PRIMARY TUBE VERSUS TRABECULECTOMY (PTVT) STUDY

Manual of Procedures

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1. Introduction

1.1 Background and Significance

1.2 Objective

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1.1 Background and Significance

Glaucoma surgery is indicated when further intraocular pressure (IOP) reduction is needed despite the use of maximum tolerated medical therapy and appropriate laser treatment. Trabeculectomy (or guarded filtration procedure) is the most frequently performed glaucoma operation. Eyes with previous ocular surgery and certain secondary glaucomas, such as neovascular glaucoma and uveitic glaucoma, are at great risk of trabeculectomy failure. Wound healing modulation with antifibrotic agents, like mitomycin C (MMC) and 5-fluorouracil (5-FU), has been shown to increase the success of glaucoma filtering surgery in high risk eyes.[1-3] The use of MMC and 5-FU in glaucoma surgery has become widespread in clinical practice. The improved efficacy of trabeculectomy with an adjunctive antifibrotic agent in high risk eyes has prompted their use in eyes considered to be at low risk for failure. A randomized clinical trial found similar IOP reduction and surgical complications with the intraoperative application of MMC and 5-FU in eyes undergoing primary trabeculectomy.[4]

Although antifibrotic agents have increased the likelihood of IOP control following glaucoma filtering surgery, they have also increased the risk of complications.[1-3] The prevalence of bleb-related infections, bleb leaks, and bleb dysesthesia associated with a perilimbal filtering bleb suggests the need to consider alternative surgical approaches. Favorable results have been reported with tube shunts (or glaucoma drainage implants),[5-13] and these devices have been growing in popularity.[14,15] In particular, the large surface of the Baerveldt glaucoma implant (Advance Medical Optics, Santa Ana, California) combined with its ease of insertion in a single quadrant offers an advantage over other tube shunts. Similar surgical results have been reported with tube shunts and trabeculectomy with MMC or 5-FU when studied separately in similar patient groups.[5-13,16-24] A comparable rate of serious complications has also been reported for the Baeveldt implant and trabeculectomy with an antifibrotic agent in a retrospective study.[25]

The Tube Versus Trabeculectomy (TVT) Study is a multicenter randomized clinical trial comparing the safety and efficacy of tube shunt surgery using the Baerveldt implant and trabeculectomy with MMC in 212 patients with previous ocular surgery.[26] Tube shunt surgery was more likely to maintain IOP control and avoid persistent hypotony or reoperation for glaucoma than trabeculectomy with MMC during the first year of follow-up in the TVT Study.[27] Tube shunt surgery and trabeculectomy with MMC produced similar IOP reduction at 1 year, but there was less need for supplemental medical therapy following trabeculectomy. There were a large number of surgical complications during the first year of follow-up in the TVT Study, but most were transient and self-limited.[28] The incidence of postoperative complications was higher following trabeculectomy with MMC than tube shunt surgery. However, severe complications resulting in reoperation and/or vision loss occurred with similar

frequency with both surgical procedures. Vision loss occurred at a similar rate following tube shunt surgery and trabeculectomy with MMC. Patients who experienced surgical complications had greater vision loss than patients without complications.

A randomized clinical trial by Wilson and colleagues compared the Ahmed glaucoma valve implant (New World Medical, Inc., Rancho Cucamonga, California) and trabeculectomy with and without and adjunctive antifibrotic agent in 117 patients.[29] Lower mean IOP was observed in the trabeculectomy group after a mean follow-up of 9.7 months, and the Ahmed group had a greater adjunctive medication requirement. The cumulative probability of success was similar between the two treatment groups. This study was performed in Saudi Arabia and Sri Lanka, and it included patients with all glaucoma types and some eyes that had undergone previous ocular surgery. A follow-up study continued enrollment in Sri Lanka to a total of 123 patients with primary open-angle glaucoma and primary angle-closure glaucoma without previous ocular surgery.[30] Lower mean IOP was noted in the trabeculectomy group than the Ahmed group during the first year of the study. However, the IOPs were similar between treatment groups with longer follow-up, and there was no difference in the cumulative probability of success.

1.2 Objective

The objective of this study is to compare the long-term safety and efficacy of placement of a 350-mm^2 Baerveldt glaucoma implant and trabeculectomy with mitomycin C in patients who have not had previous ocular surgery. Outcome discrimination between the two treatment groups will be made using typical measures of visual function (visual acuity and visual field), IOP, need for supplemental medical therapy, surgical complications, and reoperation for glaucoma or complications.

1.3 References

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2. Study Design

2.1 Inclusion Criteria

2.2 Exclusion Criteria

2.3 Sample Size Calculations

2.4 Randomization

2.5 Masking

2.6 Failure Criteria

2.7 Timetable for the Study

2.1 Inclusion Criteria

All of the criteria listed below must be present in the study eye in order for the patient to be eligible for enrollment in the study.

a. Age 18 to 85 years, inclusive.

b. Glaucoma that is inadequately controlled on tolerated medical therapy with intraocular pressure greater than or equal to 18 mm Hg and less than or equal to 40 mm Hg.

c. No previous incisional ocular surgery (including keratorefractive surgery).

2.2 Exclusion Criteria

If any of the following exclusion criteria are present in the study eye, the patient may not be entered into the study.

a. Unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits.

b. Pregnant or nursing women.

c. No light perception vision.

d. Narrow anterior chamber angle.

e. Iris neovascularization or proliferative retinopathy.

f. Iridocorneal endothelial syndrome.

g. Epithelial or fibrous downgrowth.

h. Chronic or recurrent uveitis.

i. Steroid-induced glaucoma.

j. Severe posterior blepharitis.

k. Unwilling to discontinue contact lens use after surgery.

l. Previous cyclodestructive procedure.

m. Conjunctival scarring from prior ocular trauma or cicatrizing disease (e.g. Stevens Johnson syndrome, ocular pemphigoid) precluding a superior trabeculectomy.

n. Functionally significant cataract.

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

2.3 Sample Size Calculations

Sample size calculations were determined based on projected rates of complications and surgical success in each treatment group. The results are shown in Table 1. Enrollment of 88 patients in each treatment group, or a total of 176 patients, is expected to generate statistically valid conclusions for the study. An attrition rate of 6% per year is anticipated. Therefore, enrollment in the study will be offered to a total of 242 patients, including 121 patients in each treatment group.

2.4 Randomization

Since the purpose of this study is to compare the safety and efficacy of two surgical procedures used in the management of glaucoma, a trabeculectomy with mitomycin C and Baerveldt glaucoma implant, randomization techniques are used to assure an unbiased treatment assignment to patients.

Stratification:

Previous studies have suggested that younger patients and those of African American ethnicity are at greater risk of failure with standard filtering surgery. It also seems logical to assume that a patient who has failed glaucoma filtering surgery in one eye would be at greater risk for surgical failure in the fellow eye. Therefore, patients will be stratified based upon the following prognostic factors:

1. Age (< 50 years or $\geq$ 50 years)

2. Ethnicity (African American or other)

3. Previous failed filtering surgery in the nonstudy eye (present or absent)

Randomization:

A procedure is used to randomly assign patients to treatment with either a Baerveldt glaucoma implant or trabeculectomy with mitomycin C. At each Clinical Center, half of the patients in each stratum will receive a Baerveldt glaucoma implant and half will receive a trabeculectomy with mitomycin C. Randomization takes place at the time the patient is enrolled in the study.

