Ahmed with Mitomycin-C Comparison Trial (AMC trial)

Manual of Operation

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Francis I. Proctor Foundation, University of California San Francisco
Bascom-Palmer Eye Institute
University of Colorado
University of Maryland
Zhongshan Ophthalmic Center
Asociación para Evitar la Ceguera en México (APEC)

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1. Study Personnel, Collaboration Plan and Study Organizations

This study will be a multicenter prospective single-masked, two-arm randomized clinical trial. Seven centers, including the University of California, San Francisco (UCSF), Bascom-Palmer Eye Institute (BPEI), University of Colorado, University of Maryland, Zhongshan Ophthalmic Center (ZOC) in China and Asociación para Evitar la Ceguera en México (APEC), will jointly enroll for this trial. To ensure the success of this study, we have partnered with UCSF's Francis I. Proctor Foundation (F.I. Proctor Foundation), which is a center that specializes in ophthalmology research.

All sites will be responsible for enrollment, implementation and follow up visits. The Proctor Foundation's role is to serve as the coordinating center, supporting data management and data analysis. UCSF will take the lead on analysis, writing of study-related materials, and journal publications. UCSF will have the most current protocol, consent documents and HIPAA authorization for reference. UCSF has prepared the IRB application for this study. All modifications to the IRB of record will be communicated among sites. UCSF will ensure protection of all study-related data by using de-identified information over a secure server. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy. There will be ongoing communication of problems, interim results, and study closure among all sites.

Multicenter clinical trials require an organizational structure that provides efficient operations and facilitates communication. Investigators at the 6 Clinic Centers are responsible for screening potential study patients, enrolling eligible patients, and following the patients according to the study protocol. An independent Safety and Data Monitoring Committee (SDMC) will monitor all aspects of the study. The primary responsibility of the SDMC is to review the differences in failure rates and the occurrence of adverse events between treatment groups with a view of halting randomization early if treatment benefit or risk is so great for one treatment group that continuation of patient recruitment is deemed unethical. The SDMC will perform an interim analysis to assess for safety once 30% of study participants have completed the 6-month follow-up visit. The SDMC will be led by Philip Chen, MD at the University of Washington and Donald Budenz, MD, MPH at University of North Carolina at Chapel Hill (UNC). The Statistical Coordinating Center (SCC) will receive, edit, process, analyze, and store all de-Identified study data. The SCC will coordinate activities at the Clinic Centers and monitor adherence to the study protocol. The SCC is comprised of Jennifer Rose-Nussbaumer, MD and Travis Porco, PhD, MPH, both of whom are faculty at F.I. Proctor Foundation. The Steering Committee (SC) is composed of the principal investigators from each Clinic Center and this committee has overall responsibility for directing activities and formulating policies for the study.

2. Patient selection:

2.1 Inclusion Criteria:

- Age 18 to 85 years old
- Inadequately controlled glaucoma on maximum tolerated medical therapy with IOP ≥ 18 mm Hg
- Ahmed Glaucoma Valve (AGV) implantation as the planned surgical procedure
- For patients in whom 2 eyes are eligible for enrollment, only the first eligible eye to be implanted is enrolled.

2.2 Exclusion Criteria:

- Unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits
- Pregnant or nursing women
- Previous cyclodestruction or glaucoma drainage device (GDD) surgery
- Patients with nanophthalmos
- Patients with Sturge-Weber syndrome or other conditions associated with elevated episcleral venous pressure

- Need for glaucoma surgery combined with other ocular procedures except cataract extraction (i.e., penetrating keratoplasty, or retinal surgery) or anticipated need for additional ocular surgery

- Previous scleral buckling procedure or silicone oil present

- Uveitic glaucoma, if patient have had active inflammation during last six months (we will include uveitic glaucoma patients if they haven't had active inflammation for more than 6 months)

