Study protocol

An investigation of the effectiveness of Paul Glaucoma Implant (PGI) – a pilot study

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1. Introduction

1.1. Background and Significance

Glaucoma is an eye disease characterized by optic nerve damage. This condition can develop when the fluid in the eye cannot drain properly and intraocular pressure (IOP) builds up. This damages the optic nerve of the eye, and if left untreated, can result in irreversible blindness. Glaucoma is a leading cause of irreversible blindness in the world.[1]

Figure 1: (L) in the normal eye, fluid that is continually produced is drained out through the trabecular meshwork, regulating the IOP. (R) In Glaucoma, trabecular meshwork is blocked and fluid cannot drain. Continual production of fluid causes fluid build-up in the eye

Glaucoma can be treated with eye drops, laser treatment or surgery. The treatment depends upon the nature and the severity of the glaucoma. The distribution is as shown in the table below:

Treatment Type	Drugs	Trabeculectomy	Glaucoma Drainage Devices
Number of Cases	175,000 new patients starts/ year	106,000 surgical procedures/ year	15,000 implant procedures/ year

Table 1: Distribution of treatment for glaucoma patients[2]

Eye drops are the first line of treatment and are prescribed to help patients control their glaucoma. Patient adherence to the medication is critical for the control of the disease. However several studies have shown that approximately 50% of patients have been found not adherent to their medication over 75% of the time.[3] The combination of various drops required, the frequency at which they have to be taken over the course of the day, and challenges of self-administering a drop into the eye,[4,5] are some contributors to the poor compliance. For many of these patients who are not compliant to their eye drops, their condition worsens with time. In addition, some of these eye drops also cause side effects which reduced their quality of life. In Europe, the non-drug and drug costs were evaluated- drug costs included only the medication cost, while non-drug cost included outpatient clinic attendances, inpatient days, surgical or medical procedures that were performed, and any visual field testing that were carried out.

For patients whose glaucoma progresses despite medical therapy or who are unable to take drugs for any reasons, the next course of therapy will be laser. Laser surgery such as, trabeculoplasty is used to enhance the eye drainage function in open-angle glaucoma. In this procedure, laser energy is applied to the drainage tissue of the eye, such as the trabecular meshwork, to cause chemical and biological changes in the tissues. While up to 80% of patients respond to trabeculoplasty,[6] this treatment requires repeated administration, and with each repeated treatment however, its

[1] *Tham Y-C et al, Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040: A Systematic Review and Meta-analysis. Ophthalmology 2014; 121:2081-2090*
[2] *Quigley, H., & Broman, A. (2006). The number of people with glaucoma worldwide in 2010 and 2020.. Manuscript submitted for publication, The Glaucoma Service and the Dana Center for Preventive Opthalmalogy, Wilmer Opthalmological Institute, Johns Hopkins Hospital*
[3] *Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, et al. Adherence with Topical Glaucoma Medication Monitored Electronically: The Travatan Dosing Aid Study. Ophthalmology. 2009;116:191–9*
[4] *Robin A, Grover DS. Compliance and adherence in glaucoma management. 2011; 59(Suppl1):S93-S96*
[5] *Francis B. Problems in Compliance with Glaucoma Medication Treatment.*
[6] *2011. SLT on the Front Lines of Treatment. http://www.reviewofophthalmology.com/content/i/1533/c/28664/*

effectiveness drops further. In addition, this treatment option is suitable only for patients with less severe or uncomplicated glaucoma.

The next course of action for patients in which laser treatment is not as effective is trabeculectomy surgery. In the traditional trabeculectomy surgery, the surgeon creates a new drainage hole, an episcleral fistula called a bleb, on the eye, such that a differential in pressure between the drainage hole and the inside of the eye forces instantaneous fluid flow from the inside of the eye to the outside. This surgery has demonstrated good efficacy in pressure reduction, but is associated with late-stage surgical complications such as worsening cataract, or a secondary procedure to repair or modify blebs.[7,8,9]

