressure, slit-lamp biomicroscopy and dilated eye examination to assess for recurrent or persistent inflammation and any other potential ocular changes. When available, optical coherence tomography will be conducted according to standard procedures to assess for the presence of macular edema.

The Month 12 visit will be the final study visit under this protocol for participants who underwent cataract surgery. For participants requiring ongoing care related to the cataract surgery both before and after the final study visit, such as those with persistent inflammation, clinical care may be

provided at a non-study site. In addition, participants who are also part of the PREVAIL III longitudinal cohort will continue to receive the yearly PREVAIL III eye exams. If participants are seen at a non-study site for eye care, the information collected will be used for this study. If there are surgical complications, participants will be referred to a study site or the LV Prasad eye clinic at JFK hospital, which has been engaged for assistance with management of complicated cases.

Any cases of persistent inflammation or any other ophthalmic concern noted at 12 months will be referred for clinical evaluation at the PREVAIL III eye clinic or the LV Prasad eye clinic. Transportation fees will be paid for participants referred to these clinics and participants will be treated free of charge.

Results of clinical tests and evaluations performed on this study will be shared with the participants during their study visits and with their health care providers if there are any results of concern that would require general medical attention.

4.4 End of Participation

Participants will continue to receive any needed eye care related to complications from cataract surgery for up to two years after cataract surgery on this protocol, and for the duration of PREVAIL eye care operations at JFK hospital if care is needed beyond two years. All adverse events will be followed until resolution and/or return to baseline. Clinical care visits can be conducted at sites designated to provide clinical care, while study visits will take place at designated study sites.

At the conclusion of the study, follow-up care will be arranged with an outside ophthalmologist or the participant will continue to be seen under the PREVAIL III or another protocol, if available and the participant is eligible. The participants and their physicians, with written consent, will be informed of their disease status during this study. Clinical data obtained during participation may be shared with the participants and with written permission from the participants, their private physicians. Results from the overall study may be shared once the study team has analyzed the data from all participants.

5.0 MANAGEMENT OF SAMPLES AND DATA

Analysis of the AC tap and lens samples will be performed at the Liberian Biomedical Research Institute and/or NIH.

5.1 Storage

Samples, specimens, and data collected under this protocol may be used to study eye disease in Ebola survivors. No genetic testing will be performed.

All of the stored study research samples are labeled by a code that only the investigators can link to the participant. Access to stored samples will be limited using either a locked room or a locked freezer. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples and data acquired under this protocol will be tracked per the PREVAIL data management system.

After two years, all protocol-derived samples will either be destroyed, or after NIH IRB and Liberian National Health Science Research Ethics Committee (Liberian Ethics Committee) approval, transferred to another existing protocol. Data will be archived by the study team in compliance with requirements for retention of research records; alternatively, after IRB and Liberian Ethics Committee approval, the data may be either destroyed or transferred to another repository.

Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a protocol deviation, unanticipated problem, and/or compromises the scientific integrity of the data collected for the study, will be reported to the IRB and Liberian Ethics Committee.

Additionally, participants may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the participant and to the IRB and Liberian Ethics Committee.

5.2 Data and Sample Sharing Plan

Data and samples may also be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data and/or samples from this protocol may be open-access or restricted access.

Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data and samples may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

Coded data and samples will also be added to the repository used by NIAID for Ebola specimens for future research.

6.0 RISKS/DISCOMFORTS

History and physical examination, pregnancy testing: These procedures entail minimal risk.

Vision and IOP assessments: These procedures entail minimal medical risk. In rare instances, the cornea may be scratched during measurement of intraocular pressure. A corneal abrasion of this sort may be painful, but it heals quickly and with no lasting effects. Treatment will be offered if needed.

Blood draw: Blood draws can cause discomfort and bleeding/bruising at the site of venous puncture. There is a remote risk of fainting or local infection. If any of these arise, they will be treated.