3. Randomization Scheme:

The study patients will be stratified by each Clinic Center into 3 categories based on type of glaucoma: (1) primary glaucomas, (2) secondary glaucomas (excluding neovascular glaucoma), and (3) neovascular glaucoma. Within each stratum, the patients will be randomized into two arms, either AGV with Mitosol® (for national centers) or Mitomycin-C (MMC) (for international centers) adjunctive treatment or AGV with Balanced Salt Solution (BSS) sham treatment. A randomization of 100 patients will be predetermined by the Proctor SCC before the trial starts based on block randomization using a computer program (Statistical package R; Version 3.1; R Foundation for Statistical Computing, Vienna, Austria). This randomly permuted block scheme has varied block sizes between 2 and 6 with an equal number of patients randomized to each treatment group and within each stratum.

During the trial, after informed consent is obtained and the SCC confirms patient eligibility, the local study coordinator (LSC) at each Clinic Center will assign the study participant an identification number (ID, alpha-numeric code) that will serve as the patient's ID on all study documents. The LSC at each center will login to the REDCap database and input the patient's study ID. Randomization to AGV with Mitosol®/MMC adjunctive treatment or AGV with sham treatment occurs at the time when the patient is enrolled in the study using the REDCap database. Once the patient has been randomized to a treatment arm, they will remain in the intention to treat analysis. Clinical information will be collected via baseline patient forms, follow-up patient forms, final visit patient forms and adverse event forms. The data will be entered into REDCap database by LSCs. The SCC will not have identifiable patient information and de-identified information will be shared using a password that is only known by each Clinic Center.

4. Study Visits

4.1 Baseline Visit

During this visit, eligible patients at each center will give informed consent and be enrolled in the study. A comprehensive eye exam including visual acuity (VA), intraocular pressure (IOP), gonioscopy, slit lamp exam, and dilated fundus exam will be performed, along with pachymetry, specular microscopy and perimetry, to establish a baseline. If diplopia exists, a basic motility test will also be performed. The baseline patient form will be completed.

4.2 Surgery Visit

The enrolled study participant will undergo either AGV with Mitosol®/MMC or BSS (sham) adjunctive treatment surgery.

4.3 Follow-Up Visits

During the postoperative Day 1, Week 1, Month 1, 2, 3 and 6 follow-up visits, VA, IOP, slit lamp exam, dilated fundus exam will be performed. The follow-up patient form will be completed. Mitosol®/MMC or BSS injection will be scheduled on postoperative week 1 and month 1.

4. 4. Final Visit

During the 12-month postoperative final visit, a comprehensive eye exam including VA, IOP, slit lamp exam, dilated fundus exam, specular microscopy and pachymetry will be performed. If diplopia exists, motility will be tested. The final status and follow-up patient forms will be completed.

5. Procedures

5.1 Masking

All study participants will be masked to their intervention. Surgeons will not be masked. Technicians performing study exams and imaging will be masked. The LSC at each Clinic Center will not be masked.

5.2 Mitosol®/MMC and BSS Sham preparation

Mitosol®/MMC (0.4mg/ml) will be prepared by the pharmacy within each Clinic Center. Prior to AGV surgery and follow-up appointments when Mitosol®/MMC or sham treatment is scheduled to be given, if the subject is in the Mitosol®/MMC arm, the LSC at each center will order Mitosol®/MMC. Mitosol®/MMC will be handled based on protocol for chemotherapy agents at each Clinic Center. If the subject is in the BSS arm, BSS will be either ordered or available in clinic depending on each Clinic Center's set up.

