The **A**GS **S**econd Aqueous **S**hunt **I**mplant vs. Trans**S**cleral Cyclophotocoagulation **T**reatment **S**tudy

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Short Title

ASSISTS

Long Title

The AGS Second Aqueous Shunt Implant vs. TransScleral Cyclophotocoagulation Treatment Study

1. TITLE PAGE

Protocol Number:	RCEC-2015-STSCPC
Protocol Version:	Amendment 2
Treatment Arms:	1. Second Aqueous Shunt **2.** Transscleral Diode Laser Cyclophotocoagulation
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UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-15-1053
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Protocol Signature Page

The signature below constitutes my review and approval of Protocol RCEC-2015-STSCPC titled "The **A**GS **S**econd Aqueous **S**hunt **I**mplant vs. Trans**S**cleral Cyclophotocoagulation **T**reatment **S**tudy" and attachments and provides the necessary assurances that this trial will be conducted according to all stipulations, including all statements regarding confidentiality and according to local legal and regulatory requirements and applicable U.S. FDA regulations and ICH guidelines.

Investigator Signature: _____

Date: _____

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2. SUMMARY

Study Objective	To compare the 1-, 3-, and 5-year outcomes of a second aqueous shunt (SAS) to Transscleral Diode Laser Cyclophotocoagulation (TLC) in eyes with uncontrolled glaucoma with a single existing aqueous tube shunt implant.
Study Endpoint (Failure)	1. Intraocular pressure (IOP) a. > 18 mmHg on maximum tolerated topical IOP-lowering medications, or b. reduced by < 20% on maximum tolerated topical IOP-lowering medications from medicated preoperative IOP, or c. ≤ 5 mmHg without glaucoma medications on IOP confirmation visit(s), 6 months after initial study intervention; or 2. Additional reoperation for glaucoma (enhancement procedures allowed in the first 4 months); or 3. Addition of an oral carbonic anhydrase inhibitor (CAI) for the study eye on or after the 6-month visit; or 4. No light perception (NLP)
Study Population	18 to 85 years of age with uncontrolled glaucoma on maximum tolerated topical therapy with a single existing tube shunt implant
Study Design	Prospective, multicenter, randomized, masked, parallel group
Treatment Groups	1. Second Aqueous Shunt Implant (SAS) 2. Transscleral Diode Laser Cyclophotocoagulation (TLC)
Duration of Participant Participation	5 Years
Number of Study Visits	10 – 13 visits
# of Evaluable Participants	91 in each group (182 total)
Anticipated Maximum # of Participants	280, allowing for a 35% dropout
Recruitment Period	1 year
Study Centers	Up to 70 centers
Site Funding Available	No
IRB Submission	Site's responsibility (submission, questions, fees)

3. BACKGROUND INFORMATION

Aqueous shunts (AS) are commonly used to treat eyes with glaucoma refractory to medical therapy or eyes that have failed or are at high risk of failing a filtering procedure. The Tube Versus Trabeculectomy (TVT) Study demonstrated that AS were more effective in the long term (5 years) than trabeculectomy in eyes with prior incisional surgery and uncontrolled glaucoma.[2] Largely due to the results of TVT, the frequency of AS implantation has increased 410% between 1994 and 2012.[1] Additionally, it led to the question being evaluated in the Primary Tube Versus Trabeculectomy (PTVT) Study whether primary AS surgery may be appropriate in treating uncontrolled primary open-angle glaucoma, which may further increase the rates of implantation. Despite the favorable results compared to trabeculectomy, approximately 30-50% of AS fail within the first 5 years of implantation.[2, 3]

For eyes where an initial AS fails to control IOP and medical therapy is ineffective, two surgical techniques are often used -- implantation of a second AS or cyclodestruction. Regrettably, there is very little clinical evidence to direct care in cases of initial AS failure. Published studies investigating these two approaches separately conclude that both of these procedures are valid options for eyes with failed initial AS,[4-11] in that they are successful in lowering IOP. However, these studies are small and retrospective, with the exception of one small, non-comparative, prospective case series.[12]

Two retrospective studies published compared second AS with cyclodestruction after a failed initial AS: one with 17 eyes (8 AS, 9 cyclodestruction) in pediatric patients,[13] and the other with 47 eyes (15 AS, 32 cyclodestruction) predominantly in adults.[14] Both studies reported reduction of IOP and number of IOP-lowering medications in both treatment groups. The latter study showed that eyes treated with cyclodestruction had a higher early failure rate (mean 13.5 months), while the second AS group had few early failures, but a higher rate of long-term failures and complications (mean = 6.1 years).[14] While these studies provide the best current clinical guidance for eyes that have failed an initial AS, there is no prospective, randomized, controlled clinical trial evaluating the efficacy or safety of these two treatment options, nor are there any data on the effects of these interventions in this setting on quality of life.