Aqueous humor sampling: Aqueous humor sampling may cause pain or discomfort in some cases, resulting from application of pressure on the eye. This typically resolves momentarily. Rare (less than 1 in 100 procedures) but potentially serious complications include lens or iris damage, endophthalmitis, corneal abscess, and blindness. To minimize risks of discomfort or damage to the lens or iris during fluid extraction, this step will be performed under an operative

microscope. If the lens is damaged, clinical judgement will guide management, with options including close observation until cataract surgery can be performed as planned, or accelerated cataract surgery if intraocular inflammation results from release of lens particles and cannot be well controlled otherwise. Aqueous humor taps pose no known additional, unique risks to Ebola survivors. It is unknown what number of subjects will have detectable Ebola viral RNA in the aqueous.

Because there is no known risk of transmitting Ebola based on presence of Ebola inside the eye, no additional safety procedures will be recommended or instituted for those who will have contact with any participants who test positive for Ebola on any tissue samples.

Cataract surgery: Risks of cataract surgery include: bleeding behind the eye as a result of anesthesia (peribulbar block), bleeding in the eye, infection (endophthalmitis), damage to intra-ocular structures including cornea and iris, and retinal detachment. Other risks include transient post-operative elevation in intraocular pressure, post-operative inflammation, macular edema, and dislocation of lens into the posterior chamber of the eye. Complications of cataract surgery can lead to worse vision or blindness. Sterile technique and antibiotics are used to minimize the chance of infection.

- Post-surgical complications: Participants will be provided with a phone number that they can call 24 hours per day, seven days per week. Anyone experiencing a post-surgical complication (such as pain in the eye or change in vision) will be told to call that number to speak with a member of the eye care team. If it is determined that the participant needs to be evaluated, they will be told where to go to be examined by one of the eye team members, and a transportation allowance will be provided for that visit. For participants from distant locations, transportation will be ensured.

Manifest refraction and optical coherence tomography: This procedure entails minimal medical risk.

Slit-lamp biomicroscopy and dilated eye examination using direct and/or indirect: These procedures entail minimal medical risk. The dilating drops or anesthetic drops used during the ocular examinations may sting for less than 30 seconds. They can cause an allergic reaction, and, if they are contaminated, they can cause an infection. However, neither of these problems is

likely to occur. The dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available. Exposure to lights during slit lamp and dilated eye examination can be uncomfortable.

Potential risks for lactating women and their breastfeeding child: There is minimal risk to the nursing infant of lactating women from the cataract surgery itself. A local peribulbar block is use for anesthesia and minimal systemic absorption is anticipated.

If a participant has significant intraocular inflammation after cataract surgery, they may require high dose oral steroids to prevent permanent vision loss from the uveitis. The steroids could theoretically pose additional risk to a breastfeeding infant. The potential risks to the nursing child are theoretical and minimal. Theoretically, infants who consume steroids in breast milk could have stomach upset, vomiting, restlessness, abnormal weight gain and increase in blood sugar, However, the amount of steroid that passes into the breastmilk is low and the risk to a breastfed infant whose mother is on steroids is low[6]. The NIH's toxicology website states: "no adverse effects have been reported in breastfed infants with maternal use of any corticosteroid during breastfeeding". To mitigate this potential risk, nursing mothers can wait four hours after taking oral steroid medication before breast feeding their child or even choose to temporarily switch to bottle feedings until the oral dose of prednisone is 20mg/day or less.

During the consent process, breastfeeding women will be counseled regarding the potential risks of their participation on their nursing infant. Potential participants who are lactating have the option to not be in the study, or to participate in the study but temporarily stop breastfeeding if they should require high dose systemic steroids. Alternatively, they could choose to continue breastfeeding, understanding the potential risks, and mitigate the risk to the nursing child by waiting four hours after taking the oral steroid medication before breast feeding their child. Breastfeeding women will not be advised to stop or reduce breast feeding. The timing of steroids will be adjusted for nursing mothers to mitigate impact on nursing children.