5.3 Surgical Procedure

A standard technique for AGV implantation is used, while allowing the surgeon latitude to perform the procedure in a manner with which he or she feels comfortable. The type of anesthesia is at the surgeon's discretion. An Ahmed FP-7 is used in all cases, and implantation is performed in the superotemporal quadrant. Depending on the randomized treatment, Mitosol®/MMC (0.4 mg/ml) or BSS injection will be injected into the subconjunctival space at 8-9mm from limbus. After 1 minute, this area is then copiously irrigated with BSS. A fornix-based conjunctival flap will be used. Sufficient exposure is obtained in the superotemporal quadrant to permit placement of the Ahmed end plate. A corneal traction suture may be used to rotate the globe inferonasally to improve exposure. After dissection, a 30-gauge cannula is used to prime the Ahmed valve. The Ahmed end plate is sutured to sclera at a measured distance 8-10 mm posterior to the limbus using the two fixation holes on the device. The type of nonabsorbable suture used for end plate fixation is determined by the surgeon. The tube is trimmed with an anterior bevel to extend 2-3 mm into the anterior chamber. A 23-gauge needle is used to enter the anterior chamber at the posterior limbus, parallel to the iris plane. The Ahmed tube is inserted through this entry incision and should be well positioned in the anterior chamber away from the corneal endothelium and above the iris plane. A donor patch graft composed of sclera, cornea, or pericardium is used to cover the limbal portion of the tube. The patch graft material and suture selected to fixate the patch graft are the surgeon's choice. The conjunctiva and Tenon's capsule are closed in keeping with the surgeon's usual practice. A subconjunctival antibiotic and corticosteroid are injected at the end of the case. A cycloplegic-mydriatic drop and steroid-antibiotic ointment may be instilled at the conclusion of the case, as determined by the surgeon in keeping with his or her usual practice.

5.4 Postoperative Mitosol®/MMC or BSS Sham Injection

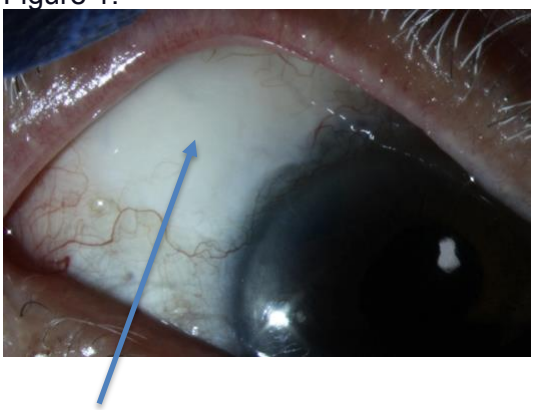
Subconjunctival injection of Mitosol®/MMC (0.4mg/ml) or BSS for 0.1ml is scheduled in the region of the end plate at 1 week and 1 month. The injectable medication will be prepared at each Clinic Center based on treatment assignment. The doctors performing injections will be able to identify whether Mitosol®/MMC or BSS is being used. In order to perform the injection, the conjunctiva will be anesthetized first by applying a topical anesthetic (such as proparacaine). Cotton tips soaked with 4% lidocaine will be applied to conjunctiva over injection area. Then 0.1 ml of 1% lidocaine will be injected subconjunctivally, which usually results in formation of an elevated "blister." Using a 30-gauge needle, another 0.1 ml Mitosol®/MMC (0.4%) or BSS, depending on treatment assignment, will be injected within the previously formed "blister" into a space between the conjunctiva and Tenon's capsule. The eye will then be copiously irrigated with BBS.

On postoperative week 1 visit, subconjunctival Mitosol®/MMC or BSS injection will be given depending on the treatment assignment. The injection will be held if any of the following conditions exist: IOP <5, wound dehiscence, choroidal detachment, shallow or flat anterior chamber, or conjunctiva over the plate of Ahmed valve is completely white and avascular (Figure 1). The patient will then be seen depending on the clinical situation. In that situation, injection will not be given within the postoperative month 1.

On the visit scheduled for the 2nd injection at 1month postoperative follow-up, injection will be held if any of the following conditions exist: IOP <5, wound dehiscence, choroidal detachment, shallow or flat anterior chamber, or conjunctiva over the plate of Ahmed valve is completely white and avascular (Figure 1). The patient will then

be followed for a clinically appropriate interval for the complication, and the 2nd injection will be given if the complication is resolved at a follow-up visit before postoperative month 3. Should the complication persist beyond postoperative month 3, no 2nd injection will be administered.