2.5 Masking

Neither the investigator nor the patient is masked as to which treatment the patient receives.

2.6 Failure Criteria

Failure in the PTVT Study is defined by following criteria:

- IOP > 21 mm Hg or not reduced by 20% below baseline on two consecutive follow-up visits after 3 months
- IOP $\leq$ 5 mm Hg on two consecutive visits after 3 months
- Additional glaucoma surgery
- Loss of light perception vision

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.

2.7 Timetable for the Study

April 2007 to October 2007:

- Prepare Reseach Protocol for the University of Miami Institutional Review Board including a Patient Consent Form.

- Write the Manual of Procedures (Version 1.0).
- Produce data collection forms.

November 2007 to April 2008:

- Meet with potential investigators from selected Clinical Centers and potential members of the Safety and Data Monitoring Committee at the annual AAO Meeting.

- Certify participating Clinical Centers by:
    a. Documenting number of patients who should be eligible.
    b. Identifying physicians at the Clinical Center who have performed requisite number of surgeries using both study treatments.
    c. Documenting IRB approval.

- Produce randomization schedules.

May 2008 to May 2012:

- Recruit and randomize patients.

- Produce follow-up schedule for each randomized patient.

- Monitor submission of forms from Clinical Centers and perform data entry.

- Monitor adverse events by treatment group.

- Perform analyses to monitor for treatment differences and success rates on a routine basis.

May 2012 to May 2013:

- Continue to monitor data for adverse events and differences in success rates between treatment groups.

- Continue to collect follow-up data.

- Perform data analyses on data on the one year outcomes from all patients, and prepare a manuscript.

Table 1. Sample Size Calculations

Complication	Rate		Required Sample Size in Each Group
	Trab	Tube	
Bleb-related infection (cumulative rate after 3 years)[1]	5.1%	0.05%	191
Bleb leaks (cumulative rate after 3 years)[2]	7.0%	0.05%	137
Diplopia	0.05%	5.0%	195
Any postoperative complication[3] (proportion after 1 year)	57%	34%	121
Failure[4] (rate after 1 year)	13.5%	3.9%	154
Failure* (relative risk at 1 year)	3.0	1	194
Failure* (relative risk at 1 year)	2.0	1	370
Failure* (relative risk at 5 years)	3.0	1	44
Failure* (relative risk at 5 years)	2.0	1	88

*Power = 80%; alpha = 0.05; median control failure = 60 months

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3. Clinical Procedures

3.1 Visual Acuity

3.2 Slit Lamp Biomicroscopy

3.3 Seidel Testing

3.4 Tonometry

3.5 Pachymetry

3.6 Motility Evaluation

3.7 Gonioscopy

3.8 Ophthalmoscopy

3.9 Perimetry

3.1 Visual Acuity

Visual acuity is an important outcome variable in the PTVT Study. Visual acuity is measured before pupil dilation, tonometry, gonioscopy, or any other technique that could affect vision. Two different techniques are used to measure visual acuity, including Snellen and ETDRS visual acuity testing. Refraction is performed prior to formal measurement of visual acuity by either technique at the Qualifying Assessment and at the annual follow-up visits. Snellen visual acuity is measured at the Qualifying Assessment and at every follow-up visit. ETDRS visual acuity is tested at the Qualifying Assessment and at the 1 year, 3 year, and 5 year follow-up visits.

Subjective Refraction:

Subjective refraction must be performed at the Qualifying Assessment and at the annual follow-up visits in order to determine best-corrected visual acuity. It is permissible to use a phoropter or trial frame to determine best-corrected Snellen visual acuity. The left eye is occluded first. An approximate beginning refraction may be determined by retinoscopy, automated refraction, or a subjective refraction from a prior visit. The sphere is refined first. The cylinder is then refined, first the axis followed by the power. Finally, the sphere is rechecked. The right eye is then occluded, and the procedure is repeated for the left eye.

If the patient wears contact lenses and has glasses also, he or she is instructed not to wear the contact lenses on the day of the Qualifying Assessment. Patients unwilling to discontinue contact lens use after surgery will be excluded from the study. In the event that the patient either has no glasses or has forgotten the instructions and reported for the Qualifying Assessment wearing contact lenses, the contact lenses are removed and at least thirty minutes allowed to elapse before subjective refraction and visual acuity testing is performed.

ETDRS Visual Acuity:

The logmar visual acuity testing for the PTVT Study has been adapted from the Early Treatment of Diabetic Retinopathy (ETDRS). The logmar visual acuity scale facilitates statistical analysis and simplifies quantification of acuity at various distances. The right eye is tested with ETDRS logmar chart 1, then the left eye is tested with ETDRS logmar chart 2. Each chart is hidden from view until the eye being examined is ready for testing. ETDRS visual acuity is measured after standardized refraction only during the Qualifying Assessment and at the 1 year, 3 year, and 5 year follow-up examinations.

The room illumination should be at a level of 50 to 100 foot candles, and between 50 and 125 foot candles should illuminate the ETDRS visual acuity chart. The distance from the patient's eye to the visual acuity chart is exactly 4.0 meters.

The patient may sit or stand, but he or she is not allowed to lean forward or backward so a constant testing distance is maintained. After proper instruction, refraction, and placement of the appropriate lenses in a trial frame, the left eye is occluded and testing is begun with the right eye. The patient is instructed that the chart has letters only and no numbers. If the patient forgets this information and reads a number, he or she is reminded that the chart contains only letters and the examiner requests a letter in lieu of the number. Each letter that is identified correctly is circled on the ETDRS Visual Acuity Worksheet. The patient is advised to read slowly, so as to achieve the best identification of each letter. When the patient says he or she cannot read a letter, he or she is encouraged to guess. The patient should be encouraged to fix eccentrically if this improves the visual acuity, but care must be taken to ensure that the fellow eye remains covered.

Eyes reading fewer than 20 letters correctly at a test distance of 4.0 meters are tested at 1.0 meter. Before testing at 1.0 meter, +0.75 sphere is added to the 4.0 meter correction already in the trial frame to compensate for the closer testing distance. The patient is asked to read only the first six lines at 1.0 meter, so the maximum score attainable at that distance is 30. Correctly identified letters are circled on the ETDRS Visual Acuity Worksheet. If the patient's visual acuity is so poor that he or she cannot read the largest letter at 1.0 meter, assess his or her ability to count fingers. After testing of the right eye is completed, chart 1 is replaced by chart 2 and the procedure is repeated for the left eye.