7.0 PARTICIPANT SAFETY MONITORING

Participants will be monitored during all study visits for adverse events by the study investigators in Liberia.

7.1 Participant Withdrawal Criteria

Participation in the study is strictly voluntary. Participants may choose to withdraw from this study for any reason at any time without penalty, without loss of benefits or prohibition from enrolling in other clinical protocols.

An individual participant will be withdrawn for any of the following:

- An individual participant's decision. (The investigator should attempt to determine the reason for the participant's decision.)
- The investigator determines that continued participation in the study would not be in the best interest of the participant.

8.0 OUTCOME MEASURES

8.1 Primary Outcome

The primary outcomes are: 1) the proportion of EVD survivors with evidence of persistence of Ebola virus in ocular tissue and 2) comparison of the amount of intraocular inflammation, as measured by average grade of anterior chamber cell by SUN criteria, between EVD survivors and controls at 1 month and 3 months following cataract surgery.

8.2 Secondary Outcome

Secondary outcomes include: 1) the proportion of survivors with at least 20/40 best corrected visual acuity (BCVA) after cataract surgery, relative to controls; 2) impact of the covariates age and gender on viral persistence and cataract outcomes in EVD survivors and controls; 3) Proportion of post-operative complications in EVD survivors versus controls, as measured by clinical examination and optical coherence tomography.

9.0 STATISTICAL ANALYSIS

This protocol has sample sizes of convenience, in that all identified Ebola survivors who are eligible for surgery and all controls in the PREVAIL III protocol will be invited to participate, in addition to some Ebola survivors from an outlying region. Therefore, statistical analysis will be limited to what can be derived using those resultant sample sizes. Controls who are seropositive will be analyzed separately and will not serve as "controls" for statistical calculations. Similarly, seronegative survivors will not be treated as survivors in the primary analyses.

9.1 Analysis of Data / Study Outcomes

If all PCR results and/or immunohistochemistry results are negative, simple models which assume independence across eyes from the same individual will be used to construct a 95% confidence interval for the probability of the aqueous humor being positive and/or the lenses being positive. If some results are positive, a more sophisticated approach will be used which recognizes the potential for an association in the outcome for eyes from the same individual. Since it is possible that some individuals receiving cataract surgery in both eyes will have discordant results, generalized estimating equations with a logistic link will be used to estimate the probability of testing positive given random effects for participants. This approach can be extended to accommodate tests for effects of age and gender (which are secondary outcomes).

Study CRFs capture the grade of anterior chamber cells for each eye according to the SUN criteria. Regression models will be fit with these grades as outcome variables and survivor status, age (less than 40 or greater than or equal to 40) and gender as explanatory variables. The test of the hypothesis of no difference in grade according to survivor status will be conducted by testing the null hypothesis that the regression coefficient associated with survivor status is zero. This will be conducted at the one and three month assessments. A significance level of 0.025 will be used for both tests to account for test multiplicity. These models will also allow for testing for the effects of gender and age, which is one of the secondary objectives. The secondary outcome about having 20/40 or better BCVA after surgery will be conducted using logistic regression with explanatory variables gender, age and survivor status.

To test for differences in postoperative structural changes after intraocular surgery between survivors and controls mixed effects models will be fit to data from the one month and three month exams for central subfield thickness and intraretinal fluid cysts. These models will also control for gender and age while testing for a difference due to survivor status. Linear models will be used for central subfield thickness and logistic regression models will be used for intraretinal fluid cysts. Tests of secondary outcomes will use a significance level of 0.05.

To examine outcomes at the nine and 12 month exams, similar models will be fit but they will be extended to these later exams.

If less than 10% of participants have any cells observed in the anterior chamber, then the second primary outcome will be having cells detected (a dichotomous outcome) and the regression modeling strategy will be replaced with a logistic regression modeling approach.