Figure 1:



The arrow points to the complete white and avascular conjunctiva over the plate of Ahmed valve.

5.5 Postoperative medication management

After the surgery, all subjects will receive an antibiotic drop to be used 4 times daily for 1 week, and a topical steroid (prednisolone acetate 1%) starting 4-6 times daily and tapered over 4 to 8 weeks depending on surgeon's preference and degree of inflammation.

Because early aqueous suppressant treatment may improve AGV implantation outcomes and reduce hypertensive phase frequency [21, 25], when IOP is above 10mmHg in either treatment arm, medications that primarily suppress aqueous humor production will be used according to the surgeon's discretion. Medications that can be used for aqueous suppression include timolol 0.5%, dorzolamide 2%, brinzolamide 1%, or brimonidine 0.1% or 0.15% or 2%. If IOP is still not controlled, as determined by the treating physician, additional therapy, including oral systemic medical therapy, laser therapy or additional surgical therapy, may be performed.

5.6 Examinations during each visit and study schedule

A list of study measurements for scheduled follow-up visits is shown in Table 1. Baseline demographic and clinical information will be collected for enrolled patients at baseline visit. The follow-up appointment schedule will be generated based on the date of surgery for each patient by REDCap. The study entry date is recorded as the date of surgery.

Follow-up visits are scheduled 1 day, 1 week, 1 month, 2 months, 3 months, 6 months and 12 months postoperatively. Patients can be brought back sooner than the required study visits if there is a postoperative complication. The follow-up study form will be filled out for those visits. Adverse event forms may be completed if appropriate. All scheduled visits would be expected in normal postoperative care. Each examination includes measurement of Snellen VA, IOP, slit-lamp biomicroscopy, and ophthalmoloscopy. Humphrey perimetry will be performed at the baseline visit to establish the severity of glaucoma. Early Treatment Diabetic Retiopathy

Study (ETDRS) VA, pachymetry, and specular microscopy will be checked at baseline and at the 6-month and 12-month follow-up visits.

Table 1: Study Protocol

	Baseline	1day	1week	1mo	2mos	3mos	6mos	12mos
Mitosol®/MMC injection			X*	X*				
Snellen Acuity	x	x	x	x	x	x	x	x
ETDRS Acuity	x						x	x
IOP (Applanation)	x	x	x	x	x	x	x	x
Motility	If diplopia present						If diplopia present	If diplopia present
Pachymetry	x						x	x
Specular microscopy	x						x	x
Gonioscopy	x							
SLE	x	x	x	x	x	x	x	x
Ophthalmoscopy	x	x	x	x	x	x	x	x
Perimetry	x							x

* 1st Injection will be held for IOP <5, wound dehiscence, choroidal detachment, shallow or flat anterior chamber, or conjunctiva over the plate of Ahmed valve is completely white and avascular at postoperative week #1 visit. In that situation, injection will not be given within the postoperative month 1.

On the visit scheduled for the 2nd injection at 1-month postoperative follow-up, injection will be held if any of the following conditions exist: IOP <5, wound dehiscence, choroidal detachment, shallow or flat anterior chamber, or conjunctiva over the plate of Ahmed valve is completely white and avascular. The patient will then be followed for a clinically appropriate interval for the complication, and the 2nd injection will be given if the complication is resolved at a follow-up visit before postoperative month 3. Should the complication persist beyond postoperative month 3, no 2nd injection will be administered.

6. Assessment of Primary and Secondary Outcomes

Technicians who perform the ocular tests should be masked to treatment assignment. The primary outcome of the study is IOP at postoperative 6 months. The secondary outcome is failure rate, which is defined by the following criteria: (1) IOP >21 mmHg or reduced < 20% from baseline at 12-month follow-up, (2) IOP ≤ 5 mmHg at 12-month follow-up with best corrected VA decreased ≥ 2 lines from baseline, (3) use of oral anti-hypertensive medication (acetazolamide or methazolamide), (4) loss of light perception vision, (5) reoperation for glaucoma, or (6) removal of implant. Successful repair of a retracted or occluded shunt will not be considered a failure, although all complications will be listed and analyzed. Eyes that have not failed and are not on supplemental medical therapy are considered complete successes. Eyes that have not failed but require supplemental medical therapy are defined as qualified successes.