Each letter read correctly and circled on the ETDRS Visual Acuity Worksheet is scored as one point. The score for each line (which is zero if no letters were read correctly) and the total score is recorded after testing is completed. If testing at 1.0 meter is not required (ie 20 or more letters were seen with testing at 4.0 meters), 30 points are automatically scored for the 1.0 meter test. The total score, equaling the sum of the 4.0 meter and 1.0 meter scores, is recorded on the data form. The ETDRS Visual Acuity Worksheet is for clinic use only and should not be sent to the Statistical Coordinating Center.

Snellen Visual Acuity:

Snellen visual acuity may be measured using any standard visual acuity chart. The same type of chart must be used throughout the duration of the study. Snellen visual acuity is measured during the Qualifying Assessment and at all follow-up visits. Standardized refraction is performed prior to Snellen visual acuity testing at the Qualifying Assessment and annual follow-up examinations.

The patient is not allowed to lean forward or backward so that a constant testing distance is maintained. After proper instruction and refraction, the left eye is occluded and testing is begun with the right eye. Progressively smaller lines are presented to the patient until he or she makes two or more errors in a line. When a patient states he or she is unable to read a letter, he or she is encouraged to

guess. If a patient misses only two letters on a line, a second chance is provided by asking the patient to read the line backwards. The patient is encouraged to fix eccentrically if this improves the visual acuity, but care must be taken to ensure that the fellow eye remains covered. The Snellen visual acuity is recorded as the smallest line in which the patient misses one or fewer optotypes. If the patient's visual acuity is so poor that he or she cannot read the 20/400 line, assess his or her ability to count fingers. After testing of the right eye is completed, the procedure is repeated for the left eye.

Testing for Finger Counting:

After proper instruction and refraction, the examiner's hand is viewed at a distance of two feet from the patient's eye. The fellow eye is closed and completely occluded by the palm of the patient's or assistant's hand. The examiner presents a random number of fingers to the patient. The patient is asked to indicate the number of fingers seen. If the number of fingers shown are correctly identified on four or more of five presentations, vision is recorded as count fingers. If the number of fingers presented cannot be identified on four or more of five presentations, test for hand motions.

Testing for Hand Motions:

In testing for hand motion, the examiner's hand is viewed with all fingers extended and separated at a distance of two feet from the patient's eye. The fellow eye is closed and completely occluded by the palm of the patient's or assistant's hand. The patient's glasses are not be worn. The examiner's hand is presented in a random order under three conditions: stationary, moving back and forth horizontally, and moving up and down vertically. The speed of movement is approximately one complete cycle of movement (up and down or back and forth) per second. The patient is instructed that the examiner's hand will be presented in one of these conditions. He or she is asked to respond to the question, "what is my hand doing now?" with either, "still", "back and forth", or "up and down". The process is repeated five times. It is considered a correct response if the patient states the hand is still or he or she cannot see it while it is stationary, and he or she is able to recognize movement and identify its direction. If hand motions are correctly identified on four or more of five presentations, vision is recorded as hand motions. If hand motions cannot be identified on four or more of five presentations, test for light perception.

Testing for Light Perception:

Light perception is tested using the same complete occlusion of the fellow eye with no other bright lights visible from the patient's position. The patient's glasses are not worn. The light of an indirect ophthalmoscope is directed into the eye from a distance of 2 feet for one or two seconds, then turned away. The patient is asked to report "on" when he or she sees the light, and "off" when it

disappears. The process is repeated five times in a nonrhythmic fashion. The visual acuity is recorded as light perception if the patient responds correctly four or more out of five times.

Testing Visual Acuity in Illiterate Patients:

Patients who are illiterate and cannot read standard letter charts have visual acuity tested using either a number chart, an illiterate E chart, a Landolt ring chart, or picture chart. The type of chart must be identified so that it can be used throughout the duration of the study. The smallest line in which one or fewer optotypes are missed is recorded as the Snellen visual acuity, and a notation is made that testing was performed in an illiterate patient.

3.2 Slit Lamp Biomicroscopy

Examination of the anterior segment using slit lamp biomicroscopy is performed at the Qualifying Assessment to document the preoperative status of the eye, and at all follow-up examinations to detect any changes in ocular status during the course of the study which may be attributable to the disease or treatment. Slit lamp biomicroscopy may be performed with any commercially available instrument, and it is used in a standard fashion starting anteriorly and working posteriorly. Standardizing subjective grading of bleb leaks and lenticular opacities is difficult, if not impossible. However, it is expected that subjective grading by each investigator is relatively reproducible. Attempts will be made to compare subjective gradings between investigators.

Lids:

The lids are examined for signs of blepharitis, including scales and crusting of the lashes, inspissated Meibomian glands, and erythema of the lid margin. Eyes with severe posterior blepharitis are excluded from the study.

Conjunctiva:

The conjunctiva is examined for scarring from prior trauma or cicatrizing disease (e.g. Stevens Johnson syndrome, ocular pemphigoid). The presence and extent of conjunctival scarring may be evaluated using a cotton tipped applicator to test the mobility of the conjuctiva. Eyes with conjunctival scarring that precludes a superior trabeculectomy are ineligible for the study.

Eyes must undergo Seidel testing at all postoperative follow-up examinations to detect conjunctival wound leaks and bleb leaks. Eyes that have undergone Baerveldt implantation are examined carefully for tube or shunt erosion. The presence of an infiltrate or exudate in the bleb of eyes that have undergone a

trabeculectomy with mitomycin C suggests the presence of a bleb-related infection.

Cornea:

The cornea is examined at high magnification to evaluate the epithelium, stroma, and endothelium. The techniques of diffuse illumination, scleral scatter, and retroillumination may be used. Findings consistent with a diagnosis of the iridocorneal endothelial (ICE) syndrome, epithelial downgrowth, or fibrous downgrowth make the eye ineligible for the study. The presence of corneal epithelial or stromal edema is noted. Eyes that have undergone Baerveldt implantation are examined for the presence of tube-cornea touch.

Anterior Chamber:

Before fluorescein instillation or pupillary dilation, the degree of anterior chamber cell and flare is determined. Eyes with chronic or recurrent uveitis are excluded from the study. Careful assessment of the anterior chamber depth is made postoperatively. If the anterior chamber is shallow, the central anterior chamber depth is measured relative to the corneal thickness. The appropriate gradation of $\geq$ 3 CT, $\geq$ 2 CT, $\geq$ 1 CT, < 1 CT, or lens-cornea touch is documented. In eyes treated with tube shunt surgery, the position of the tube in the anterior chamber is assessed and its length measured with a slit beam.

Iris:

Before pupillary dilation, the pupillary iris is examined at high magnification for the presence of neovascularization. If rubeosis iridis is present, the eye is ineligible for the study.

Lens:

After pupillary dilation, the investigator assesses the lens and grades any cataract present as mild, moderate, or severe.

3.3 Seidel Testing

Seidel testing must be performed at each postoperative follow-up examination. The Seidel test is performed using a fluorescein strip moistened with one or two drops of 0.5% proparacaine which is then applied to the conjuctiva. Alternatively, one drop of premixed fluorescein and anesthetic may be instilled. The area is closely observed using high magnification and a broad slit beam with maximal intensity illumination using a cobalt blue filter. Aqueous leakage is apparent as a light yellow stream and interrupts a dark green background of undiluted

fluorescein. If the Seidel test is positive, the leak is graded as an ooze, frank leak, or brisk leak.

