Advanced Imaging for Glaucoma Study

Manual of Procedures
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1   Introduction

1.1 Synopsis of the Advanced Imaging for Glaucoma (AIG) Project

"Advanced Imaging for Glaucoma" (AIG) is a multi-center bioengineering partnership sponsored by the National Eye Institute (NEI). The partnership includes four clinical centers, University of Pittsburgh Medical Center/University of Pittsburgh School of Medicine (UPMC), University of Miami/Bascom Palmer Eye Institute (BPEI), University of Southern California (USC), and Casey Eye Institute at Oregon Health & Science University (OHSU). The Coordinating Center and Chairman's Office are located at OHSU. There are two engineering centers, Oregon Health & Science University and Massachusetts Institute of Technology, Department of Electrical Engineering and Computer Science and Research of Electronics (For the previous participating engineering centers in Phase 1, please refer to Chapter 8, Organization). The goal of the partnership is to develop advanced imaging technologies to improve the detection and management of glaucoma. The advanced imaging technologies include optical coherence tomography (OCT), scanning laser polarimetry (SLP) and scanning laser tomography (SLT). The technologies will be evaluated in a longitudinal clinical trial composed of glaucoma suspects, glaucoma patients and normal subjects. Originally designed as a five year study, the AIG Study was renewed for a second five years of funding by NIH; the study duration has subsequently been extended from five years to 10 years.

This document details the clinical study portion of the overall project.

The engineering portion of the project aims to improve the use of existing advanced imaging platforms and develop new advanced imaging technology. These improvements will be added to the clinical study as they become available.

Study participants that continue past the 60 month period will need to be re-consented for the new study period. They must sign the new informed consent form when they come in for the next follow up visit.

1.2 Specific Aims of the AIG Study (AIGS)

The specific aims of the clinical studies are to:
1. Predict the development of glaucomatous visual field (VF) abnormality in glaucoma suspects and pre-perimetric glaucoma patients based on anatomic abnormalities detected by advanced imaging.
2. Predict the development of glaucomatous VF abnormality in glaucoma suspects and pre-perimetric glaucoma patients based on anatomic changes detected between successive advanced imaging tests.
3. Determine the sensitivity and specificity of glaucoma diagnosis based on advanced imaging tests.

1.3 Background and Significance

1.3.1 Glaucoma Diagnosis and Treatment

Glaucoma is a common ocular disease that causes irreversible visual loss due to a progressive optic neuropathy. Increased intraocular pressure (IOP) is the major risk factor in most cases of glaucoma, and current standard therapy is based on reducing IOP by drugs, laser treatment or surgery. Despite the importance of IOP elevation in causation, it alone is a poor guide to either diagnosis or management. IOP is not reliably associated with existing glaucoma or with glaucoma progression. The susceptibility of an individual optic nerve to pressure-induced damage is highly variable. Predicting a safe pressure level for a given individual is a guess that needs be confirmed or rejected based on sequential evaluation of optic nerve status.

Early diagnosis requires effective glaucoma screening in the general population. Due to its simplicity, IOP measurement is still the most common screening test for glaucoma. The usual cutoff for normal IOP is 21 mm Hg or below; however, the sensitivity and specificity of IOP for glaucoma detection is poor, as many people with high IOP do not have glaucoma and only a minority eventually develop glaucoma.[1] Ideally, a screening examination should include evaluation of the optic nerve head (ONH) appearance and VF by an ophthalmologist. This greatly expands the complexity and cost and is still not completely reliable.

The VF examination asks the subject to respond (press a button) to spots of light sequentially projected at various positions within the field of vision. The threshold of perception is quantified over many positions. VF testing is often unreliable or irreproducible due to limitations in the subjects' ability to give accurate responses over tens of minutes of tedious repetition in each test. Furthermore, VF abnormality becomes detectable only after significant retinal nerve fiber layer (NFL) loss has already occurred.[2] Inspection of the optic nerve and the peripapillary NFL can provide earlier clues to the diagnosis of glaucoma.[3-7] Glaucomatous eyes tend to have a larger depression in the ONH (large cup-to-disc ratio) and sometimes have visible focal defects in the normally symmetric nerve fiber bundles radiating out of the ONH. However, the wide range of normal anatomical variation and the subjective nature of clinical examination limit their reliability.

Management of glaucoma also suffers from a lack of reliable tests. Currently, a clinician establishes treatment goals based on lowering the pressure from the range at which glaucomatous damage has occurred. The target IOP must be validated by demonstrating stability of the optic nerve. If glaucoma progression occurs, the IOP goal must be lowered. The variability inherent in current methods for optic nerve assessment makes these decisions difficult. Progression of VF defects is poorly reproducible and requires at least one repetition for confirmation.[8] The poor reproducibility also contributes to heightened diagnostic threshold and poor sensitivity. Changes in optic disc appearance often precede VF changes.[9] But, again, the subjective nature of visual inspection by an ophthalmologist limits its sensitivity and reliability and the usefulness of photographic records is limited by difficulties with their variability and availability.

Though effective pressure-lowering therapy is available, many patients still lose their sight to glaucoma. This may reflect delay in diagnosis, uncertainties regarding treatment goals and responses, and treatment failures. A reliable objective measure of optic nerve status will address the diagnostic issues.

If subjective grading of optic nerve and NFL anatomy can detect damage prior to VF defects,[9, 10 3-7] then it is logical that objective measurements would be even more reliable for glaucoma detection and management. This provided the rationale for the development of a number of imaging tools to provide quantitative measures of the optic nerve status. The most successful of these technologies include OCT, SLP and SLT. Many studies have shown that these tests provide good reproducibility[11-14] and fair agreement with VF, optic disc grading, NFL photography and each other in terms of glaucoma diagnosis.[10, 15-44] On the other hand, these studies can only show that advanced imaging is correlated with the conventional measures of glaucoma. Because of the lack of a gold standard, they cannot show that the more expensive imaging tests are of any additional clinical utility beyond conventional VF and optic disc grading. To fully justify the use of advanced imaging in glaucoma, we must show that these modalities can diagnose glaucoma and detect glaucomatous change before detection by VF and optic disc examination. This can only be done in a large longitudinal clinical study.

On a MEDLINE literature search, we have only found one medium-sized study of this type, and it showed that SLT detected progression earlier than VF in a population of early-glaucoma patients.[45] To provide much-needed new information in this important area, we plan to test the current best advanced imaging technologies in a large longitudinal clinical study that includes glaucoma suspects, glaucoma patients and normal subjects. Our study will devote the most resources to eyes currently classified as "glaucoma suspect." These eyes have high risk factors (such as elevated IOP or increased optic disc cupping) but do not meet the glaucoma diagnostic criteria based on VF. The suspect population is larger than the one with a definitive diagnosis of glaucoma. Many of these glaucoma suspect eyes may have glaucoma or progress to glaucoma without being detected by conventional measures. On the other hand, we cannot treat all of these suspect eyes given the possible adverse side effects of drugs, laser and surgery. We believe these eyes can benefit most from the early detection of glaucomatous anatomic changes with advanced imaging.

1.3.2 Optical Coherence Tomography in Glaucoma Diagnosis

Optical coherence tomography (OCT)[46] is a new imaging technology that can perform non-contact cross-sectional imaging of tissue structure in real time. It is analogous to ultrasound B-mode imaging, except that OCT measures the intensity of reflected light rather than acoustical waves. The axial depths of reflected light are resolved in a low coherence interferometer that scans the delay of light propagation. Tomographic images are generated by scanning the optical probe beam across the tissue structure of interest. OCT has a number of features that make it attractive as a diagnostic imaging modality:

1. It has sufficient resolution for visualization of retinal sublayers, which is not possible with any other noninvasive technique. The best commercial OCT retinal scanner has a resolution of 9 μm, and 3-μm resolution retinal imaging has been reported.[47, 48]

2. OCT imaging may be performed without any contact with the eye.

3. OCT images are generated in electronic form, which facilitates the use of digital image-processing techniques to extract quantitative parameters regarding the imaged tissue anatomy.

OCT has become a common instrument for retina and glaucoma clinicians through three successive models marketed by Carl Zeiss Meditec, Inc. (Dublin, CA, USA). The most recent Stratus OCT model has ~10 micron axial resolution and is able to perform 400 axial scans per second. The standard OCT imaging protocol for glaucoma uses a 3.4-mm diameter circular scan around the optic disc. The current protocol uses 256 axial scans to form one image in 0.6 seconds. This cylindrical scan provides a complete cross-section of the retinal nerve fiber layer (NFL) as the fibers converge into the ONH. The overall and sector average of NFL thickness are used by clinicians to diagnose and monitor glaucoma.[11, 14-20, 22, 31, 33, 35, 37, 38, 44, 49-52]

1.3.3 Scanning Laser Polarimetry

Scanning laser polarimetry (SLP) measures the change in polarization of light reflected from the retina and choroid. It is a variant of confocal laser scanning ophthalmoscopy. The polarization of reflected light is used to compute the birefringence of the NFL. Birefringence is an intrinsic optical property of the nerve fibers due to their long cylindrical structure. To facilitate understanding, NFL birefringence (in degrees of phase retardation) is converted to a NFL thickness figure. SLP can rapidly image an area around the ONH in a fraction of a second. The NFL thickness is usually analyzed along a circle around the optic disc. Statistics of the NFL thickness are used by clinicians to diagnose and monitor glaucoma.[17, 21, 22, 25-28, 31, 32, 34, 42, 43, 53-62] SLP is commercially available from Laser Diagnostic Technologies, Inc. (San Diego, CA, USA). The current model, GDx-VCC, measures and compensates for the birefringence in the cornea to improve accuracy.

1.3.4 Scanning Laser Tomography

The scanning laser tomography (SLT) scanning device projects light via a confocal system that ensures that only light reflected from a defined focal plane is detected. Parallel sequential planes are scanned and the composition of all the scans enables the construction of a three-dimensional representation of the ONH. ONH parameters from the 3-D dataset are used by clinicians to diagnose and monitor glaucoma.[13, 17, 22-24, 29-31, 36, 38-41, 44, 45, 63-66] In this study, SLT scans are done with Heidelberg Retina Tomograph 2 (HRT2; Heidelberg Engineering GmbH, Heidelberg, Germany). This device has been shown to provide reproducible results,[67-73] with moderate-to-good agreement between different observers analyzing the same images.[74] The HRT2 scans a continuous grid of 384 x 384 measuring points with an image field of 15˚ x 15˚ along the ONH region and the operator is required to draw a contour line along the disc margin. Based on the mean height along 6˚ of the contour line in the temporal inferior (350-356˚) sector, the machine automatically calculates the reference plane that is located 50 μm posterior to the retinal surface in this area. Structures underneath the reference plane and within the contour line are defined as the disc cup. Structures above the reference plane and within the contour line are defined as the neuroretinal rim. Each participant has three high-quality scans recorded at one sitting.