Two alternative IOP cutoffs, 18 mmHg and 15 mmHg, will also be used in secondary analyses as suggested by the World Glaucoma Association's Guidelines on Design and Reporting of Surgical Trials.[46] All other criteria for failure are the same as in the primary analysis as outlined above.

Other outcome measures include VA, frequency of hypertensive phase (IOP increase to more than 21 mmHg in the first 6 months after surgery), number of topical medications and complication rates.

Visual Acuity. Distance VA is measured before pupil dilation, tonometry, gonioscopy, or other tests that could affect vision. Manifest refraction is performed before measurement of VA at the baseline examination and 12-month follow-up visit. VA will be measured using two techniques. Snellen VA is measured at the baseline examination and every follow-up visit. The Early Treatment Diabetic Retinopathy Study (ETDRS) VA[47] is tested at the baseline examination, 6-month and 12-month follow-up. The participating clinician will need to specify a cause for Snellen VA less than 20/30 at the baseline examination, or decrease in VA by 2 or more lines from baseline at the 6-month and 12-month follow-up.

Intraocular Pressure. IOP will be measured at all visits. Goldmann applanation tonometry will be used to measure IOP, however, for patients with irregular corneal astigmatism, corneal scarring, or corneal edema, which affect accurate measurement, pneumatonometer or Tonopen (Reichert Technologies, Depew, NY) will be used. The right eye is to be measured first and the left eye measured second. Two consecutive measurements will be taken for the study eye. If the first 2 measurements differ by > 1 mm Hg, a third measurement will be taken. If the first 2 measurements differ by 1 mm Hg or less, the IOP for the given eye will be the average of the 2 readings. If the difference between the first 2 measurements is > 1 mm Hg, the IOP for the given eye will be the median of the 3 readings. Efforts will be made to schedule follow-up visits at similar time of the day to minimize the effect of diurnal IOP fluctuation.

Pachymetry. Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea at baseline examination, 6-month, and 12-month follow-up visit. Contact pachymetry will be performed after IOP measurement and before gonioscopy.

Gonioscopy. Gonioscopy will be performed at the slit lamp at baseline examination using either a Zeiss-type indentation gonioprism or a Goldmann-type nonindentation gonioprism. The purpose of the preoperative examination of the anterior chamber angle is to document neovascularization, peripheral anterior synechiae, and to identify an appropriate implantation site for the tube.

Motility Assessment. Transient diplopia is not uncommon after tube shunt surgery. The effect of local Mitosol®/MMC injection on nearby muscles is also unknown. To address this issue, a motility assessment is performed in all patients at baseline, 6-month and 12-month visits if diplopia is reported by patients.
During each motility examination, the cover–uncover and alternate cover tests will be performed at primary gaze, upgaze, downgaze, left gaze, and right gaze for both distance and near targets. Any heterophoria or heterotropia will be documented. The deviation will be measured with a hand-held prism. In patients who are unable to fixate for cover testing, the deviation will be measured by centering the corneal light reflexes with a prism using the modified Krimsky method.

Slit-Lamp Biomicroscopy. Examination of the anterior segment using slit-lamp biomicroscopy is performed at the baseline assessment to document preoperative status and at all follow-up examinations to detect any changes during the course of the study that may be attributable to the disease or treatment. Mitosol®/MMC may slow wound healing; therefore, the presence or absence of plate or/and tube exposure or wound dehiscence will be examined and documented at each visit. In addition, placement of tube shunt may lead to long-term damage to the cornea; therefore, tube position and length within the anterior chamber in relation to the cornea and iris on slit-lamp examination will be documented at each study visit.