9.2 Power Analysis

We plan to enroll up to 120 participants of which 60 will be survivors and 60 contacts, to have cataract surgery as part of this protocol. The accrual ceiling is 120. If none of 40 samples test positive for Ebola RNA then a 95% confidence interval for the probability of testing positive will be (0.0, 0.09) indicating that we can conclude this occurs in less than 9% of cases. If 60 samples are obtained, then the 95% confidence interval for the probability of testing positive will be (0.0, 0.06) indicating that we can conclude this occurs in less than 6% of cases.

To examine the power for the association between survivor status and cell grade, we assume that we are just testing for a difference in the frequency with which anterior cells are observed in the two groups using Fisher's exact test. Results from PREVAIL III indicate that 10.4% of the eyes of survivors with cataracts have anterior chamber cells while only 0.4% of the eyes of contacts have cells observed. If we suppose that there are 60 participants in each group, then we have 38% power for detecting a difference using these two estimates (using a significance level of 0.025). If the rate among survivors is higher than this due to ongoing inflammation, then the power rapidly increases. Table 1 shows the power as it depends on the proportion of eyes with anterior chamber cells among survivors.

Table 1

Proportion	0.104	0.12	0.14	0.16	0.18
Power	0.38	0.52	0.69	0.81	0.89

Table 1: The power for the second primary aim using a dichotomous outcome. The proportion of eyes with cells among contacts is assumed to be 0.004 (the observed rate in PREVAIL III among contacts) while this proportion in survivors varies from 0.104 (the observed rate) to higher rates.

If participants do not follow instructions to take medication or return on the advised schedule, data will be analyzed using an intent-to-treat classification.

10.0 HUMAN SUBJECTS PROTECTION

10.1 Equitability

Subjects enrolled on this study include all individuals who meet eligibility criteria and would otherwise be eligible (clinically) to undergo cataract surgery.

10.1.1 Justification for Exclusion of Children under 14 Years of Age

Children under 14 years of age are not eligible to enroll on this study because they would typically require general anesthesia for safe administration of cataract surgery, which is not being provided in this study.

10.1.2 Justification for Exclusion of Pregnant Women

Pregnant women are not eligible for this study because of the risk to the fetus for potential systemic absorption of medications such as anesthetic or oral steroids as no studies have yet demonstrated the safety of such drugs in fetuses. Cataract surgery is elective and waiting until after pregnancy is not expected to alter final surgical outcome.

10.1.3 Justification for Inclusion of Children over 14 Years of Age

Children over 14 years of age are eligible for this study as Ebola affects children and it is anticipated that children over age 14 will be to comply with the procedures required for this study; however, those who are unable to do so will be excluded.

10.1.4 Justification for Inclusion of Adults Who Cannot Consent

Adults who are unable to consent are eligible for enrollment because the study has the prospect for direct benefit and because data obtained from these individuals are necessary to answer important scientific questions about this disorder. Similarly, enrolled participants who lose the ability to provide ongoing consent during study participation may continue in the study.

10.2 Safeguards for Vulnerable Populations

Pregnancy testing will be performed at screening and one week prior to the cataract surgery. Participants with positive pregnancy tests will not proceed to the cataract surgery.

The study investigators have experience working with children and cognitively/decisionally impaired adults. A capacity assessment tool will be used to assess consent capacity, if capacity is in doubt (see Appendix 2). A pediatrician will be available for consultation if necessary.

Lactating women may enroll in this study. If steroids are needed to control inflammation in a lactating woman, then a steroid dosing schedule will be used to minimize effects to the breastfed child. Breastfeeding mothers will not be advised to stop or reduce breast feeding. The timing of steroids will be adjusted for nursing mothers to mitigate impact on nursing children.

11.0 BENEFITS

EVD survivors without evidence of Ebola viral RNA in the aqueous humor will benefit from study participation by receiving cataract surgery under this protocol. Individuals who undergo cataract surgery typically experience a significant improvement in visual acuity and brightness. Cataract surgery is not routinely performed for EVD survivors because the RT-PCR technique used to assess presence of viral RNA is not routinely available in Liberia.

