# Ahmed with Mitomycin-C Comparison Trial (AMC trial)

## Statistical Analysis Plan

NCT02805257

December 12, 2017


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The Ahmed glaucoma valve (AGV) is one of the most commonly used glaucoma drainage devices (GDDs). AGV has a good safety profile compared to other glaucoma surgeries, but its application is limited by unsatisfactory long-term outcomes.[1, 2] The body's natural healing response leads to fibrotic scar tissue formation, encapsulating the device and blocking fluid outflow. Mitomycin C (MMC), an antifibrotic agent, has been broadly used intraoperatively in trabeculectomies to improve surgical outcomes. Unfortunately, intraoperative use of MMC in AGV has not been demonstrated to improve the success rate of this surgery.[3, 4] One explanation is that the AGV plate may serve as a constant stimulus for foreign body reaction, which may overcome the antifibrotic effect from a single intraoperative MMC use.[3, 5] A proposed solution for this problem is to administer subsequent postoperative MMC injections during the recovery phase when fibrotic repair occurs. Interestingly, retrospective clinical studies indicate that combined intraoperative and postoperative application of antifibrotic agents significantly improves AGV surgical performance without compromising its safety profile.[6, 7] However, no prospective study has been conducted. To further test the role of MMC in AGV use, we propose a multicenter prospective double-masked, two-arm randomized clinical trial. This study will examine initial surgical outcomes, including early and intermediate intraocular pressure (IOP) control and postoperative complications, and will serve as a pilot trial to prepare for a NIH-sponsored study to address longer term outcomes and complications in a larger cohort.

**Specific Aim 1: To compare the surgical outcomes at 12-month follow-up after AGV implantation between patients receiving adjunctive intraoperative and postoperative MMC therapy versus those receiving sham therapy.** We hypothesize that adjunctive MMC application during and after AGV implantation improves IOP control and decreases the failure rate without compromising postoperative visual acuity at 6-months follow-up.

**Specific Aim 2: To compare the frequency of hypertensive phase at 6-month follow-up after AGV implantation between patients receiving adjunctive MMC therapy and those receiving sham therapy.** We hypothesize that adjunctive MMC application decreases the occurrence of the hypertensive phase.

**Specific Aim 3: To compare the rate of complications within 12-month follow-up between patients receiving adjunctive MMC therapy and those receiving sham therapy with AGV implantation.** We hypothesize that there will be a slight increase in non-serious postoperative complications, but not in vision threatening complications, in patients who receive MMC with AGV implantation compared to sham therapy.

This study will be a multicenter prospective double-masked, two-arm randomized clinical trial. The primary objective is to compare the IOP in patients undergoing AGV with and without adjunctive MMC therapy. Six centers, including Bascom-Palmer Eye Institute, UCSF, University of Maryland, Tulane University, Zhongshan Ophthalmic Center (ZOC) in China, and Asociación para Evitar la Ceguera en México I.A.P.(APEC) in Mexico, will jointly enroll subjects for this trial. Study participants will be stratified prior to randomization into three groups: 1) Primary glaucoma, 2) Secondary glaucoma except Neovascular glaucoma, and 3) Neovascular glaucoma. Both participating surgeons and study participants will be masked to treatment assignment.

Study participants will be randomized to one of two treatment arms: 1) AGV with MMC (0.4%) intraoperative application and postoperative injections, or 2) AGV with sham injection of balanced salt solution. Based on preliminary studies and clinic experience, a maximum of two postoperative MMC injections will be given.

**Specific Aim 1: To compare surgical outcomes at 12-month follow-up after AGV implantation between patients receiving adjunctive intraoperative and postoperative MMC therapy versus those receiving sham therapy.** The primary goal of glaucoma surgery is to decrease IOP, therefore the primary outcome measure for our study is IOP at 12-months follow-up. Medication washout will not be considered before the final visit because IOP spike after medication washout may cause permanent damage for study participants due to the severity of glaucoma in patients who need AGV placement. A secondary outcome measure is rate of treatment failure. Failure will be defined as meeting any of the following criteria: (1) IOP >21 mmHg or reduced < 20% from baseline at 12-month follow-up, (2) IOP ≤ 5 at 12-month follow-up with best corrected visual acuity 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. Eyes that have not failed and are not on supplemental topical medical therapy are considered complete

successes. Eyes that have not failed but require supplemental topical medical therapy are defined as qualified successes. The third outcome measures are the number of anti-glaucoma medications and the ETDRS visual acuity at 12-months follow-up.