The goal of this study is to provide high-level evidence to guide clinical decision-making in the management of this increasing population of patients given the increasing rates of AS implantation.

4. TRIAL OBJECTIVES

4.1. Primary Aim:

The primary aim is to compare short- (1 year), mid- (3 years), and long-term (5 years) cumulative incidences of failures in participants who undergo a second aqueous shunt (SAS) to those cumulative incidences of failures in participants who undergo transscleral diode laser cyclophotocoagulation (TLC) for eyes with uncontrolled glaucoma with a single existing aqueous tube shunt implant.

The primary outcome variable is success or failure of treatment at 1, 3, and 5 years, where treatment failure is defined as meeting one or more of the following 4 criteria:

1. Intraocular pressure (IOP)
    a) >18 mm Hg on maximum tolerated topical IOP-lowering medications, or
    b) Reduction of < 20% IOP on maximum tolerated topical IOP-lowering medications from medicated preoperative IOP, or
    c) ≤ 5 mm Hg without IOP-lowering medications

    on IOP confirmation visit, 6 months after initial study intervention; or
2. Reoperation for glaucoma; or
3. Addition of an oral CAI for the study eye on or after the 6-Month Study Visit; or
4. Loss of light perception vision (NLP).

4.2. Secondary Aims

The secondary aims are to compare safety (i.e. complications, loss of best-corrected visual acuity [BCVA], and pain) and vision-related quality of life between the two treatments, including:

1. Cumulative incidence of vision-threatening complications at 1, 3, and 5 years after initial study intervention;
2. BCVA at scheduled visits after the 6-month postoperative visit. Changes of BCVA from baseline and the incidence of eyes that have lost more than 2 lines of BCVA will be compared between groups at each visit.
3. Incidence and severity of pain at the 1-week and 1-month postoperative visits.
4. Total number of visits during the first 3 months, first year, and over 5 years.
5. Changes in vision-related quality of life from baseline to 1-, 3-, and 5-year visits, assessed by the NEI VFQ-25.

5. TRIAL DESIGN

This proposed study is a prospective, randomized, multicenter, masked, parallel group study. Sites will be selected based on surgeon's surgical qualifications and experience with the two study interventions, as well as on sufficient staffing and facility resources for conducting the study examinations. The participants will be randomly assigned to receive a SAS or undergo TLC. The cumulative incidences of treatment failure at 1, 3 and 5 years will be compared between groups.

6. PARTICIPANTS

All patients who meet the following eligibility criteria may be enrolled.

6.1. Inclusion Criteria

Patients who meet the following inclusion criteria may be enrolled:

1. Women and men 18 to 85 years of age
2. Glaucoma not adequately controlled (IOP > 18 mmHg on maximum tolerated topical therapy) with a single existing aqueous tube shunt (AS). *If the participant is taking oral carbonic anhydrase inhibitors (CAI) at the time of screening, the IOP prior to initiation of an oral CAI may be used*
3. Best-corrected visual acuity (BCVA) of hand motion (HM) or better in the study eye

6.2. Exclusion Criteria

Patients who meet the following exclusion criteria may NOT be enrolled:

1. Monocular
2. Presence of more than one AS *in the study eye*
3. Previous cyclodestruction *in the study eye*
4. Presence of active iris neovascularization *in the study eye*
5. Binocular diplopia
6. Presence of scleral buckle *in the study eye*
7. History of scleritis in *either* *eye*
8. History of scleromalacia *in the study eye*
9. Insufficient conjunctiva to cover AS in the *study eye*
10. IOP cannot be accurately measured with Goldmann applanation, Pneumotonometer, or Tono-Pen *in the study eye* (e.g. keratoprosthesis)

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11. Presence of silicone oil *in the study eye*
12. Presence of retinal detachment *in the study eye*
13. Presence of intraocular or orbital tumor affecting *the study eye*
14. Need for cataract extraction or concurrent procedure at the time of study treatment, except tectonic aqueous shunt revisions for both groups is allowed
15. In the opinion of the investigator, should not be enrolled in this study (e.g. uncontrolled systemic diseases, altered mental status, etc.)
16. Unwilling or unable to give consent and satisfy requirements of the study (e.g. accept randomization, follow-up for 5 years, etc.)

6.3. Eye

If both eyes of a participant are eligible *and* the investigator plans to perform either of the study procedures in both eyes within three months of screening, the first eye to be treated will be the study eye.

7. STUDY DESIGN CONSIDERATIONS

7.1. Stratification

Eyes will be classified into neovascular glaucoma (NVG) or non-NVG group based on glaucoma diagnosis for the purposes of generalizability.

7.2. Randomization Scheme

An adaptive block randomization scheme will be implemented with a block size of 4 and balancing between NVG and non-NVG strata within each site.

Upon completion of the Screening/Baseline visit, the study eye will be randomly assigned to one of the 2 treatment groups: SAS or TLC within each stratum (NVG vs non-NVG) and each site based on the computer generated assignment.