If trabeculectomy fails, then the implantation of an aqueous shunt is used. This requires an implantation of a fairly large device, consisting of a large plate that is placed under the conjunctiva, which is connected to a tube placed in the anterior chamber of the eye. Current shunt procedures however, have their shortcomings. The shortcomings of the current glaucoma drainage devices include (i) difficulty in insertion, (ii) immediate flow control, (iii) late failure due to conjunctival scarring. Like trabeculectomy, aqueous shunts also have a high failure rate of up to 40% failure rate.[10]. The Ahmed and Krupin are valved implants that control the pressure at which the valve opens to allow fluid drainage. Reports however, have shown that these valves are not effective in controlling early phase complications of hypotony and the long-term performance is comparable to other GDDs.[11] The Baerveldt and the Molteno have no valve and therefore no resistance to fluid outflow. As a result, sudden low pressures (hypotony) may be experienced by the eye, which in severe or prolonged cases, can lead to decreased vision or haemorrhage. Hong et al also highlights one of these common late stage complications in current commercial devices- bleb encapsulation, which leads to bleb failure. About 40-80% were associated with Ahmed tubes and 20-30% with the Baerveldt and double-plate Molteno.[12] Hypertensive phase, defined as IOP >21mmHg during the first 3 months of surgery, is another problem and risk factor for aqueous shunt failures. Hypertensive phase incidence is about 56% in the Ahmed, and resolution of this phase, defined as IOP < 22mmHg is estimated to be 28% only.[13]

Although aqueous shunts have traditionally been used as the last treatment resort, a recent study with 5 years data has recently been published and has demonstrated that the performance of shunts is comparable to that of trabeculectomy. This is the TVT study,[14] which is a randomized, multicentre trial that compares the safety and efficacy of the tube shunt surgery against that of trabeculectomy with mitomycin C. The study reported higher success rates with the tube shunt than trabeculectomy, and a higher rate of re-operation in the trabeculectomy group. Early post-operative complications occurred more frequently after trabeculectomy than with the tube shunt surgery. The rates of late postoperative compliacations and reoperation for complications were similar with both surgical procedures at the 5 years follow-up, and there was no difference in vision loss found between the two groups. A recent market study also shows that the GDD/ aqueous shunt market is the most rapidly growing sector of the glaucoma device market, and is likely to continue to grow with evidence of its efficacy over current available treatments. With the publication of the TVT study, aqueous shunts are being considered as the first surgical option instead of trabeculectomy, potentially increasing our projected market size

[7] *Stuart M. 2010. Start-up. In Glaucoma, Devices go Eye-to-Eye with Drugs.*
[8] *Casson R, Rahman R, Salmon JF. Long term results and complicationsof trabeculectomy augmented wit low dose mitomycin C in patients at risk for filtration surgery. Br J Ophthalmol. 2001;85:686-688.*
[9] *Jampel HD, Solus JF etal. Outcomes and Bleb-Related Complications of Trabeculectomy. 2012;119(4):712-722.*
[10] *Rosentreter, A., Mellein, A. C., Konen, W. W., & Dietlein, T. S. (2010). Capsule excision and ologen implantation for revision after glaucoma drainage device*
[11] *Topouzis F etal (1999). American Journal of Ophthalmology. Aug 128(2): 198-204. Follow-up of the original cohort with the Ahmed glaucoma valve implant.*
[12] *Hong C-H, Arosemena A, Zurakowski D, Ayyala RS. Glaucoma drainage devices: A systematic literature review and current controversies. Surv Ophthalmol 2005; 50:48–60*
[13] *Kouros Nouri-Mahdavi, Joseph Caprioli. Evaluation of the hypertensive phase after insertion of the Ahmed Glaucoma Valve. Am J Ophthalmol 2003; 1001-1008.*
[14] *Gedde SJ, Herndon LW etal. Postoperative Complications in the Tube versus Trabeculectomy (TVT) Study During Five Years of Follow-up*