The quality of the images is assessed with the aid of HRT software and by the experience of the observer. The mean topography of the three-scan series is used for the analysis. The contour line along the disc margin is drawn by the imaging technician. The standard

reference plane is used and the following parameters are analyzed: optic disc area, cup area, cup volume, cup/disc area ratio, rim area, rim volume, Mikelberg's classification analysis and Moorfields regression analysis; however, numerous HRT parameters have been found to be of value for glaucoma detection. Brigatti et al. found good correlation between the third moment of the optic cup, which is an overall measure of the disc shape, and VF global indexes.[75] Teesalu et al. reported better correlation between the cup shape measure (third moment) and global SWAP indexes than those found with full threshold VF.[76] Since the SWAP is more sensitive for early glaucomatous damage, this might indicate higher sensitivity of this HRT parameter in detecting glaucomatous changes. Zangwill et al. reported a significant difference among normal subjects, ocular hypertensives and glaucoma patients for the neuroretinal rim area and volume.[65] Eid et al. found substantial reduction in the retinal NFL measurement, as obtained by the HRT, between glaucoma patients and age-matched healthy subjects with high correlation with VF global indices.[77, 78]

HRT2 provides two methods that combine several parameters. Mikelberg et al. presented a method that takes into account the cup shape measure (third moment), rim volume and height variation along the contour line.[79] Wollstein et al. suggested a method where the measured rim area is adjusted for the ONH size for the entire disc and for six predefined segments.[80] Both methods are capable in differentiating between normal subjects and early glaucoma patients with higher specificity and sensitivity than any given HRT parameter. Chauhan et al. suggested a method for detecting longitudinal change in glaucoma patients with the HRT.[81] This method determined the normal variability in consecutive scans in a superpixel composed of 16 adjacent pixels. This method have been found to be sensitive in detecting longitudinal changes.[82]

In summary, the HRT provides quantitative ONH measurements that have been found to be of value in distinguishing between normal subjects and glaucoma patients as well as for longitudinal evaluation.

1.3.5 Swept Source Optical Coherence Tomography

The clinical center at OHSU has an ultra-high speed Swept Source Optical Coherence Tomography (SS-OCT) device that will be used in addition to and in place of the SLP and SLT technologies used at the other clinical centers.

1.4 Preliminary Studies

1.4.1 Optical Coherence Tomography

Two of the partnership investigators, Drs. Huang and Schuman, are co-inventors of OCT[46] and participated in its initial application to retinal diseases and glaucoma.[11, 15, 83] More recently, we have developed new anatomic parameters that may improve the sensitivity of glaucoma detection. Drs. Huang and Schuman have found that the ratio of reflectivity between NFL and the outer retina decreases in glaucoma and may provide a better discrimination between glaucoma and normal subjects than looking at NFL thickness or internal reflectivity alone.[84] Dr. Schuman's group has worked on OCT algorithms to best detect focal defects in the NFL.[85] Drs. Schuman and Greenfield have

both demonstrated that macular retinal thickness is decreased in glaucoma.[19,86] Presumably, macular retinal thinning is due to thinning of the ganglion cell layer (GCL), which contains the cell bodies of axons in the NFL. Dr. Huang's group has recently developed an image-processing algorithm to measure GCL thickness from OCT macular images. Dr. Schuman's group has also developed software to map the thickness of the inner retina, which is the sum of the thickness of the NFL, GCL and inner plexiform layer (IPL). These new approaches may eventually prove to be a more sensitive and specific way to detect macular changes in glaucoma. Dr. Schuman's group has recently validated the use of OCT in measuring ONH parameters.[36] Our clinical study will employ all of these approaches to glaucoma diagnosis.

1.4.2 Scanning Laser Polarimetry

For many years, a major impediment to the accuracy of SLP has been the confounding birefringence of cornea. Polarization change in the SLP beam is introduced by passage through birefringent structures. For the SLP, the laser probe beam passes through both the cornea and NFL and the combined effect of their birefringence is measured by the polarimeter. To derive NFL birefringence alone, corneal effects must be removed. The earlier SLP models employed a fixed corneal compensation based on the average corneal birefringence. This can introduce significant error due to the wide variation of corneal birefringence magnitude and axis in the population. Drs. Knighton and Greenfield have helped to develop methods to measure and compensate for corneal birefringence to improve the accuracy of SLP.[32, 34, 61, 86-89] The latest generation of SLP, the GDx-VCC, employs this variable corneal compensation technology. Our study will utilize the GDx-VCC.

1.4.3 Scanning Laser Tomography

Dr. Schuman's group has shown that ONH analysis by SLT and OCT are both highly correlated with glaucoma disease status.[36]

1.5 Study Milestones

Sept. 30, 2003   Funding began for AIG with award of NIH Grant 1 R01 EY013516-01A1.

Sept. 23, 2008   Awarded five year NIH Grant renewal 2 RO1EY013515-06.

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2   Study Design

2.1 Synopsis of Study Design

The AIG project includes a clinical study to develop and evaluate glaucoma diagnosis with the latest generation of advanced imaging instruments. The AIG clinical study was originally designed as a five year study but was extended to ten years after further funding from NIH. The instruments to be evaluated include OCT (Stratus OCT, Carl Zeiss Meditec, Inc., Dublin, CA, USA), SLP (GDx-VCC, Laser Diagnostic Technologies, Inc., San Diego, CA, USA) and SLT (HRT2, Heidelberg Engineering, Heidelberg, Germany, (RTVue, Optovue, Inc., Fremont, CA). Other imaging platforms will be added as they are developed by the AIG engineering centers. The experimental platforms planned are ultra-high resolution OCT, polarization-sensitive OCT and multi-angle OCT.

The longitudinal study will be divided into two arms: (1) a study on glaucoma patients and age-matched normal subjects with the primary purpose of establishing normal reference ranges and diagnostic criteria, and (2) a prospective observational study on glaucoma suspects and pre-perimetric glaucoma patients to test the ability of advanced imaging technologies to predict future development of glaucomatous VF defects.

Three clinical centers at USC, UPMC, BPEI and OHSU will participate in the trial. Advanced imaging, visual fields and optic disc stereo photographs will be evaluated in a masked fashion.

The trial will be controlled by a Steering Committee composed of the clinical investigators and the study chairman. The manual of procedures is formulated by the Steering Committee.

2.2 Study of Glaucoma Patients and Age-Matched Normal Subjects

2.2.1 Goals

1. Develop anatomic parameters based on advanced imaging data.
2. Establish or validate age-adjusted normal reference ranges for imaging-derived anatomic parameters.
3. Establish criteria for glaucoma diagnosis based on imaging-derived anatomic parameters.
4. Evaluate the sensitivity and specificity of imaging-derived anatomic parameters.
5. Measure the rate of normal age-related change in imaging-derived anatomic parameters.
6. Assess the reproducibility of imaging-derived anatomic parameters.
7. Establish criteria for glaucoma progression based on changes in imaging-derived anatomic parameters.
8. Test the hypothesis that advanced imaging can detect glaucoma progression prior to VF and optic disc photography.

2.2.2 Rationale for Entry Criteria for Normal Subjects

The "normal group" is composed of subjects who have no evidence of glaucoma and no risk factor for glaucoma in either eye. They provide the normal reference values for the advanced imaging tests. The normal group should cover the age range over which the vast majority of glaucoma occurs. Inclusion and exclusion criteria are listed in Chapter 3.

2.2.3 Rationale for Entry Criteria for Perimetric Glaucoma Patients (either eye)

The "perimetric glaucoma" (PG) group is composed of patients who definitely have glaucoma based on both VF and optic nerve head appearance. They anchor the diagnostic standard for the advanced imaging tests. Inclusion and exclusion criteria are listed in Chapter 3. If the subject has only one eye that fulfills the entry criteria, the eye that satisfies glaucoma criteria will be followed in the PG. The other eye will be followed in the "glaucoma suspect and pre-perimetric glaucoma" (GSPPG) group.

2.2.4 End Point

End point for the normal group is defined as the development of elevated IOP, confirmed optic disc abnormality or confirmed VF abnormality in either eye.

Endpoint for the PG group is defined as confirmed VF progression in the eye.

Once an endpoint has been reached, the subject will continue to be followed. The advanced imaging data would be unmasked to the clinical investigators for clinical management.

Subjects who develop exclusion criteria or wish to exit from the study will be disenrolled after a review by the treating clinical investigator.

2.2.5 Sample Size and Statistical Power

One hundred and seventy-five PG patients and 170 age-matched normal subjects will be recruited. This will allow us to determine the potential of a diagnostic parameter to discriminate between normal and glaucoma subjects. The sample sizes are adequate for determining the area under the receiver operating curve (AROC) within ±0.06 with at least 95% confidence in the AROC range of 0.8-0.9 (using the pessimistic assumptions that the two eyes of the same patient are perfectly correlated). The receiver operating curve (ROC) is obtained by plotting the sensitivity v. specificity over a whole range of threshold criteria values for a diagnostic parameter. AROC is the integrated area under the curve. It is a single number that reflects the essential diagnostic potential of an instrument or diagnostic parameter regardless of the arbitrary setting of threshold values. Past studies using disc photography, HRT, GDx and OCT1/2 typically have best diagnostic parameters with AROC between 0.8 and 0.9.[1] Measurement of AROC will allow us to determine whether the new generation of instruments, novel anatomic parameters and new technologies have significantly better or worse diagnostic power compared to previously characterized diagnostic methods.

2.2.6 Statistical Analysis

Statistical analysis will be performed on each imaging-derived anatomic parameter and combined indices. Normal reference ranges (mean, standard deviation, 1 & 5 percentile points) will be established. We will perform regression analysis to determine if the reference norms need to be adjusted by age, axial eye length, refraction and disc diameter. The ability of each parameter and index to distinguish between glaucoma and normal eyes will be evaluated by the ROC (plot of sensitivity v. specificity at various diagnostic thresholds) and the AROC.

The normal range for year-to-year changes for each anatomic parameter in normal patients will be established (mean and SD). A statistically significant negative change in an anatomic parameter beyond the normal rate of change will be considered indicative of glaucoma progression. In the glaucoma group, a time-dependent proportional hazards model will be used to investigate the ability of progression in imaging parameters (with adjustment for other predictive covariates) to predict subsequent VF and disc photograph changes. In eyes with glaucoma progression by VF, the time interval between the VF progression and progression of the anatomic parameters will be analyzed by the t-test to determine whether the anatomic parameters precede or lag behind VF in detection progression. The number of significant interval changes in the anatomic parameters preceding a field progression will also be analyzed to determine whether advanced imaging can detect progression in smaller increments and over shorter intervals. Contingency table analysis will be performed on the proportion of glaucoma eyes that has glaucoma progression by VF and anatomic parameters to determine their relative sensitivity in detecting progression.

2.2.7 Clinical Management

The clinicians will treat all study patients according to current standard of care. All study data will be available for clinical decision-making except for masking of advanced imaging data until an endpoint has been reached. The masking procedure is described in Section 2.4.