7.3. Masking

Since intraocular pressure (IOP) is one of the most important measurements for determining treatment success or failure, every effort will be made to obtain unbiased measurements through a masking procedure. IOP will be performed by two study personnel, an operator and a masked reader. Masking procedures are detailed in section 10.3.7.

7.4. Sample Size Calculations

The definition of success/failure in this study is similar to the Ahmed versus Baerveldt Comparison (ABC) study.[3] In the ABC study, the 1- and 5-year failure rate for the primary Baerveldt tube shunt group was 14% and 34%, respectively. Anticipated failure rate for the SAS group is 50% more than the primary tube shunt (~21%=14% x1.5 for 1 year, and 50% = 34%x1.5 for 5 years). Setting the power at 80% and alpha at 5%, a sample size of **91** participants in each group (182 total) would allow us to detect a difference of 20% or more reduction in cumulative incidence of failures in the TLC group from an anticipated 50% failure at 5 years in the SAS group (i.e. <30% in TLC vs 50% in SAS).

The retention rate in the ABC study was 65% at the 5-year visit. A total of **280** participants would allow for a 35% dropout rate (or deaths) during the 5-year study period.

7.5. Recruitment period

The intent of this study is to answer a question that is desperately needed within the glaucoma community. In order to have the question answered in a timely manner, the study plans to involve as many sites as possible from the AGS membership and thereby shorten the recruitment period to *one* year.

7.6. Investigator/Site Selection

Study investigator/site selection will be based on the cumulative number of at least 10 TLCs and 20 ASs (at least 5 of which being inferonasal tube shunts) implanted by an investigator. Additionally, sites must have the necessary staffing and resources to conduct this study.

8. RECRUITMENT PROCEDURE

Recruitment is open for competitive enrollment. The Investigators and/or study staff will enroll qualified participants into the study. After reviewing and signing the informed consent form, a study number will be assigned to the participant in a sequential manner by site identification (assigned by REDCap) followed by participant number. All potential participants will undergo an initial screening examination (Table 2) in order to determine study eligibility.

8.1. Randomization Procedure

Upon completion of the Screening/Baseline visit, sites will enter the Screening/Baseline visit data into the research electronic data capture (REDCap) system to confirm eligibility. Once eligibility of the participant is confirmed, the REDCap system will provide the participant

randomization assignment, SAS or TLC. The participant should be treated within **45** days of the Screening/Baseline visit or the Screening/Baseline visit must be performed again.

9. SURGICAL PROCEDURES

9.1. Second Aqueous Shunt (SAS)

9.1.1. Anesthesia

Anesthesia is at the discretion of the surgeon. The site will record accordingly.

9.1.2. Placement of Aqueous Shunt

Either a *Baerveldt* Glaucoma Implant 350-mm^2 BG101-350 or an *Ahmed* Model FP7 Flexible Plate must be used for all participants unless there is insufficient space, in which case a Baerveldt Glaucoma Implant 250-mm^2 BG103-250 may be used. The implant's preferred location is approximately 180 degrees from the existing initial plate. Tube insertion through the anterior chamber, sulcus, or pars plana is acceptable and will be documented. The site will record the model selected, the quadrant in which it was implanted, the clock hour in which the tube was inserted, and complications, if any.

Implants may not be modified in anyway (e.g. trimming the plate).

9.1.3. Occlusion of Tube (Baerveldt only)

The Baerveldt Glaucoma Implant must be completely occluded in all cases. The method of occlusion is left to the discretion of the surgeon. Occlusion must be tested ensuring there is no flow through the tube or around the sclerostomy. Fenestration of the tube or wick placement is allowed. The site will document the occlusion method used by the surgeon in each case.

9.1.4. Tube Coverage

The type and use of patch graft used to cover the tube is at the discretion of the surgeon. The site will record if a graft is used and the type in each case.

9.1.5. Intraoperative Medications

The use of mitomycin-C, 5-fluorouracil or anti-vascular endothelial growth factor (VEGF) agents are ***not*** allowed at the time of aqueous shunt implantation. Other intraocular medications are allowed.

9.1.6. Concurrent Procedures

Except for tectonic aqueous shunt revisions, concurrent procedures are not allowed at the time of aqueous shunt implantation.

9.1.7. Postoperative Medications

Postoperative medication regimen is at the surgeon's discretion. The site will record accordingly.

9.2. Transscleral Diode Laser Cyclophotocoagulation (TLC)

9.2.1. Anesthesia

Anesthesia is at the discretion of the surgeon. The site will record accordingly.

9.2.2. Laser Settings

Recommended settings are 2000 mW for 2 seconds, 1850 mW for 3 seconds, or 1750 mW for 4 seconds duration, titrating the energy up or down just below where a pop is heard. The site will record starting energy, duration, end energy, and total energy used.