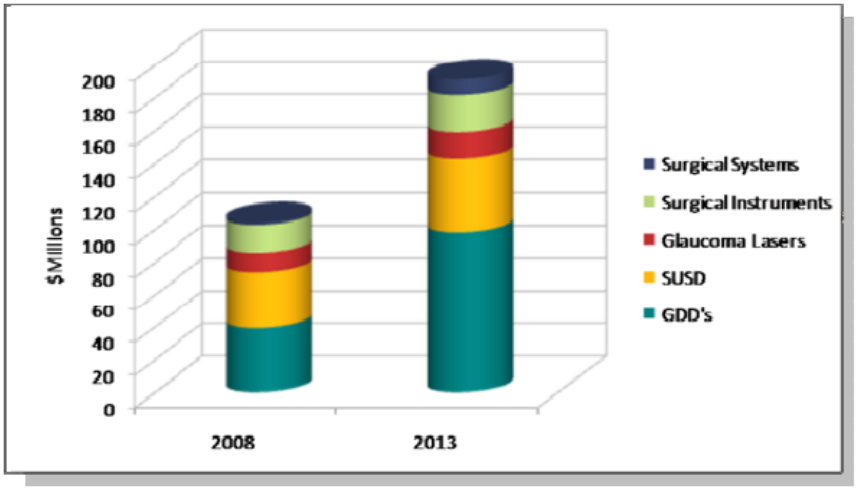

Figure 2: Global Glaucoma Device Market. This includes devices in 4 categories- surgical systems and instruments, lasers, single-use surgical devices (SUSD), and Glaucoma Drainage Devices (GDDs).[15]

The number of glaucoma worldwide in people aged 40-80 years was estimated to be 64.3 million in 2013. Asia accounted for the largest number -60% of the glaucoma cases, and Africa having the second highest number. The estimated global prevalence of glaucoma is estimated to be 3.54%. The number of glaucoma cases is expected to increase by 18.3% to 76.0 million in 2020, and 111.8 million in 2040.[16] This increase mainly results from the change in the number of older persons, especially in the regions of Asia and Africa due to the increased life expectancy in those regions. Glaucoma costs the US economy $2.9 billion every year in direct costs.[17] The financial burden of glaucoma is demonstrated to increase as the disease severity increase. The majority of the costs were medication-related at all severity stages, ranging from 42% to 56% of direct costs at each disease stage. Similarly in Europe, a study by Rahman et al examined the direct cost of glaucoma. The annual cost per patient annually was £375, the total made up of £183 for non-drugs, and £155 for the non-drug cost.[18] Over the lifetime of a patient, this cost was £2424- £1305 for non-drug costs and £906 for the drug cost - Drugs accounted for 34%. From the graph shown in Figure 3, if glaucoma can be treated and prevent from progressing at an earlier stage with an effective treatment, the cost of the burden of the disease would be greatly reduced.

[15] Snowdown and Associates Management Consultant. Ophthalmic Internationsl: Summary & Diligence Review. March 30, 2009. Retrieved from http://www.mediacapitalpartnersllc.com/wp-content/uploads/2009/04/ophthalmic_international_-diligence_review.pdf

[16] *Tham Y-C et al, Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040: A Systematic Review and Meta-analysis. Ophthalmology 2014; 121:2081-2090*

[17] *Varma R, Lee PP, Goldberg I etal. An Assessment of the Health and Economic Budens of Glaucoma. Am J Ophthalmol. 2011;152(4):515-522*

[18] *Rahman MQ, Beard SM etal. Direct Healthcare costs of glaucoma treatment. BJ Ophthalmol. 2013; 97:720-724.*