2.3 Study on Glaucoma Suspects and Pre-Perimetric Glaucoma Patients (GSPPG)

Glaucoma suspect eyes have risk factors or borderline findings that increase their risk of developing glaucoma. The risk factors include ocular hypertension and increased cupping of the optic disc. However, there is no firm evidence of glaucomatous damage to the optic nerve based on VF. There is no clear consensus on whether these patients need to be treated. The appearance of the ONH and peripapillary NFL can be sufficiently abnormal that some clinicians diagnose these cases as early glaucoma even if the VF is normal. Because biomicroscopic and photographic grading of disc and NFL provide anatomic parameters that are parallel to those from advanced imaging, we group these pre-perimetric glaucoma cases with the glaucoma suspects for the correlation with the psychophysical VF endpoint. The combined group is referred to as the Glaucoma Suspect and Pre-Perimetric Glaucoma (GSPPG) group.

The purpose of this study is to determine if advanced imaging can predict which patients will have glaucomatous VF. If the advanced imaging technologies have good predictive power, they will clearly be useful in determining which patients need to be treated early to prevent glaucoma from damaging their vision.

The study has a prospective longitudinal design and is not a treatment trial. The protocol allows participating physicians to provide the care they consider necessary for the best interests of their patients. However, since advanced imaging is not yet commonly accepted as part of the standard of care, we will partially mask advanced imaging to reduce treatment bias. The masking procedure is detailed in Section 2.4.

2.3.1 Rationale for Entry Criteria

The GSPPG group is composed of subjects who are at higher risk for developing definite (perimetric) glaucoma. Their risk factor may be high IOP, abnormal appearance of the optic nerve head and/or nerve fiber layer or glaucoma in the other eye. We believe advanced imaging is most useful in this group, in which VF is not able to distinguish those with early disease from those who are normal. The group is defined as broadly as possible to facilitate enrollment. Inclusion and exclusion criteria are listed in Chapter 3.

2.3.2 End Point

Endpoint for the GSPPG group is defined as confirmed VF conversion to glaucomatous abnormality in the study eye.

Once an endpoint has been reached, the subject will continue to be followed. The advanced imaging data would be unmasked to the clinical investigators for clinical management.

Subjects who develop exclusion criteria or wish to exit from the study will be disenrolled after a review by the treating clinical investigator.

2.3.3 Sample Size, Statistical Power and Statistical Analysis

Advanced imaging will be investigated in the cohort of 320 GSPPG patients. Initially it will be of interest to determine the prevalence of abnormal findings in this cohort at baseline. Threshold criteria for abnormality will be defined for each advanced imaging-derived anatomic parameter according to the normal-reference range. Adjustment by linear regression for disc size, age, axial length and refraction will be performed if appropriate. Definite abnormality will be defined at $p<1\%$ level and borderline abnormality will be defined at the $p<5\%$ level. For small to medium reference samples, the sample percentile cutoff values are not reliable estimates of the true population cutoff values and "parametric" estimates based on the assumption of normal distribution are more robust.

Since our normal group will only contain 170 subjects, we will set the criteria using the assumption of normal distribution with one tail. Thus 2.33 standard deviations (SD) below the normal average value will be the cutoff for $p<1\%$ level and 1.65 SD below normal will be the cutoff for $p<0.01$ level. We will set our own diagnostic cutoff values for novel diagnostic parameters that we will develop. However, most parameters that are

already in common use have cutoff values defined by the device manufacturers using their own reference database. We will use the manufacturer's diagnostic criteria if they are available, whether they are parametric or nonparametric. This would make our finding more relevant to clinicians who are already using these commonly available diagnostic criteria.

This cohort will be followed prospectively to observe the predictive ability of imaging-derived anatomic parameters on subsequent conversion to glaucoma. Anatomic parameters will be derived from advanced imaging data by computers in automated fashions or, in some cases, with human assistance in defining disc margins. Human grading of cup/disc ratio from stereo photographs will also provide anatomic parameters. The primary end point for determining sample size is the comparison of conversion rate between two subgroups of the suspect dichotomized to normal versus abnormal for each advanced imaging parameter at baseline. Assuming that 64 (20%) of the 320 patients have an abnormal advanced imaging parameter at baseline, there will be 92% power (using a one-sided test at the 0.05 level) to detect a difference whereby 14% of those with an abnormal parameter will show conversion to glaucoma compared to 2% of those with a normal parameter at baseline, giving an overall conversion rate of 4.4% reported in the total Ocular Hypertension Treatment Study (OHTS) cohort.[2] The anatomic parameters will also be looked at as continuous measures with regard to prediction of conversion to glaucoma.

Additional analyses will look at changes in anatomic parameters and analyze their correlation with VF. A statistically significant negative change in a parameter beyond the normal rate of change will be considered indicative of progression. Human grading of cupping and neuroretinal rim change from stereo photographs will also provide measures for anatomic progression. A time-dependent proportional hazards model will be used to investigate the ability of progression in anatomic parameters (with possible adjustment for other predictive covariates) to predict subsequent VF conversion. In eyes with conversion to glaucoma by VF, the time interval between the VF conversion and progression in anatomic parameters will be analyzed by the t-test to determine whether the imaging-derived parameters precede or lag behind VF in detecting progression in disease status. The number of significant interval changes in the anatomic parameters preceding a field progression will also be analyzed to determine whether advanced imaging can detect progression in smaller increments and over shorter intervals. Contingency table analysis will be performed on the proportion of glaucoma eyes that has glaucoma progression by VF and anatomic parameters to determine their relative sensitivity in detecting progression.

The analyses of the prospective cohort will evaluate the ability of advanced imaging to provide earlier prediction of glaucomatous damage and therefore suggest which patients need earlier intervention. As newer imaging technologies are developed, these will be added to the analyses to determine the extent to which they add to the predictive ability.

2.3.4 Clinical Management

All study data will be available for clinical decision-making except for masking of advanced imaging data has been reached. The masking procedure is described in Section 2.4.

2.4 Data Masking Procedures

2.4.1 Advanced Imaging

The investigators realize that the use of advanced imaging data in clinical management can bias the statistical measurement of the predictive power of imaging-derived anatomic parameters. For example, if all ocular hypertensive patients with abnormal anatomic parameters are treated with IOP-lowering medication and none of the ocular hypertensive patients with normal anatomic parameters are treated, the rate of VF conversion in the abnormal group would be reduced due to treatment effect. The treatment effect could be accounted for by including treatment and IOP in a multivariate analysis, however the bias would be difficult to remove with multivariate analysis if treatment decision closely parallels the status of the anatomic parameters.

In consultation with Dr. Ellen Liberman and Dr. Don Everette at NIH, the AIGS Steering Committee decided that all advanced imaging data will be masked to the clinical investigators until the study endpoint has been reached.

For quality control purposes, masked advanced imaging data will be presented to the investigators by the study technician/coordinators with masking of the identity of the study subject.

Advanced imaging data acquired prior to the AIGS qualifying visit and already used in clinical decision making are not masked. The availability of pre-study advanced imaging data does not preclude a subject from enrollment in the study.

2.4.2 Standard Diagnostic Information

All data that are needed to manage patients according to the current standard of care will be available to the physicians and patients. These include corneal thickness, optic disc photography and clinical examinations, and VF's. These data are available to treating clinical investigators and other physicians caring for the study subjects for clinical decision making.

Formal AIGS grading of disc photographs will be performed in a masked manner to avoid bias. The study grading procedures are detailed in later chapters. The study grading files are kept separately from the clinical charts.

2.4.3 Other Advanced Diagnostic Information

Other advanced diagnostic information such as SWAP, FDT and ORA may be included in ancillary studies approved by the Steering Committee. All advanced diagnostic data should be masked unless specifically approved by the Steering Committee. The Steering Committee has determined that SWAP may be performed at Clinical Centers at the discretion of the Center's PI. SWAP data at study baseline are not masked. But subsequent SWAP are masked until study endpoint.

2.5 Human Subjects Protocols

AIG is a multi-center bioengineering partnership sponsored by the National Eye Institute. The partnership includes three clinical centers and three engineering centers (see Section 1.1). The goal of the partnership is to develop advanced imaging technologies to improve the detection and management of glaucoma. The technologies will be evaluated in a longitudinal ten-year clinical study. The recruitment of human subjects for the clinical study will follow these guidelines:

1. All studies on subjects will be performed at the University of Southern California (USC), Bascom Palmer Eye Institute (BPEI), University of Pittsburgh Medical Center/University of Pittsburgh School of Medicine (UPMC), and Oregon Health & Science University (OHSU)/Casey Eye Institute. Approximately 665 subjects will be needed for the studies. Normal individuals, subjects who are glaucoma suspects and subjects with glaucoma will be recruited. Selection of the subjects will be performed to address issues of minority and gender inclusion in accordance with NIH guidelines.

2. Advanced imaging data will be obtained from study subjects specifically for research purposes. They will be stored in electronic form. Conventional diagnostic tests such as VFs, optic disc photography and complete eye examination are part of routine care of glaucoma patients. These clinical results will also be kept in study records.

3. Study subjects will be recruited from the clinical practices of the investigators at USC, BPEI and UPMC. The patients and families will be recruited by the participating ophthalmologists, who will explain the purpose of the study and invite the patient to enroll. Signature on the IRB-approved consent forms will be obtained by the investigator for the ten-year study with current generation of commercial FDA-approved OCT, SLP and SLT instruments. When additional investigational OCT prototypes are added to the study, separate informed consent documents will be obtained for imaging with these experimental instruments. The subjects are told that the purpose of the study is to improve glaucoma diagnosis through the development and improvement of new imaging instruments. They are told that outside of the tests that would ordinarily be performed for their disease (VF, disc photographs and complete eye examinations), they will have OCT, SLP and SLT scans. The subjects are assured of the confidentiality of their participation and the identification of data by serial numbers. They are told that they may benefit from improved long-term monitoring of their glaucoma condition by participating in this study. They are told of the general benefit to science from their participation. They are assured that if they chose not to participate in the study, the management of their problem will not be affected in any way.

4. OCT, SLP and SLT imaging poses no known risk to the subject. All exposure to laser and superluminescent diode light are kept within the limits for safe ocular exposure to laser light established by the American National Standards Institute, ANSI Z136.1-2000.[3] The commercial models to be used are approved by the FDA for retinal imaging. These include the Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA), GDx-VCC (Laser Diagnostic Technologies, San Diego, CA) HRT2 (Heidelberg Instruments, Heidelberg, Germany), RTVue (Optovue, Inc., Fremont, CA). Additional advanced OCT prototypes to be introduced will also conform to the ANSI standards for extended exposure.

5. Confidentiality of records will be maintained using the following precautions: All subject records are kept locked in a file cabinet in the office of the clinical coordinator. Each individual is assigned a serial number that will be used for all subsequent data exchange and analysis. Patients will not be identified by name in any publication that will result from this research. If there is a need to use an identifying facial photograph for any subsequent publication, permission will be obtained from the subject.

6. Subjects selected for the study will potentially receive the benefits of enhanced quantitative analysis of their condition, with no known risks of the measurement protocol. Subjects will not be charged for the examination. Normal subjects will receive $50 compensation per visit for their participation. No compensation will be provided for participants in the glaucoma and glaucoma suspect groups. All participants will receive free parking.