9.2.3. Laser Procedure

Four to eight spots should be used per quadrant for a total of up to 16 spots per 180 degrees (or 2 quadrants). Up to 180 degrees (or 2 quadrants) should be lasered during the initial treatment session. Selection of quadrants to be treated is at the investigator's discretion. The site will record the total number of treatment spots performed. If available, the site will record, the number of prior uses of the G probe.

9.2.4. Concurrent Procedures

Except for tectonic aqueous shunt revisions, concurrent procedures are not allowed at the time of TLC.

9.2.5. Postoperative Medications

Type of postoperative medications is at the surgeon's discretion. The site will record accordingly.

9.3. Enhancement Procedure

The following qualified enhancement procedure ***must*** be completed ***within 4 months*** of the "initial study treatment visit/Day 0)".

9.3.1. Second Aqueous Shunt

Needling of the bleb over the tube shunt plate is allowed within the first 4 months following the initial study treatment. Manual or laser opening of the ligature or obturator removal is ***not*** considered an enhancement.

9.3.2. Transscleral Diode Cyclophotocoagulation

One additional TLC session (up to 2 additional quadrants, not to retreat previously treated quadrants) may be performed in the first 4 months following the initial study treatment.

10. SCHEDULED STUDY VISITS AND ASSESSMENTS

10.1. Study Visit Schedule

10.1.1. Screening/Baseline Visit

After reviewing and signing the informed consent form, all potential participants will undergo a screening examination in order to determine study eligibility, establish baseline ocular characteristics, and assignment to SAS or TLC based on the computer-generated assignment. If available, the mean deviation (MD) from the most recent visual field, prior to or during the Screening/Baseline visit will be collected to further characterize the stage of disease within the study population.

10.1.2. Scheduled Follow-up Visits

Every attempt should be made to conduct each follow-up evaluation within the visit windows (Table 1): Week 1 (-3 days to +14 days), Month 1 (-8 days to +29 days), Month 3 (±1 month), Month 6 (-2 to +3 months), Month 12 (-3 to +6 months), Year 2 (±6 months), Year 3 (-6 months to +1 year), and Year 5 (-1 year to +6 months). Evaluations conducted outside the visit window will be considered protocol deviations.

Table 1. Time Windows for Scheduled Follow-Up Visits (number of days after initial study surgery)

Follow-Up Visit	Ideal Time	Preferred Time Window	Acceptable Time Window
Week 1	7 days	6-8 days	4-21 days
Month 1	30 days	23-37 days	22-59 days
Month 3	90 days	76-104 days	60-120 days
Month 6	182 days	161-203 days	121-273 days
Month 12	365 days	305-425 days	274-547 days
Year 2	730 days	670-790 days	548-912 days
Year 3	1095 days	1005-1185 days	913-1460 days
Year 5	1825 days	1735-1915 days	1461-2007 days

10.1.3. Post-Enhancement Scheduled Follow-up Visits

If an enhancement is performed after the Month 3 Study visit, the participant should be scheduled to return for a follow-up visit 1 month from the enhancement and then resume the normal study schedule. If an enhancement occurs prior to the Month 3 Study visit, the Enhancement 1 Month Study Visit is not required.

10.1.4. IOP Confirmation Visit

If a participant's study eye meets the IOP failure criteria, either at a study visit or a nonstudy visit, a confirmation visit will be scheduled at approximately the same time of day within six weeks during the first year postoperatively and within 3 months after 1 year postoperative visits. Unless an emergent intervention is required, confirmation visits should occur when:

1. IOP is >18 mm Hg on maximum tolerated topical IOP-lowering medications 6 months after initial study intervention, or
2. IOP reduction is < 20% on maximum tolerated topical IOP-lowering medications from medicated preoperative IOP 6 months after initial study procedure, or
3. IOP is ≤ 5 mm Hg without IOP-lowering medications 6 months after initial study procedure

10.2. Scheduled Assessments

Table 2 outlines the schedule of assessments at each visit throughout the study period. Data from the study visits must be entered into the REDCap system within 5 business days of the exam.

Table 2: Schedule of Assessments

Assessment	Screening / Baseline	Surgery – Day 0	Week 1	Month 1	Month 3	Enhancement Procedure	Enhancement Month 1	Month 6	Month 12	Year 2	Year 3	Year 5 / Exit	Confirmation Visit***
Informed Consent	X												
Demographics	X												
Medical / Ophthalmic History	X												
Historical VF MD*	SE												
Concomitant Medications	OU		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Inclusion/Exclusion Criteria	X												
Visual Acuity	OU		SE	SE	SE		SE	SE	SE	SE	SE	SE	
Binocular Diplopia	X				X			X	X	X	X	X	
External Ocular Examination	OU			OU	OU				OU				
Specular Microscopy (CCT and CD)**	SE								SE			SE	
Biomicroscopy	SE		SE	SE	SE		SE	SE	SE	SE	SE	SE	
Intraocular Pressure	OU		SE	SE	SE		SE	SE	SE	SE	SE	SE	SE
Ultrasonic Pachymetry	OU								SE			SE	
Ophthalmoscopy	SE								SE			SE	
OCT (macula)	SE								SE				
Procedure		SE				SE							
VFQ-25	X								X		X	X	
Randomization	X												
Pain Scale			X	X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

Perform assessment, not eye specific (**X**), study eye only (**SE**), both eyes (**OU**)

* The mean deviation from the participants last visual field (if available) prior to enrollment will be recorded to further describe the stage of disease in the study population.