3.4 Tonometry

Goldmann applanation tonometry is used to measure the intraocular pressure, except when irregular corneal astigmatism, corneal scarring, or corneal edema precludes accurate readings. In these cases, the Tono-Pen (Mentor) is used. The intraocular pressure is measured prior to pupillary dilation. Whenever possible, the intraocular pressure should be checked at the same time of the day as the Qualifying Assessment to minimize the effect of diurnal fluctuation of intraocular pressure.

Goldmann Applanation Tonometry:

The calibration of the Goldmann applanation tonometer is checked every 3 months, as described in the Haag-Streit Goldmann Applanation Tonometer Operator's Manual. Clean the prism according to your institutional infection control policy. The right eye is always tested first. Following instillation of a drop of 0.5% proparacaine, a fluorescein strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid has been sufficiently colored, the fluorescein strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic may be instilled. The patient's head is properly positioned in the chin rest and against the forehead rest without leaning forward or straining. Any tight-fitting neckwear is loosened. The patient is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the investigator holds the eyelids open against the orbital rim taking care not to apply any pressure on the globe. The patient is instructed not to hold his or her breath. If corneal astigmatism is greater than 3.0 diopters, the prism is rotated so that the axis of the minus cylinder on the prism graduation corresponds to the red mark on the prism holder. The investigator looks through the slit lamp and gently brings the tip of the prism in contact with the center of the cornea. The mires should be well focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately one tenth their diameter, the investigator instills additional fluorescein. The investigator adjusts the measuring drum until the inner borders of the two mires just touch each other. If pulsation is present, the measuring drum is adjusted until the mires separate a given distance during systole and overlap the same distance during diastole. The investigator removes the prism from the cornea and repeats the procedure in the right eye until two successive measurements are within 2 mm Hg. The investigator records the last two successive measurements. After testing of the right eye is complete, testing of the left eye follows the same technique.

Tono-Pen:

The Tono-Pen (Mentor) is used in cases of corneal edema, corneal scarring, or irregular corneal astigmatism. The Tono-Pen probe tip is covered with a new Ocu-Film Tip Cover. The instrument is calibrated immediately prior to use, as described in the Mentor Tono-Pen Instruction Manual. The right eye is always tested first. A drop of 0.5% proparacaine is instilled. The patient is positioned in the sitting position and instructed to fix on a distant object. Tight-fitting neckwear is loosened, and the patient is instructed not to hold his or her breath. The Tono-Pen is activated by depressing the activation switch momentarily. The Tono-Pen is brought in contact with the patient's cornea lightly and briefly while holding the instrument perpendicular to the cornea. A click will sound and a digital intraocular pressure measurement will be displayed each time a valid reading is obtained. After four valid readings, a final beep sounds and the averaged measurement appears on the display, along with a single line denoting statistical reliability. Measurements are repeated until two successive readings are obtained within 2 mm Hg and both have a statistical reliability of 5%, indicating that the standard deviation of the valid measurements is 5% or less of the number displayed. The investigator records the last two successive measurements. After testing of the right eye is complete, the same technique is applied to testing of the left eye.

3.5 Pachymetry

Both surgical procedures under study, placement of a Baerveldt implant and trabeculectomy with MMC, can lead to progressive endothelial cell loss and corneal edema. Central corneal thickness is measured with ultrasound pachymetry at the Qualifying Assessment and at the annual follow-up visits. The right eye is tested first. A drop of 0.5% proparacaine is instilled for anesthesia. The patient is asked to look straight ahead at a distant object or fixation target. The pachymeter probe is lined up with the center of the pupil and slowly advanced until it contacts the cornea. The probe is withdrawn when an audible signal is made indicating that a measurement has been recorded. The patient is instructed to blink. The procedure is repeated to obtain three separate readings, and the investigator records the measurements. After testing of the right eye is complete, the same technique is applied to testing of the left eye.

3.6 Motility Evaluation

Diplopia is an important complication which may occur following Baerveldt

implantation. The incidence of permanent restrictive strabismus associated with the Baerveldt implant is not precisely known, as this complication has not been studied prospectively. In order to address this issue, a formal motility evaluation is performed in all patients preoperatively and in those patients with diplopia at the 6 month follow-up visit or beyond. In addition, all patients will undergo a motility evaluation at the 1 year and 5 year follow-up visits. Transient diplopia following Baerveldt implantation is not uncommon. This study will focus on the incidence and nature of permanent restrictive strabismus associated with the Baerveldt implant.

The cover-uncover and alternate cover tests are performed with the patient looking in primary gaze, as well as in upgaze, downgaze, left gaze, and right gaze. Motility evaluation is performed with the patient looking in the distance and fixating at a near target. Any heterophorias or heterotropias are identified, and the deviation is measured with hand-held prisms. In patients who are unable to fixate for cover testing, the deviation may be measured by centering the corneal light reflexes with prism using the modified Krimsky method.

3.7 Gonioscopy

Gonioscopy is performed with the patient sitting at the slit lamp using either a Zeiss type four-mirror gonioprism or Goldmann single- or three-mirror lens. An examination of the anterior chamber angle for neovascularization is performed under high magnification for the purpose of excluding eyes with neovascularization from the study.

3.8 Ophthalmoscopy

A dilated fundus examination is performed at the Qualifying Assessment to determine the preoperative status of the eye. Ophthalmoscopy is done at the 1 week, 1 month, 3 month, and annual follow-up examinations to detect any changes in ocular status produced by the disease or treatment. Additionally, a dilated fundus examination is performed at any follow-up visit in which there is shallowing of the anterior chamber, intraocular pressure less than 6 mm Hg, or unexplained vision loss. After pupil dilation with appropriate mydriatics, the optic nerve and posterior pole are examined at the slit lamp using a Hruby lens, fundus contact lens, or Volk 90 diopter, 78 diopter, or 60 diopter lens. A head-mounted indirect ophthalmoscope and hand held condensing lens (20 diopter or 28 diopter Nikon aspheric lens) is used to evaluate the retinal periphery.

At the Qualifying Assessment, particular attention is paid for signs of proliferative retinopathy, including retinal neovascularization, neovascularization of the disc, vitreous hemorrhage, or preretinal hemorrhage. Patients with active proliferative retinopathy are excluded from the study. At postoperative follow-up visits, ophthalmoscopy is performed to evaluate for posterior segment complications, such as serous choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy.

3.9 Perimetry

Visual field assessment is an important outcome measure in the PTVT Study. Quantitative automated perimetry is performed using the Humphrey Field Analyzer. Visual field testing is performed before tonometry, gonioscopy, or any other technique that could affect vision. A visual field should be attempted in any eye that has sufficient vision to permit finger counting at two feet. Eyes with poor central vision may have an intact, off-center island of vision which may be measured with perimetry.