Controls will receive the benefit of cataract surgery on at least one eye, which they could also have outside of the study.

The knowledge gained in this study is expected to help guide ophthalmic surgical decisions made after EVD or possibly also other emerging infectious diseases.

12.0 CONSENT DOCUMENTS AND PROCESS

The consent process follows the process which has been used for the other PREVAIL studies and is consistent with Liberian norms. This meets the criteria outlined in the Federal Policy Protection of Human Subjects Common Rule (45 CRF 46), understanding that NIH OHSRP SOP 20B, which describes NIH IRB responsibilities when reviewing local context considerations for offsite research, authorizes the NIH IRB to approve procedures that are adapted to local context.

The consent involves a two-step process consisting first of a group information session accompanied by the visual aids of a flip-book. All study details are discussed in detail and questions are answered in group format. This is followed by one-on-one consenting with a trained study team member. For this protocol, the entire consent language will be communicated to all potential participants verbally, so that illiterate and visually impaired potential participants receive the same information as everyone else being consented. This will be conducted in Liberian English, which is the local language. The informed consent form contains all required elements. This protocol has a standard consent form for all participants and an assent for participation of minors and individuals without consent capacity.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study. The participants must have the ability to understand and sign an informed consent form, which must be signed prior to enrollment. The participants will have an opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves or benefits lost.

The investigator obtaining consent will document the consent process in the participant's medical record. A signed copy of the informed consent form will be provided to the participant to take home.

12.1 Consent Process for Illiterate Subjects

The process for obtaining informed consent from illiterate subjects is the two-step process described above which includes use of the visual aid flip-book and one-on-one consenting with the consent read out loud to participants in Liberian English.

12.2 Consent Process for Visually Impaired Subjects

Visually impaired subjects will participate in the same consenting process as other subjects which includes the opportunity to spend as much time as necessary to speak one-on-one with the study team member performing the consent who will read the consent out loud to participants in Liberian English and address all topics and questions.

12.3 Consent Process for Minors

Consent for participation of minors will be obtained from parents/guardians (as determined by local Liberian law and custom. Written assent will be obtained from minor subjects.

The investigators will obtain consent from both parents if available, from one parent if the second parent is not available, or from a declared guardian when both parents are not available. This follows the process used in other PREVAIL protocols and approved by the Liberian Ethics Committee and respects Liberian norms for the consenting of minors.

If a pediatric participant reaches age of majority during the course of the study, study investigators with consenting privileges will re-consent the participant following the procedures for consenting adult participants.

12.4 Consent Process for Adults Without Consent Capacity

If during the one-on-one session, the consenting investigator determines the participant's capacity to consent is in question, a capacity assessment tool, the Study Understanding Evaluation Form (Appendix 2), will be used to assess the participant's capacity to consent. If participants successfully answer all questions, consent will proceed per usual. In the event that a potential participant cannot answer all questions, they will be determined to not have the capacity to consent for themselves at that time. Once lack of capacity has been determined, an attempt will be made to find a guardian, as determined by local Liberian law and custom, who can consent on their behalf. If no guardian can be identified, then that individual will not be enrolled in the study. By way of additional background, all adult participants enrolled to date on PREVAIL protocols have had the capacity to consent, and no adults have been declined enrollment in PREVAIL protocols to date for lack of capacity to consent.

12.5 Non-English Speaking Participants

Almost all Liberians speak Liberian English, which is the language used for the standard consenting procedure. In the event that a potential participant does not understand Liberian English, the study team will attempt to identify a non-family member to provide verbal translation of the consent form and will only use a family member to provide the translation if a

non-family member is not available. As way of background, this was rarely required on the PREVAIL protocols. This practice follows Liberian norms.

13.0 DATA AND SAFETY MONITORING

Data gathered during this study will be monitored by the principal investigator for safety and compliance with protocol-specified requirements.

The principal investigator will meet monthly with the lead associate investigators to review summary statistics for participants enrolled, and safety and compliance with protocol-specified requirements, including study-related adverse events. Site visits will be performed during cataract surgery campaigns. If any study-related adverse events occur, they will be reported according to requirements of the local and NIH IRBs.