**Specular microscopy (SM) will be performed at sites where SM is available

***Confirmation visits will occur prior to the conduct of any surgical intervention in the study eye when IOP is believed to have met endpoint (failure).

10.3. Assessments

The same examiner should perform the same assessments for each participant whenever feasible throughout the study.

10.3.1. Ocular Medications

All IOP-lowering medications that the participant is taking at the time of the Screening/Baseline visit and for the duration of the study will be recorded. Concomitant medications will be captured by class of medication.

No investigational drugs may be used during the study and participants may not participate in any other medical or device study during the course of this investigation.

10.3.2. Visual Acuity

Visual Acuity testing should precede IOP measurement, the administration of eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye. A decrease in visual acuity of *more than two lines* should be reported as an adverse event (or the cause of the decrease in visual acuity).

Manifest refraction must be performed prior to Best-Corrected Visual Acuity (BCVA) at all visits assessing vision except Week 1. Pinhole visual acuity may be used for the Week 1 postoperative visit.

The Snellen visual acuity chart should be used to measure BCVA. The participant's visual acuity will be recorded as the last line read on which two or fewer letters were missed. If the participant cannot read the largest letter on the chart, the examiner should perform the following tests:

Count Fingers: The examiner should hold his/her fingers in front of the participant's eye in good light and the vision is recorded as the furthest distance that the fingers can be counted, CF (feet).

Hand Motion: If the participant cannot see or count fingers, the examiner should wave a hand in front of the eye at a distance of two feet. If movements of the hand are seen by the participant, then the vision is recorded as HM.

Light Perception: If visual acuity is so poor that the participant cannot read any of the letters and fails counting fingers and hand motion test, light perception needs to be tested with the indirect ophthalmoscope as the light source. Room lighting should remain at the level of normal visual acuity testing. The participant should close the opposite eye and cover it with the *palm* of their hand. The indirect ophthalmoscope light should be in

focus at 1 meter (3 feet) with the rheostat set at maximum voltage. From a distance of 3 feet, the beam should be directed in and out of the eye at least 4 times, and the participant should be asked to respond when he or she sees the light. If the examiner is convinced that the participant sees the light, vision should be recorded as LP. If the examiner is convinced that the participant does not see the light, vision should be recorded as *NLP*.

10.3.3. Binocular Diplopia

All participants will be assessed for presence of binocular diplopia with correction at Screening/Baseline and all visits on and after the 3-months postoperatively (except Enhancement Month 1 and IOP confirmation). It will be documented as “present” or “absent”.

10.3.4. External Ocular Examination (Exophthalmometry)

Participants will be assessed for proptosis at the Screening/Baseline, Month 1, Month 3 and Month 12 Visits. If proptosis is grossly present, a Hertel exophthalmometer should be used to measure the amount of proptosis.

10.3.5. Specular Microscopy

Three quality central corneal images of the study eye should be taken by Specular Microscopy at Screening/Baseline, Year-1, and Year-5 visits prior to any administration of drops or contact with the eyes. Central corneal thickness (CCT) and cell density (CD) will be obtained and the values will be recorded from each image. The average will be calculated for each variable.

10.3.6. Biomicroscopy

A slit lamp examination will be performed on the lids, conjunctiva, cornea, anterior chamber, iris, and lens at each visit (except surgery, enhancement, and IOP confirmation visits). Any abnormalities will be graded as clinically significant or not and severity graded as mild (=1), moderate (=2), or severe (=3). Cells will be graded as trace (1-5 cells), mild (6-15 cells), or moderate/severe (> 15 cells / High Powered Field). The study tube position will be examined in two places: (1) tube measured approximately 1mm in from the limbus, and (2) the tube tip in the anterior chamber (AC), and will be assessed as:

(a) Touching cornea

(b) Close to cornea

(c) Mid-AC

(d) Close to iris, or

(e) Touching iris.

If the study tube is present and visible in the AC, the length of the tube will be measured with the slit beam in millimeters. If the tube is behind the iris, document whether the tube is tenting the iris. The initial AS tube will be measured in the same fashion as the study tube at the Screening/Baseline, Year-1, Year-3, and Year-5 Visits.