For the PTVT Study, a 24-2 threshold test is performed in all patients using a size III white stimulus. Visual field testing may be performed with the Swedish Interactive Thresholding Algorithm (SITA) or full threshold strategy, but the same testing strategy must be used throughout the duration of the study. The pupil diameter should be 3 mm or greater before visual field testing is undertaken, and this may require pharmacologic dilation. Standardized refraction is performed to determine the patient's distance refraction and best-corrected visual acuity prior to visual field testing. The age appropriate plus lens is added to the distance refraction. Patient education is provided, and the instrument is set up for the test. The technician should monitor the patient during testing. Visual fields are performed preoperatively (within one month of enrollment in the study) and annually thereafter. Copies of all visual fields are faxed to the Statistical Coordinating Center for evaluation.

4. Surgical Procedures

4.1 Trabeculectomy with Mitomycin C

4.2 Baerveldt Implantation

4.1 Trabeculectomy with Mitomycin C

Anethesia:

The type of anesthesia is at the surgeon's discretion.

Conjunctival Flap:

The trabeculectomy is performed in a superior quadrant. A limbus-based or fornix-based conjunctival flap may be used depending on the surgeon's preference. Eyes with conjunctival scarring that precludes a superior trabeculectomy are excluded from the study. A corneal traction suture or superior rectus traction suture may be used to rotate the globe inferiorly and improve exposure.

Mitomycin C Application:

A fluid retaining sponge soaked in mitomycin C (0.4 mg/ml) is applied to the sclera in the region of the trabeculectomy site for a period of exactly two minutes (120 seconds). The mitomycin may be applied before or after scleral flap dissection, as determined by the surgeon. This area is then copiously irrigated with balanced salt solution or Tis-U-Sol solution to remove any residual mitomycin C. The type of sponge used for mitomycin C application is selected by the surgeon in keeping with his or her usual practice.

Scleral Flap:

A corneal-based scleral flap is dissected approximately one-half scleral thickness. The shape and size of the scleral flap is determined by the surgeon in keeping with his or her usual practice.

Paracentesis Tract:

A peripheral clear cornea paracentesis tract is made.

Excision of Limbal Tissue:

A block of limbal tissue is excised from underneath the trabeculectomy flap using a sharp blade and Vannas scissors or a Kelly punch. The amount of limbal tissue excised is at the surgeon's discretion.

Peripheral Iridectomy:

A peripheral iridectomy is performed in all cases. The sclerostomy opening is inspected for entrapped iris tissue, and a cellulose sponge is used to test for the

presence of vitreous. Vitreous presenting to the surgical wound is excised. The method used to remove vitreous present at the surgical site is at the surgeon's discretion.

Scleral Flap Closure:

The scleral flap is reapproximated to the scleral bed with interrupted or releasable 10-0 nylon sutures. The number and tension of scleral flap sutures is determined by the surgeon. Following injection of balanced salt solution into the anterior chamber through the paracentesis tract, the anterior chamber should remain formed with a visible leak present around the scleral flap at equilibrium.

Conjunctival Flap Closure:

The type of suture material and needle used for the conjunctival flap closure is of the surgeon's choice. Either a double layered closure (conjunctiva and Tenon's closed separately) or single layered closure (conjunctiva and Tenon's together) may be performed.

Reformation of the Anterior Chamber and Bleb Elevation:

Balanced salt solution is injected through the paracentesis tract to deepen the anterior chamber and elevate the bleb. A moistened fluorescein strip is used to check for a conjunctival leak or leakage from the paracentesis tract, which may be closed with additional sutures.

Intraoperative Medications:

The use of intraoperative medications is at the surgeon's discretion. Subconjunctival antibiotics and corticosteroids may be injected, and 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.

4.2 Baerveldt Implantation

Anesthesia:

The type of anesthesia is at the surgeon's discretion.

Conjunctival Flap:

A 350-mm^2 Baerveldt is used in all cases, and implantation is performed in the superotemporal quadrant. A limbus-based or fornix-based conjunctival flap may be used depending on the surgeon's preference.

Scleral Exposure:

Sufficient exposure is obtained in the superotemporal quadrant to permit placement of the Baerveldt plate. A corneal traction suture or episcleral traction suture may be used to rotate the globe inferonasally and improve exposure.

Insertion of Episcleral Plate:

The 350-mm^2 Baerveldt plate may be positioned under or over the superior rectus and lateral rectus muscles, depending on the surgeon's usual practice. The implant is sutured to the sclera at a measured distance of 10 mm posterior to the limbus using the two fixation holes on the plate. The type of nonabsorbable suture used is of the surgeon's choice.

Occlusion of Tube:

The Baerveldt tube must be completely occluded in all cases in order to restrict aqueous flow to the plate until it becomes encapsulated. This is done to minimize the incidence of postoperative hypotony. The method of tube occlusion is left to the discretion of the surgeon. Ligation of the tube with a polyglactin suture near the tube-plate junction, ligation with a polypropylene suture which is inserted into the anterior chamber with the tube, or internal occlusion of the tube using a "rip-cord" technique have all been used effectively. A 30-gauge cannula is used to cannulate the end of the tube and confirm complete occlusion of the tube. Following tube occlusion, the surgeon may fenestrate the tube if desired. The method of tube fenestration is left to the discretion of the surgeon.

Preparation of Tube:

The tube is trimmed bevel-up to extend 2 to 3 mm into the anterior chamber.

Insertion of Tube 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 Baerveldt tube is inserted through this entry incision and should be well positioned in the anterior chamber away from the corneal endothelium and just above the iris. A 23-gauge needle produces an adequate entry incision for the tube without causing aqueous leakage around the tube.

Coverage of Tube:

A donor patch graft composed of donor sclera, dura mater, or pericardium is used to cover the limbal portion of the tube. The suture selected to fixate the patch graft is of the surgeon's choice.

Conjunctival Closure:

Tenon's and conjunctiva are reapproximated to the limbus. The suture used for the conjunctival closure is determined by the surgeon in keeping with his or her usual practice.

Intraoperative Medications:

The use of intraoperative medications is at the surgeon's discretion. Subconjunctival antibiotics and corticosteroids may be injected, and 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. Study Organization

5.1 Introduction

5.2 Clinical Centers

5.3 Statistical Coordinating Center

5.4 Safety and Data Monitoring Committee

5.5 Steering Committee

5.1 Introduction

Multicenter clinical trials require an organizational structure that provides efficient operations and facilitates communication. The following resource centers work together in this study:

- Clinical Centers (CC)
- Statistical Coordinating Center (SCC)
- Safety and Data Monitoring Committee (SDMC)
- Steering Committee (SC)

5.2 Clinical Centers:

Each CC is responsible for screening potential study patients, enrolling an adequate number of eligible patients, and following the patients according to the protocol until the termination of the study. Each CC has one principal investigator. The responsibilities of the CC are as follows:

- To assess the eligibility of patients for the PTVT Study.
- To enroll an adequate number of patients in the study through informed consent.
- To manage each patient in accordance with the randomized assignment provided by the SCC.
- To examine patients using the techniques and schedules established for the study.
- To complete the proper forms and obtain visual fields and quality of life assessments at the appropriate follow-up visits.
- To respond promptly to requests made by the SCC.
- To maintain patient records for the PTVT Study in an easily accessible and confidential manner.