Ophthalmoscopy Examination. A dilated fundus examination will be performed at all visits. At the baseline examination, particular attention is paid to detect signs of proliferative retinopathy, retinal neovascularization, vitreous hemorrhage, or preretinal hemorrhage. At all postoperative follow-up visits, ophthalmoscopy is performed to evaluate posterior segment complications of surgery, such as serous choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy.

Specular Microscopy: Endothelial cell density will be assessed using specular microscopy performed on the central cornea at baseline examination, 6-month and 12-month follow-up visit. Three images are to be acquired and transmited to the SCC, and the best quality image will be selected for quantitative analysis of central

endothelial cell density, determined by manual cell count at a reading center.

Perimetry. Visual field examinations will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or Swedish Interactive Thresholding Algorithm [SITA] Standard**,** size III, white stimulus, Carl Zeiss Meditec, Dublin, CA). Visual field testing will be performed before tonometry, gonioscopy, or other technique that could affect vision. A visual field is attempted in any eye that has vision equal or better than finger counting at a distance of 2 feet. Perimetry will be performed before surgery (within 1 month of enrollment in the study) to establish the severity of glaucoma and one year after surgery.

7. Management of Breach of Protocol

7.1 Instructions for the Patients

Patients will be instructed to strictly follow the study visit schedule and to report all changes in their condition to the Clinic Center. Patients will also be reminded to contact the study site if they are experiencing any difficulties during their study participation. Patients will be reminded of the importance of medication compliance during each postoperative visit and provided with written and oral instructions on the medication regimen.

7.2 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well being of patients during the study period. Follow-up study forms should be completed for each unscheduled visit. An assessment of any adverse event should be completed.

7.3 Compliance with Protocol

Patients must be able to adhere to the study visit schedule. Patient screening and enrollment should strictly follow appropriate inclusion, exclusion, and treatment criteria as described in the protocol. At each study visit, patients will be asked if they have used their eye drops as instructed and whether they have used any concomitant medications/therapies or had any concurrent procedures since the previous visit. Patients should be scheduled for study visits as closely to the day specified in the visit schedule as possible.

The investigator at each Clinic Center must adhere to the study protocol and randomization. Any violation of the protocol will be reported to the HSC to decide whether the corresponding study participant should stay in the trial. The SCC will be informed of the decision to allow for appropriate data management.

7.4 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. Notification of early patient discontinuation from the study and the reason for discontinuation will be sent to the SCC and will be clearly documented on the appropriate case report form.

7.5 Withdrawal Criteria

The investigator should consider withdrawing a patient from the study early if any of the following criteria are met:

1. Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk by continuing study participation
2. Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, compromises the patient's ability to participate in the study
3. Patient is unwilling or unable to continue to comply with study procedures
4. Patient is unwilling or unable to continue in the study

Whenever possible, the decision to withdraw a patient from the study or study treatment should be discussed with SCC.

7.6 Study Termination

The study may be stopped at his/her study site at any time by the site investigator.

8. Diagnoses and Management of Adverse Events (AEs)

8.1 Definitions of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient who has received AGV in this trial and that does not necessarily have a causal relationship with this treatment. However, progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

During 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 subject's chart and the AE form.

8.2. Manage Adverse Event

All AEs should be followed until they are resolved or until a stable clinical endpoint is reached. Each AE is to be classified by the Investigator as SERIOUS (SAE) or NONSERIOUS (NSAE). A SAE is any adverse event that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity.

If a SAE occurs, the investigator at each study site must verbally and/or in writing notify their medical center or its designee within 24 hours of the occurrence of the SAE. The initial SAE report must be followed by a written report, signed by the investigator, and received by their medical center or its designee via fax within two working days. The investigator must provide written follow-up reports until the SAE or clinically significant AE has resolved or until a stable clinical endpoint is reached. Notification of an SAE or clinically significant AE must also be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) in accordance with its requirements. All AEs must be reported from the time that the subject provides informed consent through the last study visit.