13.1 Criteria for Stopping the Study

Preliminary post-operative data will be reviewed after 30 cases once available by the principal investigator and lead associate investigators. An improvement in visual acuity is expected from cataract surgery. Therefore, the study will be stopped early if participants on average appear to experience loss of vision. Additionally, transmission of Ebola or death will result in pausing the study until further review by the NIH IRB and Liberian Ethics Committee.

14.0 QUALITY ASSURANCE

The Principal Investigator will oversee the quality assurance process in this study with assistance from the Liberian Principal Investigator, Dr. Amegashie, Adjunct Principal Investigator, Dr. Eghrari, and the following Associate Investigators: Drs. Ross, and Yeh. Monitors will perform QA review at random intervals and will communicate directly with the principal investigator.

15.0 REPORTABLE EVENTS

Reportable events will be tracked and submitted to the IRB as outlined in Policy 801.

16.0 ALTERNATIVE THERAPIES

The alternative to participation is to either not pursue cataract surgery at this time or to pursue cataract surgery outside of the study.

For control participants, this would be standard of care surgery which would be arranged through normal mechanisms in Liberia. Access to cataract surgery is variable in Liberia and depends on geography and means. The public hospital in Monrovia, which treats all patients free of charge, does not currently have the capacity to perform cataract surgery. Surgery is available privately in Monrovia to those with means to pay for it. There are also some free surgical outreach efforts which are performed by a cataract surgeon in regions outside of Monrovia, on a schedule determined by the surgeon.

For Ebola survivors, the ability to get surgery is currently limited by the lack of available safety data. At the completion of this study, additional safety data should be available to better inform standard of care management of Ebola-associated cataracts.

17.0 PRIVACY

All research activities will be conducted in as private a setting as possible.

18.0 CONFIDENTIALITY

Samples and data will be stored using codes assigned by PREVAIL data operations. Data will be kept in in password-protected computers. Samples will be kept in locked storage. Only study investigators will have access to the samples and data.

19.0 CONFLICT OF INTEREST

The NIH guidelines were distributed to all the investigators. There are no conflicts-of-interest to report for NIH investigators. Non-NIH investigators will abide by the conflict-of-interest policies of their own institutions.

20.0 TECHNOLOGY TRANSFER

No technology transfer agreement is in place for this protocol.

21.0 COMPENSATION

An allowance for transportation will assist with travel to the proposed surgical site and to the sites of follow-up study and clinical care visits. There will be no penalty for failure to complete the protocol. The allowance values will be consistent with those used throughout the PREVAIL III

study. The allowance will consist of $20 US for the information session, consenting, screening and for all visits to ELWA Hospital and $10 US for all visits at JFK Hospital. Participants will also receive a $10 US allowance for transportation for clinical care visits which may take place at any designated clinical care site for this study.

Participants will receive compensation for all study visits per standard PREVAIL procedure, where they collect the allowance at JFK for visits at JFK (in the amount of $10 US) and collect the allowance at ELWA for visits at ELWA (in the amount of $20 US, which is increased in amount since ELWA is a further transportation distance for most of the participants). In addition, participants will receive free of charge housing and food when they are at the ELWA location overnight, such as the night before and after cataract surgery. In addition, participants will receive a travel allowance (in the amount of $10 US) for any additional clinical eye examinations that are required for optimal healing.

Participants from distant locations will be transported to Monrovia free of charge for all visits which require them to be in Monrovia, including for consent, screening, procedures to include aqueous tap and surgery, and certain post-operative visits. Participants from distant locations will be provided transportation, accommodations, and food during the period of time when they must stay in Monrovia to receive consent, examinations including history and physical and screening, surgery, and certain post-operative visits. Local participants from Monrovia will be asked to present the night before surgery and will be provided accommodations and food so that they will be available for surgery the next day. All participants will spend the night after surgery at accommodations provided by the study so that they are available for the postoperative day one visit. Food will be provided whenever participants receive accommodations as part of this study.