- To obtain approval for the study and consent form from the local Institutional Review Board.

- To provide annual reports to the local IRB while the study is collecting follow-up data.

- To promote patient satisfaction and commitment to the trial.

- To provide representation at all meetings of the SC.

5.3 Statistical Coordinating Center

The SCC is located at the Department of Biostatistics at the Bascom Palmer Eye Institute. The SCC receives, edits, processes, analyzes, and stores all study data. The SCC coordinates the activities at the CC and monitors adherence to the study protocol. The responsibilities of the SCC are listed below:

- To provide guidance in the development and implementation of the design of the primary study and ancillary studies.

- To confirm local IRB approval of the study and consent form before initiating participation of a CC.

- To verify eligibility of the patient and completion of the consent form prior to randomization.

- To randomize study patients.

- To review data received, process, and store all study data.

- To produce extensive monitoring reports for the SC and SDMC every six months and upon request.

- To assist in the preparation of manuscripts.

5.4 Safety and Data Monitoring Committee

The SDMC is responsible for the ethical conduct of the study. This committee oversees the informed consent process and major changes in the protocol. The SDMC reviews the accumulating data for evidence of adverse and beneficial

treatment effects. This committee meets twice each year for the duration of the study. Telephone conferences will occur as needed. The responsibilities of the SDMC are as follows:

- To review the study design and study documents before the start of the study to identify any problems that may affect future data analysis or patient safety.
- To monitor adherence to the study protocol at each CC.
- To review treatment reports prepared by the SCC for evidence of adverse and beneficial treatment effects.
- To terminate the study if treatment benefits or treatment risks are so high for one treatment group that continuation of the trial is deemed unethical.
- To advise the SC on interpretation of study data.
- To recommend to the SC changes in study protocol based on periodic data analysis.
- To review and approve all publications and presentations.
- To determine when data collected in the study should be released to study investigators, study patients, the medical community, and the public.

5.5 Steering Committee

The SC is composed of the principal investigator from each CC and the Study Chairmen. The SC provides leadership for the trial. This committee has overall responsibility for directing activities and formulating policy for the study. This committee meets twice each year for the duration of the study. Telephone conferences will occur as needed. The specific functions of the SC are as follows:

- To evaluate and approve operational procedures in the study, including the Manual of Procedures and data forms.
- To change procedures and resolve technical issues during the course of the trial.

- To review study progress and take steps to correct deficiencies, such as patient recruitment, adherence to protocol, or data collection procedures.

- To appoint and disband subcommittees needed for execution of the study.

- To review and approve ancillary studies.

- To collaborate in preparing manuscripts of study findings for publication.

Policy Matters

6.1 Patient Consent

6.2 Publication and Presentation Policy

6.3 Ancillary Studies Policy

6.4 Policy of Confidentiality

6.5 Authorship Policy

6.1 Institutional Review Board Approval and Ethical Conduct

The Primary Tube Versus Trabeculectomy (PTVT) Study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The principal investigator of each Clinical Center is responsible for obtaining approval for the study protocol and consent form from the local Institutional Review Board (IRB). A copy of each Clinical Center's approved consent and documentation of IRB approval must be submitted to the Statistical Coordinating Center prior to beginning patient enrollment in the study. A copy of the consent form prepared for the Institutional Review Board for the University of Miami, Miller School of Medicine is provided at the end of this section.

The PTVT Study requires that written consent be obtained from each patient enrolled in the study. It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB approved consent form document, including the objective and procedures of the study and the possible risks involved in inclusion in the study. The signed consent form is kept with the study records at the Clinical Center. A copy of the signed consent is given to the patient, and a second copy is sent to the Statistical Coordinating Center.

6.2 Publication and Presentation Policy

A PTVT Study publication is one which contains details of the design, methods, or results of the PTVT Study, and is written by investigators from the PTVT Study. Any paper classified as a PTVT Study publication must be approved by the Safety and Data Monitoring Committee prior to submission for publication. Similarly, any presentation made on behalf of the PTVT Study must be approved by the Safety and Data Monitoring Committee. All papers of the PTVT Study will be published under conventional author format with acknowledgement of the PTVT Study Group.

6.3 Ancillary Studies Policy

A PTVT ancillary study is defined as any investigation which is carried out at one or more, but not all, of the participating PTVT Study Clinical Centers and which utilizes the resources of the PTVT Study. The resources may involve the participants themselves (through collection of added items of data for special

analyses) or the PTVT Study database of one or more of the Clinical Centers. All PTVT ancillary studies require review and approval from the Steering Committee and Safety and Data Monitoring Committee before they are implemented. No PTVT ancillary study will be approved which interferes with the data collection, treatment, or recruitment process of the study. Papers arising from ancillary studies will, as a rule, be published under the name of the investigator(s) responsible for the work, with or without the acknowledgement of the PTVT Study, depending on dictates of the Steering Committee. Provisions for access to the main study file for the purpose of linking data from the ancillary study with the main study file must be discussed and approved by the Clinical Center and the Statistical Coordinating Center during approval of the project.

6.4 Policy of Confidentiality

Materials distributed for Steering Committee and Safety and Data Monitoring Committee meetings are confidential. Minutes from all study meetings are confidential. Access to a participant's record by any unauthorized individual is prohibited. Tabulations or listings which reveal the identity of individual study participants are confidential.

6.5 Authorship Policy

Mainline Papers: Original papers detailing design, methods, or results of the TVT Study.

- The individual who writes the paper is listed as first author.
- Conventional author format.
- Acknowledgement of the PTVT Study Group.
- Full credit roster, indicating participating centers and associated personell, as well as a listing of all standing committees and their members.
- Only investigators who have enrolled patients will be included in publications.

Ancillary Papers: Original papers dealing with a secondary aim of the study or dealing with a question developed and pursued by PTVT Study investigators using PTVT Study data.

- Conventional author format.

- Full acknowledgement of the PTVT Research Group, if the Steering Committee so dictates.

Presentations: Any paper presented on behalf of the PTVT Study by one or more PTVT Study investigators.

- Abstract and program listing indicate presentation is made on behalf of the PTVT Study Group.

- Name of presenter is listed in abstract and program.

INFORMED CONSENT FORM

PRIMARY TUBE VERSUS TRABECULECTOMY (PTVT) STUDY

PURPOSE:
Your doctor feels that you should have surgery as treatment for your glaucoma. A trabeculectomy with mitomycin C or Baerveldt glaucoma implant are the two most common types of glaucoma operations performed. Both procedures work by providing a route by which aqueous fluid can drain out of the eye to lower the intraocular pressure. The Baerveldt implant does so by placing a tube into the eye which shunts aqueous fluid to a silicone plate which is attached to the sclera (white portion of the eye). A trabeculectomy allows aqueous fluid to drain through a trap door-like incision in the sclera, and mitomycin C is applied to this region to reduce the likelihood that the trap door will scar closed. Comparable success rates and complication rates have been observed separately for the Baerveldt implant and trabeculectomy with mitomycin C. While both procedures have been shown to be safe and effective, it is unclear if one is superior to the other. The purpose of this study is to determine if one type of surgery works better with fewer complications. This form documents a request for your participation in this study.