**Specific Aim 2: To compare the frequency of the hypertensive phase at 6-month follow-up after AGV implantation between patients receiving adjunctive MMC therapy and those receiving sham therapy.** In this study, the hypertensive phase is defined as an IOP of more than 21 mmHg in the first 6 months after surgery.

**Specific Aim 3: To compare the rate of complications within 12-month follow-up between patients receiving adjunctive MMC therapy and those receiving sham therapy with AGV implantation.** The application of MMC during trabeculectomy improves treatment success, but is associated with higher instances of postoperative complications.[11-15] Thus it will be important to monitor for postoperative complications in the setting of MMC application. Both intraoperative and postoperative complications will be compared between the two arms. Intraoperative complications include hyphema and suprachoroidal hemorrhage. Early and late postoperative complications include tube occlusion with iris or vitreous, choroidal effusion, suprachoroidal hemorrhage, cystoid macular edema, shallow anterior chamber, hypotony maculopathy, endophthalmitis, cataract, diplopia, corneal edema, tube or shunt erosion, uveitis, and tube malposition.

Because of potential corneal toxicity from MMC, corneal endothelial cell density (ECD) will be monitored. Significant endothelial cell loss has been reported during or immediately after trabeculectomy with MMC application. However, no progressive cell loss was observed postoperatively beyond 3 months.[43-46] In this trial, central ECDs measured by specular microscopy and central corneal thickness by ultrasound pachymetry will be monitored at baseline, 6 months and 12 months postoperatively.

**Sample Size Calculation:**

Sample size calculation for this study is based on the primary outcome of IOP. In our retrospective study comparing AGV implant with intraoperative and postoperative antifibrotic agents versus AGV implant without these agents, we found approximately 4.0 mmHg lower mean IOP in the antifibrotic-agent treated groups with a standard error of 1.4 mmHg.[7] With 50 patients per arm, we conservatively estimate that we would have at least 80% power to detect a 2 mmHg or more IOP difference between groups with a two-tailed alpha of 0.05, assuming a standard deviation in IOP of 3 mmHg and 15% loss to follow up. The criterion of detecting 2 mmHg difference in IOP has been used in several large glaucoma trials[47,48] and the dropout rate of 15% is decided based on recent glaucoma trial experience[49]. We anticipate that stratification will not cause appreciable changes in sample size calculation.[50]

**Statistical Considerations:**

For specific aim 1, the primary outcome variable is IOP measured at 12 months. This will be analyzed using linear regression, considering the stratified randomization. Analysis will be two sided at alpha of 0.05. Secondarily, we will analyze success (as a binary outcome), the number of glaucoma medications, visual acuity, and time to failure. For specific aim 2, the occurrence of a hypertensive phase will be compared using logistic regression, adjusting for the stratified design. For specific aim 3, complications will be compared between groups using logistic regression. Tabulations of each complication will be prepared. The central ECD and pachymetry difference between the two arms will be compared at 6 and 12 months with linear regression, adjusting for the stratified design. Further details of the statistical plan will be provided in the Manual of Operations.

**Data Management and Sharing Plan:**

For this trial, the REDCap database platform will be used for data entry/collection. To save participating surgeons' time, data will be collected via paper study forms, and then entered into the REDCap database via double data entry methods at the enrollment site during every visit. All data will be stored and transferred using a secure database server with de-identified information. To ensure the success of this study, we have partnered with UCSF's F. I. Proctor Foundation, which is a center that specializes in ophthalmology research. The Proctor Foundation's role is to serve as the coordinating center, supporting data management and data analysis.

We will take steps to keep participants' personal information confidential. Health information will be kept secure and separate from information that identifies participants. Upon enrollment, participants will be assigned

a code that will be used instead of their name, medical record number or other personal identifying information. Electronic files for data analysis will contain only the participant code. Information may be released to others outside of the enrollment center, but information which could identify the participant will be kept secure. Data management and sharing plan will be fully discussed in the Manual of Operation.

- low-up period to study long-term IOP control and late stage complications.