2.6 Division of enrollment

2.6.1 Division by Group and Clinical Center

In order to set a reachable target by 8/31/2011, the minimal retention rate has been reduced from 80% to 75%. To facilitate new recruitment to make up for dropouts, the cap has been raised to 133% for the final target. Relocation of the group recruiting quota within UPMC and USC has been adjusted while keeping the combined target for three groups unchanged within each center, in order to ensure the centers reach their individual goals as well as the overall goal for the entire study.

Table 1: Reallocated group targets within each center

#Eyes	UPMC			UM (unchanged)			USC		
	N	GSPPG	PG	N	GSPPG	PG	N	GSPPG	PG
Original Target	140	220	80	100	180	110	100	240	160
New Target	180	190	70	100	180	110	110	220	170

Table 1 Target recruitment (# subject) in the AIG longitudinal clinical study (complete recruitment by August 2010)

*If the number of active+completed participants in any group falls below 75% of the target recruitment for the clinical center, replacements should be recruited. However, the total number of participants (active, completed and closed) shall not exceed 133% of the target in each group. The number of active+completed participants relative to the total should be traced on a monthly basis.

2.6.2 Inclusion Enrollment Target

Planned Enrollment: Number of Subjects
Sex/Gender

Ethnic Category	Female	Male	Total
Hispanic or Latino	34	33	67
Not Hispanic or Latino	299	299	598
Total ethnic categories	333	332	665
Racial Categories			
American Indian/Alaska Native	9	9	18
Asian	18	18	36
Native Hawaiian or Other Pacific Islander	9	9	18
Black or African American	78	78	156
White	219	218	437
Total Racial categories	333	332	665

2.6.3 Projection of Active Target Recruitment for Centers

Table 3 shows the projection of active target recruitment by month for each center from 12/01/2009 to 8/31/2010. The projection is extrapolated using current recruiting rate. The table serves as a progress check. The center should stop recruiting if both the final target and active target are reached or if the hard cap for the center is reached. The recruiting recommend report can be obtained from AIGS central database.

Table 3: Projection of active target recruitment by centers

#Eyes	UPMC			UM			USC		
Date	Normal	GSPPG	PG	Normal	GSPPG	PG	Normal	GSPPG	PG
12/1/2009	108	111	43	78	147	92	74	167	115
1/1/2010	111	115	44	80	150	94	76	170	118
2/1/2010	114	118	46	81	152	96	77	174	120
3/1/2010	117	122	47	83	155	98	79	177	123
4/1/2010	120	125	48	84	157	100	80	181	125
5/1/2010	124	129	50	86	160	102	82	184	128
6/1/2010	127	132	51	87	162	103	83	187	130
7/1/2010	130	136	52	89	165	105	85	191	133
8/1/2010	133	139	53	90	167	107	86	194	135
8/31/2010	136	143	55	92	170	109	88	198	138

2.7 References

1.   Optic nerve head and retinal nerve fiber layer analysis. American Academy of Ophthalmology. Ophthalmology 1999;106:1414-24.

2.   Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701-13; discussion 829-30.

3.   American National Standard for Safe Use of Lasers. Orlando: Laser Institute of America, American National Standards Institute, Inc., 2000.

3   Eligibility Criteria

Appendix: Eligibility Checklist

3.1   Introduction

There will be three groups of subjects enrolled in the AIGS:

- Normal (N)
- Perimetric Glaucoma (PG)
- Glaucoma Suspect & Pre-Perimetric Glaucoma (GSPPG)

In this chapter, the eligibility criteria for these three groups are discussed.

3.2   Eligibility for AIGS: Normal Group

All of the following inclusion criteria must be satisfied completely with both eyes for normal subjects:
  a) No history or evidence of retinal pathology or glaucoma
  b) No history of keratorefractive surgery
  c) Normal Humphrey SITA 24-2 visual field: a mean deviation (MD) and corrected pattern standard deviation (CPSD) within 95% confidential limits of normal reference, and glaucoma hemifield test (GHT) within normal limits (97%)
  d) Intraocular pressure (IOP) < 21 mm Hg
  e) Central corneal pachymetry > 500 μm
  f) No chronic ocular or systemic corticosteroid use
  g) Open anterior chamber angle: gonioscopy must show 75% or more of the angle to be Grade 2 or wider by Shaffer's grading system
  h) Normal-appearing optic nerve head (ONH) and nerve fiber layer (NFL): intact neuroretinal rim without splinter hemorrhages, notches, localized pallor or NFL defect
  i) Symmetric ONH between left and right eyes: CDR difference < 0.2 in both vertical and horizontal dimensions

3.3   Eligibility for AIGS: Perimetric Glaucoma Group

3.3.1 Inclusion Criteria

At least one eye must fulfill the following criteria for perimetric glaucoma (PG) subjects:
  a) Glaucomatous (abnormal) visual field (VF) loss defined as a CPSD (p < 0.05), or GHT (p < 1%) outside normal limits, in a consistent pattern on both qualifying Humphrey SITA 24-2 VF, and
  b) ONH or NFL defect visible on slit-lamp biomicroscopy or stereo color fundus photography defined as one of following:
     - diffuse or localized thinning of the rim
     - disc (splinter) hemorrhage

- notch in the rim
- vertical cup/disc ratio greater than the fellow eye by > 0.2

3.3.2 Mixed Enrollment

If the subject has only one eye that fulfills the eligibility criteria, that eye will be followed in the PG group and the other eye will be followed in the GSPPG group.

3.4 Eligibility for AIGS: Glaucoma Suspect and Pre-Perimetric Glaucoma (GSPPG) Group

The GSPPG group consists of glaucoma suspect eyes and pre-perimetric glaucomatous eyes. Glaucoma suspect eyes have risk factors or borderline findings that increase their risk of developing glaucoma. GSPPG participants having glaucomatous ONH or NFL defect are subclassified as PPG; the remainder are subclassifed as GS.

3.4.1 Inclusion Criteria

GSPPG eyes must have one or more of the following risk factors or abnormalities in both eyes:

1. Ocular hypertension is defined as any eye that has pre-treamtment IOP $\geq$22 OR has a baseline average IOP $\geq$= 22 May record pre-medication IOP.
2.
3. ONH or NFL defect visible on slit-lamp biomicroscopy or stereo color fundus photography as defined for the PG group.
4. The fellow eye meeting the eligibility criteria for the PG group

3.4.2 Exclusion Criteria

Glaucomatous (abnormal) VF loss as defined for the PG group.

3.5 Exclusion Criteria for AIGS

The following exclusion criteria are common to the N, PG and GSPPG groups and any forfeits the eligibility of the eye:
   a) Best corrected visual acuity worse than 20/40
   b) Age < 40 or > 79 years
   c) Refractive error > +3.0D or < -7.0 D
   d) Previous intraocular surgery except for uncomplicated cataract extraction with posterior chamber IOL implantation
   e) Diabetic retinopathy
   f) Other diseases that may cause visual field loss or optic disc abnormalities
   g) Inability to clinically view or photograph the optic discs due to media opacity or poorly dilating pupil

h) Inability to obtain advanced imaging data with acceptable quality
i) Inability to perform reliably on automated visual field testing
j) Life-threatening or debilitating illness making it unlikely patient could successfully complete the study
k) Refusal of informed consent or of commitment to the full length of the study

3.6   Eligibility Review

Since normal subjects must fulfill the eligibility criteria with both eyes, there will be no mixed group eyes in the same normal subject (e.g. normal in one and glaucoma [or GSPPG] in the other). Group mixing within an individual can happen only with one PG eye and one GSPPG eye. The exclusion criteria supersede all eligibility criteria.

The AIGS Eligibility Checklist should be used to review the eligibility of a prospective study subject. It should be filled out during the prelimnary review. Confirmation or changes should be entered at the final review.

Preliminary eligibility review and group assignment should be made during the qualifying visits prior to scheduling the baseline visits. The preliminary review should include the clinical examination (including dilated examination of the fundus and optic nerve head) and reading of the VF(s) obtained at the qualifying visit(s).

Final eligibility determination should be made after the baseline visit. In addition to the data from the preliminary review, the final review should take into account the protocol disc photography reading, any confirmatory VF that has been deferred to the baseline visit, and the ability to obtain advanced imaging data of admissible quality during the baseline visit. Once final eligibility has been determined, the study coordinator at the clinical center should enter the group assignment (N, PG, GSPPG or ineligible) into the Central Database. Ineligible patients are not followed further by the study.

Subjects who receive glaucoma surgery will remain in the AIGS but their data will be analyzed separately. They will receive no study measurements in the first 3 months postoperative period. New axial length, VF and optic disc baseline measurements will be obtained between 3 and 6 months after trabeculectomy.

Subjects who reach their 80th birthday prior to completion of the study will remain eligible to stay in the study.

AIGS ELIGIBILITY CHECK LIST

Subject Name: _____

Subject 4-letter Initials: _____

Subject Study ID: _____

Preliminary Review Date: _____

Visit Code: _____

Final Review Date: _____

Normal Group

Eligibility requires all entries to be on the left for both eyes

	OD		OS	
Retinal pathology or glaucoma	No	Yes	No	Yes
Keratorefractive surgery	No	Yes	No	Yes
Normal VF x2	Yes	No	Yes	No
IOP < 21 mmHg	Yes	No	Yes	No
Corneal thickness > 0.500 mm	Yes	No	Yes	No
Corticosteroid use	No	Yes	No	Yes
Open angle	Yes	No	Yes	No
Normal ONH & NFL (biomicroscopy)	Yes	No	Yes	No
Symmetric CDR	Yes	No	Yes	No

Eligible ☐ ☐

Perimetric Glaucoma Group

Eligibility requires all entries to be on the left for at least one eye

	OD		OS	
Glaucomatous VF loss	Yes	No	Yes	No
ONH/NFL defect or progression (biomicroscopy)	Yes	No	Yes	No

Eligible ☐ ☐

Glaucoma Suspect & Pre-Perimetric Glaucoma (GSPPG) Group

Must have one or more of the following risk factors

	OD		OS	
Ocular hypertension (IOP >22 in either eye)	Yes	No	Yes	No
ONH/NFL defect or progression (biomicroscopy)	Yes	No	Yes	No
Perimetric glaucoma in fellow eye	Yes	No	Yes	No

Eligible ☐ ☐

Exclusion Criteria

Any entry in the right side column forfeits eligibility

	OD		OS	
Best corrected VA worse than 20/40	No	Yes	No	Yes
Age < 40 or > 79 years	No	Yes	No	Yes
Refractive error > +3.0D or < -7.0D	No	Yes	No	Yes
Intraocular surgery except for uncomplicated cataract	No	Yes	No	Yes
Diabetic retinopathy	No	Yes	No	Yes
Other disease that may affect VF and/or ONH	No	Yes	No	Yes
Inability to obtain acceptable disc photography, VF or advanced imaging data	No	Yes	No	Yes
Possibility of study incompletion due to subject condition	No	Yes	No	Yes
Refusal of informed consent / completing the study	No	Yes	No	Yes

Eligible ☐ ☐

Group Assignment

OD		OS	
☐	Normal	☐	Normal
☐	PG	☐	PG
☐	GSPPG	☐	GSPPG
☐	Not Eligible	☐	Not Eligibl

4   Patient Entry and Informed Consent

4.1 Introduction

Successful completion of the AIGS will require the development of a strong, long-term relationship between participants and staff at the clinical centers. The procedures followed during patient enrollment and informed consent must provide the basis for this relationship, providing the patient with the required information to understand the study goals and objectives. Long-term compliance with study visits will depend greatly upon establishing trust with patients from the outset. Detailed eligibility and exclusion criteria are listed in Chapter 3. If a candidate meets these criteria, the study coordinator will be contacted for initial patient screening for eligibility and enrollment.