If there is no view beyond the cornea, “inadequate view” will be marked on the data collection form.

10.3.7. Intraocular Pressure

IOP measurements should be performed at all study visits at approximately the same time of day from the Screening/Baseline visit. All IOP checks must be performed prior to dilation.

Two *individuals (an operator and a masked reader) must perform the IOP measurements. The operator will be responsible* for operating the instrument while the masked reader will read and record the results. In order to minimize the measurement variation, all IOP measurements for any individual participant should preferably be performed by the same operator with the same tonometer.

Starting with the right eye, alternating between the two eyes, two IOP measurements should be performed on each eye. The mean of the two measurements will be used for analysis. If the difference between the two measurements for an eye is greater than 2 mm Hg, a third measurement must be taken. The median of the three measurements will be used for analysis.

Three instruments for measuring IOP are allowed and will be chosen based on the participant’s cornea status. The same type of instrument should be used for the duration of the study unless new pathology has developed that prevents accurate usage of the initial method.

Goldmann Applanation Tonometry: Following instillation of a drop of fluorescein and anesthetic, ensure the participants head is properly positioned in the chin rest and against the forehead rest; encourage the participant to continue breathing normally. The operator will look through the slit-lamp and adjust the dial while the masked reader records the IOP measurement. The reader will be masked to the participant’s treatment.

Pneumotonometry: A pneumotonometer will be used in cases of corneal edema, corneal scarring, or irregular corneal astigmatism. The technique described in the user’s manual should be performed. The operator will turn the display facing away from himself/herself while the masked reader records the measurements.

Tono-Pen: The Tono-Pen will be used in cases of corneal edema, corneal scarring, or irregular corneal astigmatism at sites where a pneumotonometer is not available. The

technique described in the user's manual should be performed. The operator will hold the display out to the reader for the IOP and reliability to be recorded.

10.3.8. Ultrasonic Pachymetry

CCT measurements will be obtained by Ultrasonic Pachymetry 5 times for each eye. The median of the 5 measurements will be used as the CCT.

10.3.9. Ophthalmoscopy

Any vitreous or retinal abnormalities will be noted and graded as clinically significant or not clinically significant. A vertical cup-to-disc ratio will be measured with a slit lamp lens.
If a dilated exam has been performed within 1 month prior to Screening/Baseline visit, the information collected from that visit may be used for the study.

If there is no view of the posterior chamber, "inadequate view" will be marked on the data collection form.

10.3.10. Optical Coherence Tomography (OCT)

OCT of the macula should be performed at the Screening/Baseline and Month 12 visits to assess for presence or absence of macular edema. Sites will be asked for the central macular thickness at Screening/Baseline and future visits requiring OCT if a participant presents with a decrease in visual acuity of more than 2 lines and macular edema is suspected. Sites will provide a deidentified copy of the macular thickness map to the DCC when performed.

10.3.11. Universal Pain Scale

Following the initial study treatment, participant pain or discomfort will be assessed at Week 1 and Month 1 visits with the Universal Pain Scale (Appendix 1).

10.3.12. Visual Function Questionnaire (VFQ-25)

Participant-reported visual function will be assessed with the National Eye Institute (NEI) Visual Functioning Questionnaire 25 (VFQ-25, see Appendix 2) at Screening/Baseline, Year 1, Year 3, and Year 5 visits. The VFQ-25 will be administered by site study personnel.

11. PROTOCOL DEVIATIONS

Protocol deviations must be reported by the Study Site to the DCC within five business days. Sites will be notified of protocol deviations discovered during data monitoring and source

document verification. Study Sites must also submit protocol deviations to their IRB pursuant to their IRB policy.

12. ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a participant who isadministered a test article. The AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with study treatments.

A nonserious AE is defined as a change in a participant's ophthalmic and/or medical health that is not life-threatening, does not require hospitalization, does not prolong a current hospitalization and is not disabling. All AEs must be reported to the DCC using REDCap. All AEs must be reported whether they are considered study-related or not.

12.1. Serious Adverse Events

A serious adverse event is defined as any adverse experience occurring at any time during the study that results in:

- Death
- Life-threatening
- Inpatient hospitalization
- Prolongation of existing hospitalization
- Disability or permanent damage (including vision threatening complications)
- A congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage and/orother serious important medical events

SAEs will be documented the same as adverse events, but flagged as a SAE. All SAEs should be submitted in REDCap within five business days of the Investigator's knowledge of the event. When new significant information is obtained as well as when the outcome of an event is known, the Investigator must provide updates in REDCap. If the participant is hospitalized, a deidentified copy of the discharge summary must be uploaded into the REDCap system as soon as it becomes available. All SAEs must be submitted to the sites IRB pursuant to their IRB policy.

12.2. Recording Instructions

Mild, moderate, or severe should be used to describe the maximum intensity of the event.