PROCEDURE:
If you agree to participate in this study, you will be assigned by chance (like a flip of a coin) to undergo either a trabeculectomy with mitomycin C or Baerveldt implant. Your doctor will perform the normal postoperative examinations at 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, 18 months, 2 years, 3 years, 4 years, and 5 years after surgery, in addition to any other visits he or she feels are necessary. Information collected at these visits will be analyzed for this study.

RISKS:
The surgical risks are similar for the Baerveldt implant and a trabeculectomy with mitomycin C. They include a risk of bleeding, infection, too low an intraocular pressure after surgery, failure of the operation to control the intraocular pressure, cataract, retinal swelling, and corneal swelling. In addition, there is a risk of tube erosion and double vision associated with the Baerveldt implant, and a risk of leakage from the bleb and eye discomfort produced by the bleb with a trabeculectomy with mitomycin C. There appears to be a higher risk of serious infection associated with a mitomycin trabeculectomy compared with a Baerveldt implant. You would experience these surgical risks whether you participate in the study or not. This study will not produce any change in the typical care you would receive following your surgery, so there are no additional risks to you for participating in the study.

BENEFITS:
No direct benefit can be promised to you for your participation in this study.

ALTERNATIVES:
You have the alternative not to participate in this study, and receive either a trabeculectomy with mitomycin C or Baerveldt implant as determined by your doctor.

COSTS:
You or your insurance company will be responsible for medical costs of participating in this study. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. You will not incur any added costs by participating in the study.

COMPENSATION FOR INJURY:
You may be exposed to risk of injury from participation in this study. If injury occurs, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not routinely available.

CONFIDENTIALITY:
By signing this consent, you authorize the Investigator(s) and his/her/their staff to access your medical records and associated information as may be necessary for purposes of this study. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The investigator and his/her collaborators will consider your records confidential to the extent permitted by law. The Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) may review these research records. Your records may also be reviewed for audit purposes by authorized University of Miami employees or other agents who will be bound by the same provisions of confidentiality.

RIGHT TO REFUSE OR WITHDRAW:
Your participation in this study is voluntary. You are free to refuse to participate in the study or withdraw your consent at any time during the study. Your withdrawal or lack of participation will not prejudice further/additional medical treatment. The investigator reserves the right to remove you from the study without your consent at such time that they feel it is in the best interest for you medically or for administrative reasons. You may ask and will receive answers to any questions during the course of the study. If you have any questions about this study, please contact Dr. Steven Gedde at 305-326-6435 (daytime) or 305-867-9029 (nighttime). If you have questions about your rights as a research participant, you may contact The Human Subjects Research Office at 305-243-3195.

_____	_____
Signature of Subject	Date
_____	_____
Signature of Witness	Date
_____	_____
Signature of Person Obtaining Consent	Date

Principal Investigator's Name: Steven J. Gedde, M.D.
Day Phone: (305) 326-6435
Night Phone: (305) 867-9029

7. Clinical Center Procedures

7.1 Qualifying Assessment

7.2 Assignment of Patient Identification Number

7.3 Randomization Procedure

7.4 Schedule of Visits

7.1 Qualifying Assessment

The Qualifying Assessment establishes whether the patient satisfies PTVT Study eligibility criteria. If the patient appears to be eligible for the study, the Clinical Center (CC) completes the Qualifying Assessment Form and Preoperative Form. Both forms are faxed to the Statistical Coordinating Center (SCC), along with a copy of the consent form. Informed consent is an eligibility criterion because it is an agreement by the patient to be randomized and complete follow-up in their treatment group. The SCC reviews each of the inclusion and exclusion criteria to ensure that the patient is eligible. **It is vital to the scientific validity of the study that every eligible patient be offered enrollment.**

7.2 Assignment of Patient Identification Number

Any patient who is confirmed by the SCC to meet the eligibility criteria and is enrolled in the study is assigned a patient identification number. The SCC provides a list of patient identification numbers to each CC. The patient identification number is a six digit, three letter code which is unique for each patient. The first two digits refer to the CC. The third digit refers to the patient's stratum. The fourth, fifth, and six digits are a sequential number for each patient within a stratum. The final three letters are selected from the patient's name by any system chosen by the CC. For example, an identification number 03-1-003-AZE refers to the third patient in stratum 1 enrolled at CC 3.

7.3 Randomization Procedure

Randomization takes place at the time the patient is enrolled in the study. After patient eligibility is confirmed and a patient identification number is provided, the SCC assigns treatment by saying, "trabeculectomy with mitomycin C" or "Baerveldt implant". The CC then repeats the assigned treatment. The surgery date is the study entry date, and the dates for all postoperative follow-up visits are computed from this date.

The randomization schedule is constructed using a computer pseudo-random number generator. The allocation ratio is equal between the two treatment groups. The randomization is blocked by clinic and study stratum using a scheme with small variable blocks. This procedure ensures that there is an equal number of patients in each treatment group even early in the trial, and that the CC is not able to predict the next treatment assignment.

7.4 Schedule of Visits

All study investigators must be familiar with the schedule of visits to ensure that required data is collected and that future visits are scheduled within the appropriate time windows. The need for continued follow-up and timely visits should be stressed to the patient during the informed consent process and throughout the study. An appointment schedule is generated for each patient by the SCC and sent to the patient's CC. Time windows for follow-up visits are shown in Table 2. Table 3 summarizes the required data at each of the scheduled visits.

Table 2. Time Windows for Follow-Up Visits

Follow-Up Visit	Number of Days After Surgery		
	Ideal Time	Preferred Time Window	Acceptable Time Window
1 Day	1 day	1 day	1–3 days
1 Week	7 days	6–8 days	4–14 days
1 Month	30 days	23–37 days	15–59 days
3 Month	90 days	76–104 days	60–120 days
6 Month	182 days	161–203 days	121–270 days
12 Month	365 days	305–425 days	271–455 days
18 Month	547 days	487–607 days	456–637 days
2 Year	730 days	670–790 days	638–912 days
3 Year	1095 days	1005–1185 days	913–1277 days
4 Year	1460 days	1370–1550 days	1278–1642 days
5 Year	1825 days	1735–1915 days	1643–2007 days

Table 3. Schedule of Visits

	Preoperative	1 Day	1 Week	1 Month	3 Month	6 Month
Refraction	**X**					
Snellen VA	**X**	**X**	**X**	**X**	**X**	**X**
ETDRS VA	**X**					
Slit Lamp Biomicroscopy	**X**	**X**	**X**	**X**	**X**	**X**
Seidel Testing		**X**	**X**	**X**	**X**	**X**
Tonometry	**X**	**X**	**X**	**X**	**X**	**X**
Pachymetry	**X**					
Motility Evaluation	**X**					#
Gonioscopy	**X**					
Ophthalmoscopy	**X**	$	**X**	**X**	**X**	$
Humphrey 24-2	**X**					
Informed Consent	**X**					