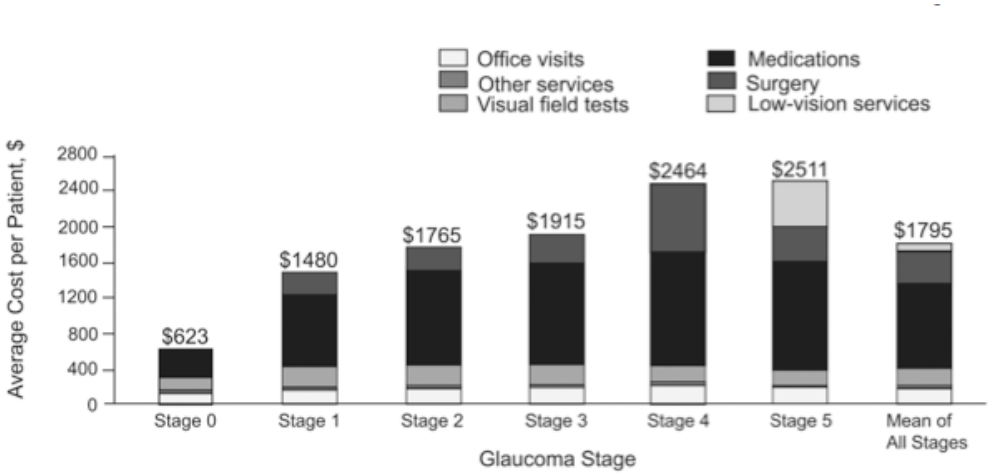

Figure 3: The financial burden of glaucoma increases with disease severity. Total annual direct cost of glaucoma treatment per patient by stage.[17]

The shortcomings of the current treatment options, and the growing cost burden of glaucoma call for further innovation in this space. A new class of devices has been recently emerging. Minimally-invasive glaucoma surgery (MIGS) consists of a new class of devices that allow glaucoma surgery to be done less invasively. However, these procedures are only suitable for a limited group of patients as they cannot produce a large pressure lowering effect[19] as trabeculectomy or glaucoma drainage devices do. Also, several of the MIGS procedures utilize a new drainage pathway to remove aqueous fluid from the anterior chamber of the eye, and their long-term effectiveness has yet to be proven.

Therefore, clinicians and patients alike are looking for a solution that is has good pressure lowering effect, long-term effectiveness with good fluid control, and which patients can comply with.

1.2 Objectives

The primary objective of this study is to determine the safety and efficacy of a new shunt that has been developed to eliminate some of the disadvantages of current shunts in the treatment of refractory/severe and moderate glaucoma in severity.

It is hypothesized that this new device will lower intraocular pressure with nil to diminished frequency of commonly encountered problems (hypotony, shallow anterior chamber, early and late bleb failure) with the present day aqueous shunts.

The outcome of the clinical study will provide the team validation on: the effectiveness in IOP reduction; indications for use in the target population.

[19] http://www.brightfocus.org/glaucoma/brightfocus-insights/minimally-invasive-glaucoma-procedures-migs.html

2. Study Design

2.1 Study Design

This study will be a multi-centre prospective study involving up to 5 centres in Asia. We aim to recruit 6 subjects per centre (3 severe/refractory glaucoma and 3 with moderate glaucoma in severity) with a follow-up period of 12 months.

1. Endpoints

The following endpoints will be used:

Primary Endpoints

- IOP reduction of ≥ 20% from baseline at 12M post-operatively

Secondary Endpoints

- Change in the number of ocular hypertensive glaucoma medication
- Complications – intra-operative and post-operative (at < than 3 months and > 3 months) such as flat anterior chamber, hypotony maculopathy causing 2 lines or worse visual loss

2.2 Inclusion Criteria

- Age between 21 - 80 years old
- Eyes with severe, refractory glaucoma defined as IOP exceeding 21 mmHg on maximal tolerated medical therapy with any of the following: i) failed 1 or more incisional glaucoma surgeries (glaucoma filtering surgery, trabeculectomy, tube shunt); ii) failed 1 or more cilioablative procedures(e.g. cryotherapy, cyclodiode therapy); iii) have any other conditions (conjunctival scarring, uveitis) in which conventional incisional glaucoma surgery like trabeculectomy would be more likely to fail)
- Eyes with moderate glaucoma defined as eyes with glaucomatous visual field defects not affecting the central 5 degrees of fixation, requires more than 1 IOP-lowering eyedrops and has visually-significant cataract requiring cataract surgery
- Maximally-tolerated medicated IOP at two preoperative visits of >21 mmHg and ≤35 mmHg
- Area of free, healthy and mobile conjunctiva in the targeted quadrant

2.3 Exclusion Criteria

- Unwilling or unable to give consent, or unable to return for scheduled visits.
- Fellow eye VA worse than 6/60.
- other significant ocular disease, except cataract
- active ocular infection or inflammation
- expected ocular surgery in next 12 months