- Mild – Does not interfere with the participant's usual functions
- Moderate – Interferes to some extent with the participant's usual functions
- Severe – Interferes significantly with the participant's usual functions

It should be noted that a severe intensity does not necessarily mean it is an SAE.

The investigator will also be asked to determine the likelihood of the relationship between the study intervention and the AE.

12.3. Follow-up of Adverse Events

For participants who have ongoing ocular adverse events at the time of their exit visit, it is recommended that the Investigator schedule a follow-up visit to determine the outcome of the event.

13. MONITORING

Complete source documents will be monitored for the first participant enrolled in the study at each site and randomly thereafter. A deidentified copy of the source document will be submitted to DCC for source verification. Random monitoring of 10% of study visits will be performed; monitoring of additional study visits will be undertaken based on performance and queries. Deidentified source documents must be provided upon DCC request. Onsite monitoring visits may be required if Study Sites are unresponsive to DCC requests or excessive discrepancies are found.

14. DATA AND SAFETY MONITORING BOARD

Throughout the course of the study, all adverse events will be monitored and reported on an adverse event case report form, including seriousness, action taken and relationship to study treatment. A Data and Safety Monitoring Board (DSMB), independent from the study, will review all serious adverse events (SAE). The committee members will be selected for this study by the Chair, Dale Heuer, based on their experience and qualifications. If adverse events occur, the first concern will be the safety of the study participant. For additional details of the conduct and procedures for the DSMB please see the DSMB charter.

15. WITHDRAWAL OF STUDY PARTICIPANT

If a participant wishes to withdraw from the study, the reason for withdrawal should be documented in the source document and REDCap. An exit visit should be performed if possible. If a participant does not return for a scheduled visit, every effort should be made to contact the participant and document the participant's outcome.

Relevant tests and assessments should be performed according to the schedule for Year 5/Exit visit if withdrawal occurs between surgery and Year 5 visits.

16. DATA ANALYSIS

16.1. Interim Analysis/Safety Monitoring

A number of interim analyses will be performed. The purpose of these analyses will be:

a. To monitor recruitment targets in subgroups of interest (NVG vs non-NVG) and to monitor balance between treatment groups with regard to prognostic factors.
b. To provide a regular mechanism for evaluating data quality, protocol adherence, and side-effect patterns including adverse reactions.
c. To determine whether the study should be terminated early. Negative results could suggest that there is no possibility of ever establishing significance between-group differences.
d. To assess the possibility that a positive but nonsignificant trend might require an increase in the originally projected sample size or an increase in the study duration.

Interim analyses will be performed every 3 months for the first year of enrollment and every 6 months thereafter. Interim analyses may also be performed at any time upon the request of the DSMB. The DCC will provide the results to the DSMB for making all decisions regarding the future conduct of the study. All investigators will be masked as to the results of interim analyses.

16.2. Primary Analysis

In the primary analysis, the null hypothesis is that there is no difference in one-year cumulative failure rates between the SAS group and the TLC group. The cumulative failure rates will be compared with Fisher exact test with one degree of freedom. The survival time from the treatment to failure will be estimated by Kaplan-Meier survival curve for each group and compared between the two treatment groups with the log-rank test. The potential effect of covariates will be assessed with the Cox proportional hazards models.

16.3. Secondary Analysis

16.3.1. To compare changes in vision related to quality of life from baseline to 1-, 3-, and 5-year visits between SAS and TLC groups, measured by NEIVFQ-25

Differences between study groups in NEI-Visual Function Questionnaire (NEI-VFQ-25) and its subscales will be analyzed both cross-sectionally and longitudinally. Either a Student's t-test or a nonparametric Wilcoxon rank sum test will be used for the cross-sectional comparison between groups and a mixed-effect model with repeated measurements will be used to compare two groups over the study period.

16.3.2. To compare cumulative incidence of vision-threatening complications at 1, 3, and 5 years post-treatment between groups

Vision-threatening complications will be defined by the DSMB. The safety effect of treatment will be assessed by comparing the cumulative proportions of vision-threatening complications or the event rates per person-year from the time of randomization with asymptotic X^2 test with one degree of freedom. The survival curve from the time of randomization to the first occurrence of vision-threatening events will be compared between the two randomization groups with the log-rank test. The potential effect of covariates will be assessed with the Cox proportional hazards models.

16.3.3. To compare BCVA at visits after the 6-month postoperative visit

Snellen BCVA will be converted to line scale by logMAR. Differences between study groups will be analyzed both cross-sectionally and longitudinally. Either a Student's t-test or a nonparametric Wilcoxon rank sum test will be used for the cross-sectional comparison between groups and a mixed-effect model with repeated measurements will be used to compare two groups over the study period.

The incidence of loss more than 2 lines from baseline to each follow-up visit will be compared with a Fisher exact test.