4.2 Initial Patient Screening for Eligibility

The qualifying visit(s) is designed to determine whether a referred patient meets the eligibility requirements. If, after a preliminary review of the patient's history and examination data, the patient meets the eligibility requirements, a baseline visit will be scheduled. Details of the procedures to be performed at the qualifying and baseline visits are in Chapter 5.

4.3 Patient Education

At the time of the qualifying visit(s), the investigator and the clinical coordinator will explain the AIGS and the implications of participation in the study on the patient's eye care. Clinical centers must provide interpreter services for patients who do not speak English. Discussion with the participant should include, but is not limited to, the following:

1. Glaucoma is one of the leading causes of blindness in the United States and is the leading cause of blindness in African-Americans. Intraocular pressure elevation is the most important risk factor for glaucoma.
2. Evaluation for characteristic changes in the optic nerve and visual field are how glaucoma is initially diagnosed.
3. Once a patient has been diagnosed with glaucoma, treatment to lower the pressure is prescribed and the optic nerve and the visual field are monitored to reduce the risk of further disease progression.
4. Technological advances allow imaging of the optic nerve and retina, and these advances appear to be very promising in diagnosing glaucoma and detecting progression of glaucoma damage at an earlier stage than tests that have been used until now.
5. The AIGS is designed to evaluate these newer imaging tests, to compare them to each other and to the older tests and to determine how glaucoma can be best diagnosed and managed using the information obtained from them.
6. During the course of participation in the AIGS, study physicians will continue to use their best judgment about what treatment their patients require. The type of treatment used is not regulated by the study.
7. Patients or their insurance companies will be responsible for the costs of the standard care they receive for their glaucoma.
8. The study will pay for the extra tests mandated by the study protocol that are not routinely covered by insurance, including all advanced imaging tests. The results of advanced imaging tests will be hidden from the treating physician and patients until there is definite initial evidence of glaucoma or worsening of glaucoma on the visual field test.

9. The patient may also benefit from the study through his or her close medical follow-up by experts in the treatment of glaucoma. All treatments and diagnostic tests that are recommended are based upon the current standard of care.

4.4 Informed Consent

After the educational discussions outlined in Section 4.3, the patient is to sign an informed consent form to participate in the AIGS. The form must be signed at the baseline visit. An individual is ineligible for participation in the AIGS until such written consent is obtained.

Individuals are informed that they can withdraw from the study at any time and that withdrawal will not interfere with their ability to obtain follow-up care. Subjects enrolled as glaucoma patients or glaucoma suspects are also told they will not receive remuneration for participation. Subjects enrolled as normal controls are told they will receive monetary compensation of $50 per study visit. All participants are informed that their parking expenses will be paid.

One copy of the signed informed consent is supplied to the participant and one is filed with the study records at the Clinical Center. To protect confidentiality, copies of the signed informed consent form will not be sent to the Coordinating Center, but will be held at each individual clinical center. Informed consent forms must be signed, kept in proper order and available for audit at all times.

Participants who have completed the 60 month follow up visit (from the original baseline visit) are considered complete. Those participants that wish to continue on to the new study period must sign a new informed consent form.

4.5 Patients who Decline to Participate

Patients who decline to participate will be assured that their decision will have no bearing on their future medical care.

4.6 Assignment of Patient Identification Numbers

The primary study coordinator, upon preliminary determination of eligibility of a patient, will issue a unique, four-digit study subject identification number (SIDN). The first digit of the identification number will indicate the clinical center "2"=University of Pittsburgh; "3"=University of Miami, "4"=University of Southern California). The final three digits will reflect the individual patient within that clinical center. This number will be forwarded to the study coordinator, who will record and use that number on all study documents. A four-letter name code consisting of the first initial of the patient's first name and the first three letters of the patient's last name will also be used. To avoid the unnecessary use of the patient's name and protect confidentiality, only the study number and four-letter name code will be recorded in the AIGS Central Database. Only the SIDN will be used for masked reviews of study data.

4.7 Study Entry Date

The study entry date will be determined by the date of performance of the baseline visit at which the initial imaging tests are performed. This date will determine the time windows during which follow-up examinations must be completed.

4.8 Method of Ensuring Age-Matched Allocation

To maintain comparability between the study groups on the basis of age, recruitment targets based on age will be established for each category of study subject (see Table 1). Enrollment will be monitored during the two-year recruitment phase of the study and will be closed in any category that reaches the target for that category. At approximately six-month intervals, enrollment will be reviewed and the targets may be adjusted to enhance further enrollment. However, overall balance on the basis of age will be maintained between the Perimetric Glaucoma (PG) group, Glaucoma Suspect and Pre-Perimetric Glaucoma group (GSPPG) and Normal (N) group.

Table 1. Recruitment Targets by Age at Time of Enrollment

Age Category	PG	GSPPG	N
40 to 49 (10%)	18	32	17 - closed
50 to 59 (20%)	34	64	34- closed
60 to 69 (40%)	70	128	68
70 to 79 (30%)	53	96	51
Total	175	320	170

5   Schedule of Visits

5.1   Introduction

All study personnel must be familiar with the schedule of visits to ensure that required data are collected and that future visits are scheduled within appropriate time windows. The necessity for timely examinations should be stressed during participant orientation and during continuing education.

5.2   Qualifying Visit(s)

The following data and procedures are required to determine eligibility. These should be obtained during one to three qualifying visit(s) within a three-month (90-day) period. The following order of data collection is recommended:

1. Initial medical and ophthalmic history
2. Manifest refraction
3. Best spectacle-corrected visual acuity
4. External and slit-lamp examination of the eye and adnexa
5. Standard automated visual field(s) (Humphrey SITA 24-2). Pre-study VFs taken within 6 months of the last qualifying visit and satisfying AIGS criteria may be used. The second VF may be performed at either a qualifying or baseline visit.
6. Applanation tonometry
7. Gonioscopy
8. Dilated fundus examination
9. Determination of eligibility and group assignment by investigator
10. Patient education regarding glaucoma, ocular hypertension and other risk factors, treatment options, traditional diagnostic methods and the AIGS. Discuss the longitudinal nature of the study and the need for four to five years of committed follow-ups
11. Obtain informed consent
12. Schedule baseline visit(s), and, if needed, additional qualifying visit
13. Optic disc photography. Pre-study photographs taken within 6 months of the last qualifying visit and satisfying AIGS quality criteria may be used as the initial AIGS disc photograph. Disc photography may also be performed at the baseline visit.

The clinical investigator enrolling the study subject should review the overall information to determine eligibility. Optic nerve head assessment by biomicroscopy is used for the initial eligibility determination. This is confirmed later by review of the disc photographs. The coordinator is responsible for scheduling the visits and presenting the information for investigator review in a timely fashion.

5.3   Baseline Visit(s)

The baseline visit(s) should be scheduled within three months (90 days) of the last qualifying visit. The purpose of the baseline visit is to perform special AIGS testing that

may not be part of a routine ophthalmic examination. The following procedures should be performed in the listed order during the baseline visit(s).

1. SWAP/FDT (optional)
2. Confirmatory VF (if needed and if not done at a qualifying visit)
3. GDx- ECC, performed three times
4. HRT 2, performed twice
5. Stratus OCT, AIGS scan patterns performed twice
6. Pachymetry (central corneal thickness)
7. Axial length (A-scan) measurement
8. Optic disc photography, if not already done at the qualifying visit
9. RTVue OCT AIGS scan patterns

Pre-study pachymetry and axial length measurements obtained within one year of the last qualifying visit may be used in lieu of a measurement at the baseline visit, if no corneal or intraocular surgery has been performed during that interval. New axial length, VF and optic disc baselines will be obtained between 3 and 6 months after trabeculectomy.

5.4   Follow-up Visits

For subjects in the perimetric glaucoma (PG) and glaucoma suspect & pre-perimetric glaucoma (GSPPG) groups, scheduled follow-up visits continue at six-month intervals from the date of the baseline visit. For subjects in the Normal (N) group, scheduled follow-up visits continue at 12-month intervals from the date of the baseline visit.

Ideally, follow-up visits should occur ± one month of the scheduled target date. However, follow-up visits ± three months of the target date are acceptable. Regularly scheduled follow-up visits should be at least 90 days apart. If a regularly scheduled visit is not completed within ± three months of the target date, the visit is defined as a "missed visit." There are two types of regularly scheduled follow-up visits — the six-month follow-up visit and the 12-month follow-up visit.

5.4.1 Semi-Annual (Six-Month) Follow-up Visit

The first six-month follow-up visit will occur six months after the baseline visit and will be repeated every 12 months thereafter — i.e., at 6, 18, 30, 42, etc. months after baseline visit. All study subjects will have semi-annual follow-up visits except for the normal group.

The following data collection and procedures are required at the six-month follow-up visits in this order:

1. Interval medical and ocular history
2. Manifest refraction
3. Best spectacle-corrected visual acuity

4. Standard automated visual field (Humphrey SITA 24-2)
5. External and slit-lamp examination of the eye and adnexa
6. Optic nerve head evaluation
7. Applanation tonometry
8. GDx-VCC and GDx-ECC, performed three times
9. HRT 2, performed twice
10. Stratus OCT, AIGS scan patterns performed twice
11. RTVue OCT AIGS scan patterns

5.4.2 Annual (12-Month) Follow-up Visit

The first 12-month follow-up visit will occur 12 months after the baseline visit and will be repeated every 12 months thereafter; i.e., 12, 24, 36, 48, etc. months after baseline. All study subjects will have semi-annual follow-up visits. The following data collection and procedures are required at 12-month follow-up visits, to be performed in the following recommended order.

1. Interval medical and ocular history
2. Manifest refraction
3. Best spectacle-corrected visual acuity
4. Standard automated visual fields (Humphrey SITA 24-2) (for normal group, VF is needed only at the 48-month visit)
5. SWAP/FDT (optional)
6. External and slit-lamp examination of the eye and adnexa
7. Applanation tonometry
8. GDx-VCC and GDx-ECC, performed three times
9. HRT 2, performed twice
10. Stratus OCT, AIGS scan patterns performed twice
11. Dilated fundus examination
12. Optic disc photography, 2 high quality sets (for normal group, photography is performed only at the 48-month visit).
13. RTVue OCT AIGS scan patterns

5.5   Confirmation Visits for Conversion and Progression

If a VF is suspicious for conversion to glaucoma or progression of glaucomatous defects on a regular follow-up examination, confirmatory test(s) of the same type should be scheduled within three months (90 days). VF change requires two confirmatory tests.