- no suitable quadrant for tube implant
- systemic corticosteroid therapy > 5 mg/day prednisone
- intolerance to eye exams
- mental impairment interfering with consent or compliance
- pregnant or nursing women
- known sensitivity to anticipated medications used at surgery
- significant co-morbid disease
- concurrent enrolment in another drug or device study

2.4 Sample size calculations

Since this is a pilot series, non-comparative trial, statistical calculations were not used to determine the number of subjects to be recruited for the study. Problems regarding compliance to study procedures & visits by recruited subjects are not highly anticipated. Based on our previous experience, having participated in an international multicenter trial on aqueous shunts (ahmed & baerveldt), the rate of loss to follow-up is 10% after 1-year. Therefore, we estimate that the lost to follow-up rate in this trial to be 10%.

2.5 Failure Criteria

- IOP reduced by < 20% on 2 consecutive study visits at visits > 3 months
- Removal of implant for any reason

	Preop	1 Day	1 Week	1 Mon.	3 Mos	6 Mos	12 Mos
Refraction	x					x	x
Visual Acuity	x	x	x	x	x	x	x
Slit Lamp examination	x	x	x	x	x	x	x
Goldman Applanation Tonometry*	x	x	x	x	x	x	x
Indentation gonioscopy	x						x
Dilated fundus examination	x			x	x	x	x
Pachymetry	x						x
Specular microscopy	x						x
Ocular motility	x					x	x

2.6 Timetable for the study

Evaluation							

* or Tono Pen

3. Clinical Procedures
3.1 Visual Acuity
3.2 Slit Lamp Biomicroscopy
3.3 Tonometry
3.4 Pachymetry
3.5 Motility Evaluation
3.6 Gonioscopy
3.7 Ophthalmoscopy

3.1 Visual acuity
Visual acuity is an important outcome variable in this study. Visual acuity is measured before pupil dilation, tonometry, gonioscopy, or any other technique that could affect vision. Refraction is performed prior to formal measurement of visual acuity by either technique at the Qualifying Assessment and at the annual follow-up visits. ETDRS visual acuity is measured at the Qualifying Assessment and at every follow-up visit.

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. 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.

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 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.

Conjunctiva:

Eyes are examined carefully for tube or shunt erosion.

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 are examined for the presence of tube-cornea touch. An assessment is made of the position and length of the tube in the eye.

Anterior Chamber:

Before fluorescein instillation or pupillary dilation, the degree of anterior chamber cell and flare is determined. Eyes with vitreous in the anterior chamber are ineligible for the study if it is anticipated that a vitrectomy will be needed at the time of glaucoma surgery. 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 > 3 CT, > 2 CT, > 1 CT, < 1 CT, or lens-cornea touch is documented.

Iris:

Before pupillary dilation, the pupillary iris is examined at high magnification for the presence of neovascularization. If rubeosis iridis is present, this should be documented.

Lens:

After pupillary dilation, the investigator assesses the lens and grades any cataract present as mild, moderate, or severe. In pseudophakic eyes, the presence of a posterior chamber or anterior chamber intraocular lens is documented. Aphakic eyes are excluded from the study.

3.3 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 tightfitting 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 1 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 TonoPen 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 1 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.

3.4 Pachymetry
Aqueous shunt implantation has been implicated in long-term damage to the cornea. In this study the position of the tube will be documented in relation to the cornea and the central corneal thickness monitored throughout the study. Central corneal thickness will be measured in each eye, by ultrasound pachmetry. A minimum of 5 measurements will be taken and the lowest recorded. Standard operating procedure (this relates to hard-tipped probe such as the Altair ultrasonic pachymeter, DGH pachymeter, 20 MHz solid tip probe, Optikron 2000, but can apply to any similar device):
1. Place 1 drop of local anaesthetic in each eye.
2. Ask patient to fixate on a target set in the distance
3. Line up pachymeter probe to centre of pupil and advance probe so that it gently touches central cornea
4. Once audible signal heard (signifying measurement obtained) withdraw probe so that it is no longer in contact with the cornea and request that the patient blink.
5. Repeat procedure to obtain 3 readings
6. Record pachymetry measurement and standard deviation if available.