16.3.4. To compare incidence and severity of pain between groups at the initial 1-week and 1-month postoperative visits.

The incidence and severity of pain at the 1-week and 1-month follow-up visits will be compared with a Fisher exact test and a Student t test (or a Wilcoxon rank sum test), respectively.

16.3.5. To compare the total number of visits during the first three months, during the first year, and during all five years of the study between groups.

Differences between study groups in total number of visits during the first three months, during the first year, and during all five years of the study will be compared between study groups on the distributions with either a Student's t-test or a Wilcoxon rank sum test.

The large number of measures used to assess safety and the frequency of interim analyses to monitor safety introduce the problem of multiple comparisons, i.e. some comparisons are statistically significant because of the large number of statistical tests conducted. Analyses that adjust for multiple comparisons will be conducted and both adjusted and unadjusted multiple comparisons will be reported to the Data and Safety Monitoring Committee.

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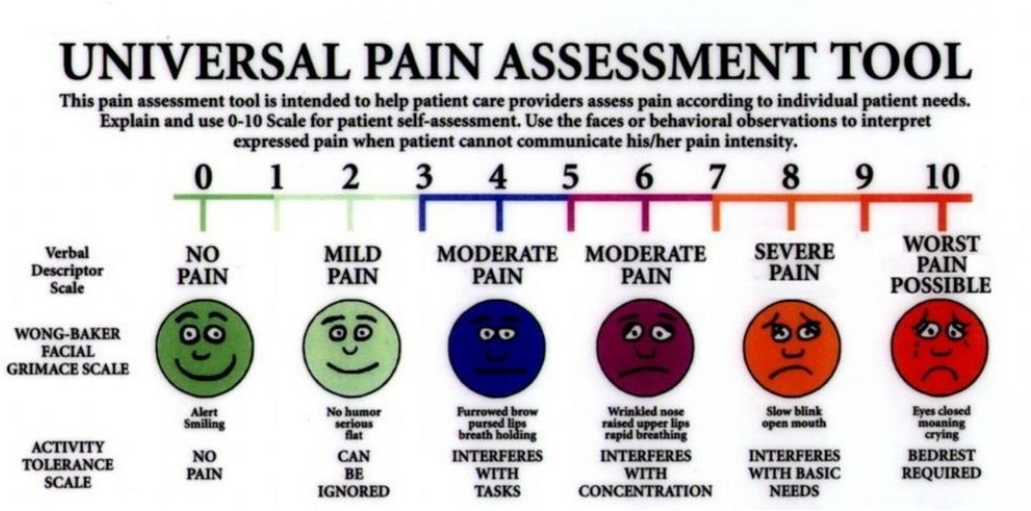
APPENDIX 1.



APPENDIX 2.

National Eye Institute Visual Functioning Questionnaire – 25 (VFQ-25) version 2000 (INTERVIEWER FORMAT)

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-15-1053
IRB APPROVAL DATE: 08/20/2020

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent 1
Very Good.....2
Good 3
Fair 4
Poor..... 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent 1
Good 2
Fair 3
Poor..... 4
Very Poor.....5
Completely Blind.....6

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time.....1
A little of the time.....2
Some of the time.....3
Most of the time 4
All of the time?.....5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None.....1
Mild.....2
Moderate.....3
Severe, or.....4
Very severe?.....5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

6. **How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

7. **Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

8. **How much difficulty do you have <u>reading street signs or the names of stores</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

9. **Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</u>?**

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty 2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u> ?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes. .....1 *Skip To Q 15c*

No.....2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove. ..... 1 *Skip To Part 3, Q 17*

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty.....4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Have you stopped doing this because of your eyesight.....5
Have you stopped doing this for other reasons or are you not interested in doing this 6

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Have you stopped doing this because of your eyesight.....5
Have you stopped doing this for other reasons or are you not interested in doing this 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.....	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your <u>overall health</u>, on a scale where zero is <u>as bad as death</u> and 10 is <u>best</u> possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

A4. Because of your eyesight, how much difficulty do you have <u>figuring out whether bills you receive are accurate</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A5. Because of your eyesight, how much difficulty do you have doing things like <u>shaving, styling your hair, or putting on makeup</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have <u>recognizing people you know from across a room</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

A7. Because of your eyesight, how much difficulty do you have <u>taking part in active sports or other outdoor activities that you enjoy</u> (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have <u>seeing and enjoying programs on TV</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight.....5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have <u>entertaining friends and family in your home</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all.....1
A little difficulty.....2
Moderate difficulty.....3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10.[This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you <u>all</u>, <u>most</u>, <u>some</u>, <u>a little</u>, or <u>none</u> of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. **<u>Do you have more help</u> from others because of your vision?.....**	1	2	3	4	5
b. **<u>Are you limited</u> in the kinds of things you can do because of your vision?.**	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
A13. I don't go out of my home alone, because of my eyesight.	**1**	**2**	**3**	**4**	**5**