5.6   Repeat Visits for Unreliable or Missing Data

If any clinical data, VF, disc photography or advanced imaging test is missed during a regularly scheduled visit, a repeat visit should be scheduled within three months of the regular visit schedule to make up the data. VF, disc photography and advanced imaging data should all be reviewed within one month of data acquisition. If any is found to be

unsatisfactory upon review, a visit should be scheduled within one month of the review date to retake the data.

5.7   Unscheduled Visits

The unscheduled visit can be made for a variety of reasons:

- Eye problems not related to the study (i.e., conjunctivitis)
- For participant-initiated visits

The content of these visits will vary with the circumstances.

5.8   Participant Retention

It is important to retain near 100% of the enrolled participants for the full duration of the study. The quality of the data and the estimates of the time of conversion to glaucoma are greatly affected by loss to follow-up.

Approximately one month before scheduled visits, the clinic coordinator will contact the participant to remind the participant of the upcoming examination. If the participant cannot attend the scheduled appointment, another appointment within the time window is arranged. Approximately one week before the scheduled appointment, the participant receives a letter or phone reminder from the clinic coordinator. Some participants may require additional calls or assistance to arrange transportation.

If participants are moving to another geographic area, it is important to arrange return visits to the original Clinical Center or to transfer the participant to a more convenient AIGS Clinical Center.

5.9   Visit Codes

The following codes are used to designate patient visits in the data collection forms and central database:

Q = qualifying visit(s)
B = baseline visit(s)
6m = 6-month follow-up visit(s)
12m = 12-month follow-up visit(s)
18m = 18-month follow-up visit(s)
24m = 24-month follow-up visit(s)
30m = 30-month follow-up visit(s)
36m = 36-month follow-up visit(s)
42m = 42-month follow-up visit(s)
48m = 48-month follow-up visit(s)
54m = 54-month follow-up visit(s)
60m = 60-month follow-up visit(s)

66m = 66-month follow up visit(s)
72m = 72-month follow up visit(s)
78m = 78-month follow up visit(s)
84m = 84 month follow up visit(s)
90m = 90 month follow up visit(s)
96m = 96-month follow up visit(s)
102m = 102-month follow up visit(s)
108m = 108-month follow up visit(s)
114m = 114 month follow up visit(s)
120m = 120 month follow up visit(s)

Repeat visits and confirmation visits are coded and recorded under the corresponding regularly scheduled visits.

5.10 Subject Status Classifications

Each eye could be classified as:

Active Complete: The eye is actively being followed. Data is complete (or waived after audit) as of the last visit date.

Active Pending: The eye is actively being followed. Data has yet to be completely entered into the database website and is not past due.

Active Delinquent: The eye is actively being followed. Data is incomplete. Has not been entered into the database website and is past the due date.

Disenrolled: The subject is unable to complete the Qualifying/Baseline examination. The data will not be analyzed.

Closed: The patient is not returning for follow up. However, the Qualifying/Baseline data is complete. Data can be analyzed. The date the case closed is the date of the last complete visit date.

5.11 Schedule of Visits

In the following tables, the qualifying visit(s) and baseline visit(s) are bundled into the "initial visit."

Table 1: Investigational Events for Subjects in the Normal Group

	Initial Visit	12 mo (± 1mo)	24 mo (±1mo)	36 mo (±1mo)	48 mo (±1mo)	60 mo (±1mo)
Informed consent	X					
Initial history	X					
Interval history		X	X	X	X	X
VA, MR, SLE	X	X	X	X	X	X
Gonioscopy	X					
IOP	X	X	X	X	X	X
Pachymetry	X					
Axial length	X					
ONH Evaluation	X	X	X	X	X	X
Dilated examination	X	X	X	X	X	X
VF	2X**				X	
ONH photography	2X	*	*	*	2X	*
Stratus OCT	2X	2X	2X	2X	2X	2X
GDx-ECC	3X	3X	3X	3X	3X	3X
HRT2	2X	2X	2X	2X	2X	2X
RTVue OCT	X	X	X	X	X	X

Table 2: Phase 2 Investigational Events for Subjects in the Normal Group

	72 mo (±1 mo)	84 mo (±1mo)	96 mo (±1mo)	108 mo (±1 mo)	120 mo (±1mo)
Informed consent					
Initial history					
Interval history	X	X	X	X	X
VA, MR, SLE	X	X	X	X	X
Gonioscopy					
IOP	X	X	X	X	X
Pachymetry					
Axial length					
ONH Evaluation	X	X	X	X	X
Dilated examination	X	X	X	X	X
VF			2X		
ONH photography	*	*	2X	*	*
Stratus OCT	2X	2X	2X	2X	2X
GDx-ECC	3X	3X	3X	3X	3X
HRT2	2X	2X	2X	2X	2X
RTVue OCT	X	X	X	X	X

∗ ONH photography should be performed if any change is noted on clinical ONH evaluation.

**Standard automated visual field(s) (Humphrey SITA 24-2). Pre-study VFs taken within 6 months of the last qualifying visit and satisfying AIGS criteria may be used. The second VF may be performed at either a qualifying or baseline visit.

Table 3: Investigational Events for Subjects in the Glaucoma & GSPPG Groups

	Initial Visit	6 m (±1m)	12 m (±1m)	18 m (±1m)	24 m (±1m)	30 m (±1m)	36 m (±1m)	42 m (±1m)	48 m (±1m)	54 m (±1m)	60 m (±1m)
Informed consent	X										
Initial history	X										
Interval history		X	X	X	X	X	X	X	X	X	X
VA, MR, SLE	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X										
IOP	X	X	X	X	X	X	X	X	X	X	X
Pachymetry	X										
Axial length	X										
ONH evaluation	X	X		X		X		X		X	
Dilated examination	X		X		X		X		X		X
VF	2X	X	X	X	X	X	X	X	X	X	X
SWAP/FDT (Optional)	± X optional		± X optional		± X optional		± X optional		± X optional		± X optional
ONH photography	2X	*	2X	*	2X	*	2X	*	2X	*	2X
Stratus OCT	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X
GDx-ECC	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X	3X 3X
HRT2	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X
RTVue OCT	X	X	X	X	X	X	X	X	X	X	X

Table 4: Phase 2 Investigational Events for Subjects in the Glaucoma & GSPPG Groups

	66 mo (±1m)	72 m (±1m)	78 m (±1m)	84 m (±1m)	90 m (±1m)	96 m (±1m)	102 m (±1m)	108 m (±1m)	114 m (±1m)	120m (±1m)
Informed consent										
Initial history										
Interval history	X	X	X	X	X	X	X	X	X	X
VA, MR, SLE	X	X	X	X	X	X	X	X	X	X
Gonioscopy										
IOP	X	X	X	X	X	X	X	X	X	X
Pachymetry										
Axial length										
ONH evaluation	X	X		X		X		X		X
Dilated examination	X		X		X		X		X	
VF	X	X	X	X	X	X	X	X	X	X
SWAP/FDT (Optional)	± X optional		± X optional		± X optional		± X optional		± X optional	
ONH photography	*	*	2X	*	2X	*	2X	*	2X	*
Stratus OCT	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X
GDx-ECC	3X	3X	3X	3X	3X	3X	3X	3X	3X	3X
HRT2	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X
RTVue OCT	X	X	X	X	X	X	X	X	X	X

∗ ONH photography should be performed if any change is noted on clinical ONH evaluation.

5.12 Missed Visits

If the participant cannot attend the scheduled appointment, another appointment within the time window is arranged. Approximately one week before the scheduled appointment, the participant receives a letter or phone reminder from the clinic coordinator. Some participants may require additional calls or assistance to arrange transportation. If the patient absolutely cannot return within the time window, a missed visit may be excluded from delinquent status by completing the Missing Visit data collection form. This form should only be used after all attempts have been made to get the patient to return within their window. The form should be faxed to the Central Coordinator who will then verify and approve the missed visit so that it does not show as delinquent on the data status report.

If a GSPPG or PG participant missed four visits, the file will be considered "closed". If a normal participant misses three visits, the file will be considered "closed". Follow ups are not scheduled once a participant's file is closed.

AIGS Missing Visit Data Collection Form

Study ID: _____

Visit Code: _____   Coordinator: _____

Missed Visit Date: _____   Investigator Initials: _____

_____

Complete only after every attempt has been made to have the pt return within the 3 mo visit window.

Patient Information

Reason for missed visit *(check all that apply)*

Patient was too ill	( )
Unable to contact patient via phone & mail	( )
Unable to take time off work	( )
Pt. temporarily away from the area	( )
Patient with transportation problems	( )

Quality Control

If able to interview the patient via telephone:
Did the patient report any eye problems?   YES NO

If yes, what   _____

Scan and email this form to zhangxin@ohsu.edu

Verified & Approved by:

_____

6   Clinical History, Examination and Tests

Version 8.3

6.1 Clinical History

The relevant clinical history should be recorded on the AIGS Clinical Data Collection Form for either the qualifying examination or follow-up examination, as appropriate (Chapter 6 Appendices 2 and 3).

Special attention is paid to conditions and medications relevant to the causation or treatment of glaucoma. The classification of glaucoma medications and other treatments can be found in Chapter 7. If the medication information is not available at the time of the visit, the coordinator should fill out such information at a later time by telephone interview.

6.2 Refraction

Refraction is required at each visit prior to visual acuity and visual field testing. Refraction should be performed by certified AIGS personnel. The results should be recorded on the AIGS Visual Acuity Worksheet.

Because refraction is particularly important to visual field testing, refraction should be performed using the following standard protocol (adapted from the Diabetic Retinopathy Vitrectomy Study refraction protocol).

6.2.1 Refraction Technique

Any standard visual acuity chart, such as ETDRS Refraction Chart R or a Projecto-chart, may be used for determining the best lens correction in each eye. The right eye is refracted first, then the left.

Beginning approximate refraction: The result of the subjective refraction from a previous visit can be used as the beginning approximate refraction. If a participant wears contact lenses, he or she can be refracted over the lenses. If the result of the subjective refraction is not available, then:

- If the participant's uncorrected visual acuity is 20/100 or better and the participant does not have glasses for distance vision, the beginning approximate refraction is plano (no lens correction).

- If the participant's uncorrected visual acuity in either eye is less than 20/100 with the participant's present distance glasses (or without correction if the participant does not have glasses), retinoscopy should be performed by an examiner proficient in this procedure, or an automated refractor may be used. An acceptable alternative is to conduct an arbitrary trial with any lenses in an effort to bring acuity to 20/100 or better. The lens corrections obtained are used as the beginning approximate refraction in the procedure outlined below for determination of best-corrected visual acuity.

- If the participant's visual acuity is 20/100 or better with the participant's present distance glasses, the glasses are measured with a lensometer and these measurements are used as the beginning approximate refraction.

Subjective refraction: The trial frame is placed and adjusted on the participant's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. (It is permissible to use a phoroptor for the subjective refraction. However, for visual acuity testing, the lenses from the final phoroptor refraction must be placed in a trial frame and the final sphere must be rechecked as described in the last paragraph of this section.) The left eye is occluded and the beginning approximate refraction as determined above is placed in the right lens cell with the cylindrical correction anterior. The standard chart may be read at a distance of 10 to 20 feet either directly or with a mirror.