22.0 REFERENCES

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5. Bausch DG, Towner JS, Dowell SF, Kaducu F, Lukwiya M, Sanchez A, Nichol ST, Ksiazek TG, Rollin PE. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. J Infect Dis. 2007 Nov 15;196 Suppl 2:S142-7.
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APPENDIX 1: SCHEDULE OF EVENTS

VISIT SCHEDULE	Baseline Screening±	Surgery	Day 1	Day 7	Month 1	Month 3	Month 6	Month 9	Month 12
TARGET DAY FROM SURGERY	(-)30	0	1	7	30	90	120	270	365
VISIT WINDOWS				± 4 days	± 14 days	± 21 days	± 21 days	± 1.5 months	± 1.5 months
GENERAL PROCEDURE/ASSESSMENTS									
Informed Consent	X								
HIV/Syphilis Pre-Counseling[1]	X								
Medical / Ophthalmic History	X								
Physical Examination	X								
HIV/Syphilis Post Counseling[1]		X							
VISUAL ASSESSMENTS									
Presenting Vision	X		X	X	X	X	X	X	X
Pinhole Vision	X		X	X	X	X	X	X	X
Manifest Refraction (BCVA)	X				X	X	X	X	X
Intraocular Pressure (IOP)	X		X	X	X	X	X	X	X
Slit Lamp Examination	X		X	X	X	X	X	X	X
Fundus Examination	X				X	X	X	X	X
Optical Coherence Tomography (OCT)					X	X	X	X	X
Assessment of Adverse Events		X	X	X	X	X	X	X	X
LABORATORY/SAMPLE COLLECTION									
Blood draw	X								
Aqueous humor sampling with RT-PCR*	X								
Urine pregnancy testing	X[2]								
Aqueous fluid tap#		X							
Syphilis and HIV testing[1]	X								
Lens collection[3]		X							

± Screening procedures performed under the PREVAIL protocol may be used if performed within 30 days of the scheduled surgery date.

* For EVD participants only. This will occur after screening and before surgery for EVD participants.

\# For control participants only. This procedure will be performed during the cataract surgery.

1 For participants not previously tested under a PREVAIL protocol.

2 Pregnancy testing will be repeated one week prior to the surgery.

3 All three parts of the lens will be collected.

APPENDIX 2: STUDY UNDERSTANDING EVALUATION FORM

Subject I.D. #: __ __ __ Subject Initials: ___ ___
Protocol IRB # ___ Protocol Title: _____ _____ _

PROCEDURE: Make a subjective judgment regarding item 1 below. Ask the patient questions 2-6. The evaluator may select the language to use in asking the questions in order to help the patient understand them. Subjects can self-consent with total score of 6.

ITEMS: **SCORE**

1. Is the patient alert and able to communicate with examiner? _____
0= no 1= yes

2. Ask the patient to describe the purpose of the study
0= not able to describe or doesn't answer 1= able to describe

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3. Ask the patient to name at least two (2) potential risks incurred as a result of participation in the study.
0 = not able to list or doesn't answer 1 = able to list two risks

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_____ _____

4. Ask the patient to name at least two (2) things that will be expected of him/her to do while in the study.
0 = not able to list expectations, or doesn't answer 1 = able to list two expectations

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_____ _____

5. Ask the patient to explain what he/she would do if he/she decides not to participate in the study any longer.
0 = doesn't know or doesn't answer, 1 = talk to any staff member

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_____ _____

6. Ask the patient to explain what he/she would do if he/she is experiencing distress or discomfort.
0 = doesn't know, or doesn't answer 1 = talk to any staff member

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TOTAL _____

SIGNATURES

I hereby certify that the above patient is alert, able to communicate and able to give acceptable answers to items 2-6 above. ___ ___

_____ _____ _____

Rater Initials Rater Signature Date

Witness Date