Table 3. Schedule of Visits (continued)

	12 Month	18 Month	2 Year	3 Year	4 Year	5 Year
Refraction	X		X	X	X	X
Snellen VA	X	X	X	X	X	X
ETDRS VA	X			X		X
Slit Lamp Biomicroscopy	X	X	X	X	X	X
Seidel Testing	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X
Pachymetry	X		X	X	X	X
Motility Evaluation	X	#	#	#	#	X
Gonioscopy						
Ophthalmoscopy	X	$	X	X	X	X
Humphrey 24-2	X		X	X	X	X

= if diplopia
$ = if shallowing of the anterior chamber, IOP < 6 mm Hg, or unexplained vision loss

8. Statistical Coordinating Center Procedures

8.1 Data Management

8.2 Data Security

8.3 Data Forms

8.1 Data Management

A master log is kept of each patient randomized in the PTVT Study. An appointment schedule is made for each patient and sent to the patient's Clinical Center. When a data form is received at the Statistical Coordinating Center, it is processed for filing and data entry. Each form is data entered by a data entry clerk and then verified by double entry by the SCC Research Coordinator. Edit checks, such as missing data and out-of-range values, will be clarified within the Clinical Center.

The statistical package SPSS is used for data entry, management, and analysis. Each of the study's two statisticians has a personal computer and one more is dedicated to data entry. The Research Coordinator also has a personal computer to use for data management, study correspondence, reports, and manuscripts. Each computer, except the one dedicated to data entry, has access to the University of Miami's network for e-mail, Internet access, and data file transfer.

8.2 Data Security

The paper data forms for the PTVT Study are kept in file cabinets in the Biostatistics facility in the Clinical Research Building. The building is locked and access is by card key entry. A security guard is present during working hours. The computer files for the study are kept on computers in the same location. These rooms are kept locked when not in use, and the study computer files are password-protected. The data is backed up weekly, and monthly backups are stored at a remote facility. Computer data files used for publication are saved and stored as separate files.

8.3 Data Forms

The data forms were designed to be self-explanatory. Their completion should not require reference to separate information manuals. The data forms contain information to be collected at a given point in time during the study. Information collected at another date is incorporated into a separate form. Data forms are faxed to the Statistical Coordinating Center for data entry. Forms will be reviewed periodically and revised as dictated by protocol changes. The various data forms are provided at the end of this section.

8.4 Data Management

A master log is kept of each patient randomized in the PTVT Study. An appointment schedule is made for each patient and sent to the patient's Clinical Center. When a data form is received at the Statistical Coordinating Center, it is processed for filing and data entry. Each form is data entered by a data entry clerk and then verified by double entry by the SCC Research Coordinator. Edit checks, such as missing data and out-of-range values, will be clarified within the Clinical Center.

9. Corneal Endothelial Change Ancillary Study

9.1 Background

9.2 Clinical Procedures

9.3 Main Outcome Measures

9.4 Statistical Analysis

9.5 Sample Size

9.1 Background

Historically, there has been widespread concern that tube shunts placed in the anterior chamber angle may mechanically damage peripheral corneal endothelial cells and result in long-term endothelial failure in susceptible eyes. In eyes with glaucoma that require tube shunts, there are often a number of confounding influences including the severity and duration of intraocular pressure elevation, the number of previous intraocular surgical procedures, and the presence of co-existing corneal disease. In the types of glaucoma for which shunts were traditionally indicated, the small risk of corneal endothelial failure was considered a low risk relative to the high risk of blindness from progressive glaucoma. In such eyes, there was usually no effective alternative to tube shunt implantation. However, if tube shunt surgery is to receive widespread acceptance as a primary surgical option for primary open angle glaucoma, it will be important to test the hypothesis that shunts implanted in the anterior chamber angle can be positioned so that they are not associated with long-term progressive loss of corneal endothelial function in excess of the rate of loss that would have otherwise occurred. This ancillary study to the PTVT Study is designed to compare long-term corneal endothelial changes following tube shunt surgery and trabeculectomy with mitomycin C.

9.2 Clinical Procedures

It is expected that Clinical Centers with the equipment for obtaining corneal endothelial cell counts will participate in this ancillary study. PTVT patients undergo specular microscopy in both eyes at the Qualifying Assessment and at 1 year, 3 year, and 5 year follow-up visits. Additionally, patients in the tube group have the entry site of the tube assessed with gonioscopy at the 1 year, 3 year, and 5 year study visits.

Specular Microscopy:

Specular microscopy is performed at the Qualifying Assessment, and measurements are repeated at the 1 year, 3 year, and 5 year follow-up visits using the same instrument. Central corneal endothelial cell counts are obtained in both eyes while in primary gaze. The coefficient of variation of cell size and percentage hexagonality is used to indicate the degree of polymorphism and pleomorphism, respectively. Three images are acquired and the best image selected for morphological analyses. A frame area that contains 75 cells or more is used to reduce sampling errors, and only whole cells with continuous cell borders are accepted for the planimetric endothelial cell analysis. In corneas in which obtaining good quality specular images proves difficult, the corneal

endothelial cell density is estimated by averaging the density from 3 best images taken.

Gonioscopy:

In patients randomized to the tube group, gonioscopy is used to identify the position of the tube entry site in the angle relative to a fixed landmark at the 1 year, 3 year, and 5 year follow-up visits. Schwalbe's line serves as this landmark, and it is the peripheral limit of the corneal endothelium. The tube entry is graded as all of tube posterior to Schwalbe's line, some of the tube but less than 50% anterior to Schwalbe's line, more than 50% and less than 100% of tube Anterior to Schwalbe's line, and all of tube anterior to Schwalbe's line.

9.3 Main Outcome Measures

Central corneal endothelial cell density and central corneal thickness are the main outcome measures in this study. Data are analyzed to explore the relationships between these outcome measures and tube entry site position, position of tube tip, postoperative intraocular pressure levels, complications, patient demographics, and time from glaucoma surgery.

9.4 Statistical Analysis

The principal aim of this ancillary study is to compare the rates of loss of endothelial cells in the two randomized groups of the PTVT Study. These rates are quantified as the difference in counts between baseline and follow-up measurements. The largest differences are expected at the 5 year follow-up visit. However, comparisons are made at 1 and 3 years postoperatively as there may be substantial loss to follow-up of study patients by 5 years. The significance of the difference between loss rates in the two treatment groups are assessed with analysis of covariance. Covariates include baseline counts and classification of the tube site by gonioscopy in patients randomized to the tube group. Baseline patient demographic variables are included in exploratory analyses. Other analyses focus on coefficient of variation and percentage hexagonality measurements. Another secondary analysis involves endothelial cell count loss rates in the study eye compared to the non-study eye. The longitudinal measurements of count data are used to examine the characteristics of loss with time.

9.5 Sample Size

The PTVT Study has a fixed sample size. This ancillary study is performed on all enrolled patients at Clinical Centers that are able to measure corneal endothelial density.