Determination of spherical refraction: A +0.50 sphere is held in front of the right eye and the participant is asked if the vision is "better," "worse" or "no different" while he or she is looking at the smallest line read well.

- If vision is improved or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is held again in front of the right eye and again the participant is asked if the vision is "better," "worse" or "no different."

- This process of increasing the plus sphere in the trial frame is repeated until the participant says that the +0.50 sphere held in front of the trial frame makes the vision worse.

- Whenever the participant says that vision is "worse," the +0.50 sphere is removed from in front of the trial frame.

By this process, the highest plus or least minus sphere that will minimize blurring of the participant's vision is determined. After determining the highest plus or least minus sphere, the participant is asked to read the smallest line possible.

Next, a -0.37 sphere is held in front of the trial frame and the participant is asked if the vision is "better," "worse" or "no different."

- If it is not improved, the +0.50 sphere is tried again to see if the participant will accept still more plus.

- If vision is improved by the –0.37 sphere, the participant is requested to read the chart and if one more letter is read, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus.

Minus spherical power is added by -0.25 diopter increments in the above fashion until the participant shows no further improvement in vision.

Determination of cylindrical refraction: For purposes of this discussion, only plus cylinder techniques are presented. The equivalent minus cylinder technique can also be used.

- Cylinder axis determination: If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by using a 0.25, 0.37, or 0.50 diopter cross-cylinder, first with the positive axis 45 degrees to one side of the cylinder axis and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image, the participant is encouraged to select the position producing "less blur" while fixing on a single round letter on the line above the lowest line on the chart he or she is able to read well when the cross-cylinder is not held up before the trial frame. If the participant cannot choose between the two positions of the cross-cylinder at the beginning of this test, the axis of the cylinder is moved 5 to 15 degrees, first in one direction and then in the other, with the cross-cylinder being checked in each position to confirm that the original axis was indeed correct. If the participant does prefer one position of the cross-cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder when in the position found less blurry by the participant. (When the power of the cylinder is low or the participant's discrimination is poor, larger shifts will produce more clear-cut answers.) The cross-cylinder is tried again with the positive axis 45 degrees first to one side and then to the opposite side of the new cylinder axis to determine which position is producing less blur. If the participant finds one position less blurry, the axis of the plus cylinder is moved toward the positive axis of the cross-cylinder. Testing for change of axis is repeated until the subject finds both positions of the cross-cylinder equally blurred.

- Cylinder power determination: Change in cylinder power is now tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. For this test, the participant is requested to focus attention on a round letter on the lowest line on the chart he or she is able to read. If the participant prefers the positive axis coincident with the cylinder axis, the power of the corrected plus cylinder is increased by an additional plus 0.25 diopter. If the participant prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the subject finds the two positions equal. When 1 diopter of the cylindrical power has been added, 0.5 diopter of sphere of opposite sign should be added, and for every 0.50 diopter of further change of cylinder power added, a further 0.25 diopter of sphere of opposite sign should be added to the spherical refraction.

If the beginning refraction is a "pure" sphere, the presence of astigmatism is tested by arbitrarily placing a plus 0.25 cylinder at 180 degrees in the trial frame, after having determined the highest plus or least minus sphere producing minimal blurring of vision as described above. The refraction is then continued by using the cross-cylinder to test for cylinder power with the cross-cylinder technique outlined above. If the preference with cross-cylinder indicates that the plus 0.25 cylinder should be removed, then before doing so, the 0.25 cylinder should be rotated 90 degrees from its original position and the test for cylinder power should be performed once again. At this point, if the participant prefers additional power, it should be added. If the

participant prefers to remove the plus 0.25, it should be removed and the final refraction is then purely spherical.

Example: Starting refraction: -2.50 + 0.25 axis 37 degrees. Use of the cross-cylinder to check cylinder axis indicates that the participant prefers the 37-degree axis. If on using the cross-cylinder to check cylinder power, one finds that the participant wants the 0.25 cylinder removed, rotate the cylinder to 127 degrees and test for cylinder power once again. If additional power is preferred, add it.

If the preference is to remove the 0.25 cylinder, this should be done. If 0.50 or more diopters of cylinder have been added, the cylinder axis should be refined, if possible, by using the cross-cylinder as described above.

Minus cylinders may be used instead of plus cylinders to determine the best correction for the power and axis of the cylinder. If minus cylinders are used, the foregoing procedure must be revised to reflect the change in sign.

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is rechecked by adding +0.50 and -0.37 spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the participant can perceive no improvement in vision. If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made. The lens corrections obtained in this way for the right eye are recorded on the AIGS Visual Acuity Worksheet. The process is repeated for the left eye and the lens corrections are recorded on the worksheets for refraction and visual acuity.

6.3   Visual Acuity

Best spectacle-corrected visual acuity is measured after refraction and before pupil dilation, tonometry, gonioscopy or any other technique that would affect vision. AIGS-certified personnel should administer the test at the qualifying and regular follow-up study visits. The results should be recorded on the AIGS Visual Acuity Worksheet.

6.3.1 Visual Acuity Testing Procedure

The LogMAR visual acuity testing protocol for this study has been adapted from protocols used in the Early Treatment of Diabetic Retinopathy Study (ETDRS), Diabetes Control and Complications Trial (DCCT), Macular Photocoagulation Study (MPS), Prospective Evaluation of Radial Keratotomy (PERK) and the Longitudinal Optic Neuritis Study (LONS).

The LogMAR visual acuity scale offers important practical advantages over other methods of acuity testing. In particular, the LogMAR scale facilitates statistical analysis and simplifies quantification of acuity at various distances. The ETDRS LogMAR charts should be used (Chart 1 for the right eye and Chart 2 for the left eye).

The room illumination should be between 80 and 320 cd/m^2. The preferred distance from the participant's eyes to the visual acuity chart is 4 meters and the minimum distance is 2 meters. The participant may stand or sit. If the participant is seated, his or her back should firmly touch

the back of the chair. The examiner should ensure that the participant is standing or sitting comfortably and that their head does not move forward or backward during testing. After careful instruction, refraction and placement of the proper lenses in the trial frame, the left eye is occluded and testing begins with the right eye.

The testing procedure for visual acuity is based on the principle that the objective is to test visual acuity and not intelligence or ability to concentrate or follow/remember instructions (although all of these factors are involved). The participant should be told that the chart has letters only and no numbers. If the participant forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter.

The participant should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and not to proceed until giving a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C..." If, at any point, the participant reads quickly, he or she should be asked to stop and read slowly. If the participant loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the examiner should ask the participant to go back to the line where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test.

When the participant says he or she cannot read a letter, he or she should be encouraged to guess. If the participant identifies a letter as one of two or more letters, he or she should be asked to choose one letter. The examiner may suggest that the participant turn or shake his or her head in any manner if this improves visual acuity. If the participant does this, care must be taken to ensure the fellow eye remains covered. When it becomes evident that no further meaningful readings can be made, despite urgings to read or guess, the examiner should stop the test for that eye.

There are several reasons for encouraging participants to guess: (1) Participants' statements that they cannot identify a letter are often unreliable; (2) It helps to maximize the participant's effort; (3) It helps assure uniformity among procedures performed in different clinics; and (4) It helps prevent participant bias.

Each letter is scored as right or wrong. Once a participant has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the participant changes a response aloud (e.g. "That was a "C," not an "O") <u>before</u> he or she has read aloud the next letter, then the change should be accepted. If the participant changes a response <u>after</u> beginning to read the next letter, the change is <u>not</u> accepted.

After the test of the right eye is completed, occlude the right eye and repeat for the left eye.

6.3.2 ETDRS Visual Acuity Scoring

The AIGS Visual Acuity Worksheets (Appendix 1) are used for scoring the test result. The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. The examiner records letters read incorrectly and letters for which the participant makes no guesses with an "x" or a line. Each letter read correctly is scored as one

point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. The total score for each eye and the distance used for testing is recorded on the AIGS form for that visit.

6.3.3 ETDRS Visual Acuity Testing Discontinuation

If the participant's Snellen visual acuity is worse than 20/200, ETDRS visual acuity does not have to be performed.

6.4   Afferent Pupillary Defect

Afferent pupillary defect is tested by certified AIGS personnel or an AIGS clinical investigator.

The findings should be recorded on the AIGS Clinical Data Collection Form for either qualifying examination or follow-up examination, as appropriate.

6.5   Slit-Lamp Examination

Slit-lamp examination is performed by an AIGS clinical investigator. The findings should be recorded on the AIGS Clinical Data Collection Form for either qualifying examination (Appendix 2) or follow-up examination (Appendix 3), as appropriate.

Slit-lamp examination can be performed with any commercially available instrument. The examiner will conduct a complete examination in an orderly fashion of lids, lashes, bulbar and palpebral conjunctiva, cornea, anterior chamber, iris, lens and anterior vitreous. Clinical grading of corneal opacity and cataract density should be done on a scale of 1 to 4 in increments of 0.5. The examination should be recorded in the AIGS Clinical Data Collection Form.

6.6   Tonometry

IOP is measured using a Goldmann applanation tonometer. The tonometer is calibrated every month. It is suggested that a log be kept of calibration measurement and dates. Two collaborators, an operator and a reader, both of whom are certified for the procedure, perform the IOP measurement. Both eyes are tested, with the right eye preceding the left eye. The measurement must be made on an eye that has not received pupil-dilating medications. Clean the prism tip according to your institutional infection control policy. Whenever possible, IOP should be checked at about the same time of day at all visits to minimize diurnal fluctuation of IOP.

IOP measurement must be made at least one hour after digital ocular compression.

The requirements for the timing of tonometry in relation to the use of glaucoma medications are as follows:

- <u>At least one but not more than six hours</u> after the last glaucoma medication prescribed to be taken four times a day.

- <u>At least one but not more than eight hours</u> after the last glaucoma medication prescribed to be taken three times a day.

- <u>At least one but not more than 12 hours</u> after the last glaucoma medication prescribed to be taken twice a day.

- <u>At least one but not more than 24 hours</u> after the last glaucoma medication prescribed to be taken once a day.

- <u>At least four but not more than 24 hours</u> after use of pilocarpine 4% ointment.

- <u>At least 10 hours but not more than 6 days</u> after change of a pilocarpine Ocusert.

6.6.1 Tonometry Technique

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to determine IOP.

A single measurement is made as follows:

- The reader adjusts the tonometer dial to an initial setting corresponding to 10 mm Hg. The slit-lamp magnification is set at 8X or 10X. The light source is positioned at an angle of approximately 45°, and the aperture is maximally opened. A cobalt blue filter is employed.

- After instillation of 0.5% proparacaine, a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic (Fluress, Barnes Hind) may be instilled. The examiner should use the same technique each time, be it a paper strip or a pre-mixed eye drop.

- The participant and slit lamp are adjusted so that the participant's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The participant is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the operator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The participant is cautioned not to hold his breath.

- The investigator looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally and positioned vertically so they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.

- The operator adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.

- The operator removes the tip from the cornea and the reader records the reading on the dial, rounded to the next highest integer. If, for example, the measurement indicated is between 16 and 17, 17 is recorded as the measurement.