3.5 Motility Evaluation

Diplopia is an important complication which may occur following glaucoma drainage implantation. The incidence of permanent restrictive strabismus associated with glaucoma drainage implantation 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 glaucoma drainage implantation is not uncommon. This study will focus on the incidence and nature of permanent restrictive strabismus associated with the glaucoma drainage implantation. 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. 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. An estimate of restriction of abduction, adduction, elevation and depression of each eye is made using a 0 – 4 empirical grading scale.

3.6 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. A preoperative examination of the anterior chamber angle is essential to document neovascularization and peripheral anterior synechiae, to identify the presence of silicone oil in the angle and to identify an appropriate implantation site for the tube.

3.7 Ophthalmoscopy

A dilated fundus examination is performed at the Qualifying Assessment to determine the preoperative status of the eye, and at all postoperative follow-up examinations to detect any changes in ocular status produced by the disease or treatment. 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. At all postoperative follow-up visits, ophthalmoscopy is performed to evaluate for posterior segment complications, such as serous choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy.

4. Surgical Procedures

4.1 Tube Implantation

Under general anesthesia, peritomy and blunt dissection are done. The Paul Glaucoma Implant (PGI) is checked for patency and a rectangular pericardial patch graft (Tutopatch®) is placed on top of the plate posterior to the valve before the plate is sutured in place 8.5-10mm away from the limbus using Nylon 8/0. Anterior chamber paracentesis is done.

If it is a combined cataract and glaucoma surgery, the surgeon proceeds with phacoemulsification with intraocular lens implant.

The pupil is then miosed and the anterior chamber is reformed with viscoelastic. The tube is then cut to desired length and the track for the tube towards the anterior chamber is created. The tube is then fixed in place with interrupted sutures and covered with Tutopatch® using a fibrin sealant (Tisseel VH S/D, Baxter Healthcare Pte Ltd). Approximately 0.3mL of cross-linked viscoelastic is then injected around & above the plate before closing the conjunctiva. Subconjunctival injection of Gentamycin 20mg with Dexamethasone 4mg is then given at the end of the procedure.

5. Policy Matters
5.1 Patient Consent
5.2 Publication and Presentation Policy
5.3 Surgical Components/Supplies

5.1 Patient Consent

The Study requires that written consent be obtained from each patient enrolled in the study. The patient is requested to sign the consent form only after patient education is completed. 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 kept in the Center. The principal investigator of the study is responsible for obtaining approval for the study and consent form from the local Institutional Review Board A copy of the consent form approved by the Institutional Review Board for the National Healthcare Group is provided in the investigator pack.

Personal data is kept anonymous with non-recognizable code on study document and will follow the HA policy on handling of patient data privacy. To protect participants' privacy, all research data would be handled in line with HA / Hospital's policy in handling / storage / destruction of patients' medical records. They would be locked in cabinets where the department or ward keeps patients' confidential information. Electronic data should be saved in secured computer of the hospital with restricted access.

5.2 Publication and Presentation Policy

The study paper or publication is one which contains details of the design, methods, or results of the study, and is written by investigators from the study participant's record by any unauthorized individual is prohibited. Tabulations or listings which reveal the identity of individual study participants are confidential. All the data would be collected and then submitted to Advanced Ophthalmic Innovations Pte Ltd for centralized collection. The analysis will be conducted under the leadership of Prof. Donald Budenz and Prof. Keith Barton. All the authors will be named collectively as PGI study group.

5.3 Surgical Components/Supplies

For the purpose of this study, Advanced Ophthalmic Innovations Pte Ltd will be providing the following items complimentary for the study:

1) PGI (one per participant)
2) Bovine pericardium patch (Tutopatch®)

6. Literature references relevant to the study

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121:2081-90.
2. Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC; Tube Versus Trabeculectomy Study Group. Postoperative complicaions in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. Am J Ophthalml 2012;153:804-814.
3. http://aoi.sg/product.