- If refractive astigmatism is greater than 3.0 D, IOP will be taken with the white line on the prism at 90 and 180 degrees and the average of the two readings will be used.

- The above procedure is repeated on the same eye. If the two measurements differ by 2 mm Hg or less, the average becomes the recorded IOP pressure. For example, if the two measurements are 22 and 23, 22.5 is the recorded IOP. If the first two measurements differ by greater than 2 mm Hg, a third measurement is made, and the median becomes the recorded IOP. (The median is the middle measurement after arraying the measurements from low to high. For example, if the three measurements are 15, 21 and 16, then 16 is recorded.) Testing of the left eye follows using the same technique.

The IOP should be recorded on the AIGS Clinical Data Collection Form for either qualifying examination or follow-up examination, as appropriate. The pre-treatment IOP will be entered into the central database.

6.7   Gonioscopy

Gonioscopy is performed by an AIGS clinical investigator. The findings should be recorded on the AIGS Clinical Data Collection Form for either qualifying examination or follow-up examination, as appropriate.

Gonioscopy is performed with the participant sitting at the slit lamp. The eye to be examined receives topical anesthesia. We recommend using the Zeiss four-mirror lens or equivalent lens that does not require a viscous coupling fluid. This better preserves the corneal clarity for subsequent tests.

The angle is graded according to the standard Shaffer system:
- **Grade IV** — angle between peripheral iris and trabecular meshwork is greater than 45°
- **Grade III** — angle 30-45°
- **Grade II** — angle 20-29°
- **Grade I** — angle 10-19°
- **Slit (0.5)** — angle less than 10°
- **Closed (0.0)** — no trabecular meshwork seen without pressure on the lens.

Gonioscopy may reveal secondary causes of elevated IOP including exfoliation, angle closure or neovascularization.

6.8   Ophthalmoscopy

Ophthalmoscopy is performed by an AIGS clinical investigator. The findings should be recorded on the AIGS Optic Disc Examination Form for either qualifying examination or follow-up examination, as appropriate.

The morphology of the optic disc is assessed by stereoscopic biomicroscopy after pupil dilation with appropriate mydriatics during the qualifying visit. This examination is carried out at the slit lamp with a Hruby lens, contact lens or Volk 78- or 90-diopter lens. The retinal periphery is examined with a head-mounted indirect ophthalmoscope and a hand-held condensing lens (a 14D, 20D or 28D Nikon aspheric lens is recommended). This result of the examination is used to determine eligibility for the study.

During the study, the clinician performs direct ophthalmoscopy at every follow-up visit and a dilated stereoscopic examination of the disc at the annual follow up visits. These examinations are done to detect glaucomatous damage (notches, localized pallor, progressive cupping) or other signs of possible future damage (e.g., disc hemorrhages). Any interval change in the optic nerve appearance noted on clinical examination should be confirmed by disc photography. If disc photography is performed during a follow up visit, the protocol reading should be recorded in the AIGS Central Database. If disc photography is not performed during a follow up visit, the results of the clinical examination should be entered into the AIGS Central Database.

6.9   Ancillary Tests

Central corneal thickness (pachymetry) and axial eye lengths are measured by certified AIGS personnel during the baseline visit(s). The findings should be recorded on the AIGS Clinical Data Collection Form for the qualifying examination. Central corneal thickness should be measured by an ultrasound pachymeter. Axial eye length should be measured by an immersion or contact ultrasound a-scan system, or on the IOL Master (Carl Zeiss Meditec, Inc., Dublin, CA).

6.10 Personnel

Two AIGS personnel at each site should be trained and certified to administer the following tests: refraction, visual acuity measurement, tonometry, central pachymetry and axial eye length measurement.

The Clinical Coordinator at each clinical center is responsible for maintaining a complete file of Clinical Data Collection Forms and Visual Acuity Worksheets. The coordinator is also responsible for entering data into the web-based Central Database.

The clinical investigator(s) at the clinical centers are responsible for performing the slit-lamp examination and ophthalmoscopy and for formulating diagnosis and treatment decisions.

6.10.1 Certification of AIGS Personnel

The principal investigator at each clinical center is responsible for certifying the appropriate personnel to perform clinical tests.

6.10.1.1 Basic Qualification

The operator must be a qualified ophthalmic technician (COA, COT or COMT), ophthalmic photographer, ophthalmic ultrasonographer or medical doctor.

6.10.1.2 Demonstration of Practical Competency

The principal investigator of the clinical center should verify that the person to be certified demonstrated competency in one or more of the following tests:

- Refraction
- Visual acuity testing
- Tonometry
- Afferent pupillary defect
- Central pachymetry
- Axial eye length measurement

6.10.1.3 Certification Documentation

The principal investigator of the clinical center should issue certification to certified personnel listing the clinical tests they are certified to perform (Chapter 6, Appendix 5). A copy of these certificates should be kept in the files of the clinical coordinator and also sent to the coordinating center.

AIGS Visual Acuity Worksheet

Study ID: _____   Visit Code: _____   Date: _____

VA examiner:_____

4 Meter Acuity Test: **Circle each** letter the patients identifies correctly, write the total correct for each row in the space provided, and compute the total for all rows.

Right Eye-OD

Row	Acuity Equivalent	Chart 1 Letters	Number Correct
1	20/200	N C K Z O	_____
2	20/160	R H S D K	_____
3	20/125	D O V H R	_____
4	20/100	C Z R H S	_____
5	20/80	O N H R C	_____
6	20/63	D K S N V	_____
7	20/50	Z S O K N	_____
8	20/40	C K D N R	_____
9	20/32	S R Z K D	_____
10	20/25	H Z O V C	_____
11	20/20	N V D O K	_____
12	20/16	V H C N O	_____
13	20/13	S V H C Z	_____
14	20/10	O Z D V K	_____
		Total(a):	_____

Left Eye-OS

Row	Acuity Equivalent	Chart 2 Letters	Number Correct
1	20/200	D S R K N	_____
2	20/160	C K Z O H	_____
3	20/125	O N R K D	_____
4	20/100	K Z V D C	_____
5	20/80	V S H Z O	_____
6	20/63	H D K C R	_____
7	20/50	C S R H N	_____
8	20/40	S V Z D K	_____
9	20/32	N C V O Z	_____
10	20/25	R H S D V	_____
11	20/20	S N R O H	_____
12	20/16	O D H K R	_____
13	20/13	Z K C S N	_____
14	20/10	C R H D V	_____
		Total(a):	_____

1 Meter Acuity Test: If the total correct at 4 meters is **less than 20**, position the patient 1 meter from chart, add +0.75 D sphere to the distance in the trial frame, test visual acuity using only the first 6 rows, and fill in the totals.

Right Eye-OD

Row	Acuity Equivalent	Chart 1 Letters	Number Correct
1	20/800	N C K Z O	_____
2	20/640	R H S D K	_____
3	20/500	D O V H R	_____
4	20/400	C Z R H S	_____
5	20/320	O N H R C	_____
6	20/252	D K S N V	_____
		Total(c):	_____

Left Eye-OS

Row	Acuity Equivalent	Chart 2 Letters	Number Correct
1	20/800	D S R K N	_____
2	20/640	C K Z O H	_____
3	20/500	O N R K D	_____
4	20/400	K Z V D C	_____
5	20/320	V S H Z O	_____
6	20/252	H D K C R	_____
		Total(c):	_____

Refractive Correction:

OD: + / - ___.___ + / - ___.___ x _____

OS: + / - ___.___ + / - ___.___ x _____

a) Total correct at 4 meters   _____
b) If ≥ 20 enter 30. If not, enter 0   _____
c) Total correct at 1 meter   _____
Visual acuity Score (a+b+c) _____

a) Total correct at 4 meters   _____
b) If ≥ 20 enter 30. If not, enter 0   _____
c) Total correct at 1 meter   _____
Visual acuity Score (a+b+c) _____

AIGS Clinical Data Form, Qualifying Visit

1. Patient name code (4 letters) ___ ___ ___ ___   2. Study ID ___ ___ ___ ___
3. Date of visit (mm/dd/yy) ___ ___-___ ___-___ ___
Technician: _____ Investigator:_____

Demographic Information
4. Date of birth (mm/dd/yyyy)___ ___-___ ___-___ ___ ___ ___
5. Gender (M=male, F=female) ____
6. Race (Circle any of the following that applies)
     a. American Indian/Alaska Native
     b. Asian
     c. Native Hawaiian or Other Pacific Islander
     d. Black or African American,
     e. White
7. Ethnic Category (circle one of following):
     a. Hispanic or Latino
     b. Not Hispanic or Latino

Family History (Y=yes, N=no)
8. Family history of glaucoma   ____

Medical History (Y=yes, N=no)
9.   Systemic hypertension   ____
10. Diabetes mellitus   ____
11. Cardiac disease   ____
12. Cerebral vascular disease   ____
13. Migraine   ____
14. Pre-baseline photographic evidence of progressive disc rim or RNFL loss _____
15. List other major medical and surgical history: _____
_____

Medications
16. Corticosteroid   (Y=yes, N=no) ____
17. List others:_____

Ophthalmic History

18. Eye diseases? (Y=yes, N=no)	Right Eye	Left Eye
a. Ocular hypertension	_____	_____
b. Glaucoma	_____	_____
c. Cataract	_____	_____
d. Diabetic retinopathy	_____	_____
e. Macular degeneration	_____	_____
f. Optic neuropathy	_____	_____
g. Other eye diseases (list): _____	_____	_____

_____

19. Is the patient using eye medication(s) (Y=yes, N=no) **Right Eye**   **Left Eye**
    a. β-blocker   _____   _____
    b. Prostaglandin   _____   _____
    c. α-2 Agonist   _____   _____
    d. Oral or topical CAI   _____   _____
    e. Nonselective adrenergic agonist   _____   _____
    f. Miotic agent   _____   _____
    g. Corticosteroid   _____   _____
    h. Others (list):_____   _____   _____

20. Has the patient had ocular surgery or laser treatment? (Y=yes, N=no)
                                                  Right Eye   **Left Eye**
    a. Cataract extraction & PC-IOL   _____   _____
    b. Corneal refractive surgery (LASIK/PRK/RK)   _____   _____
    c. Trabeculectomy   _____   _____
    d. Laser trabeculoplasty   _____   _____
    e. Glaucoma drainage device   _____   _____
    f. Laser   _____   _____
    g. Other procedure (list):_____   _____   _____

Eye Examination (Y=yes, N=No)

                                                    Right Eye   **Left Eye**
21. Afferent pupillary defect?   _____   _____
22. Slit-lamp examination (Grade 0-4, 0.5 increment)
    a. Corneal epitheliopathy   _____   _____
    b. Central corneal opacity   _____   _____
    c. Cortical cataract   _____   _____
    d. Nuclear sclerosis cataract   _____   _____
    e. Posterior cortical cataract   _____   _____
    f. Posterior subcapsular cataract   _____   _____
    g. Other positive finding (list):_____   _____   _____

23. Last use of medication affecting IOP

                                                        OD   OS

Medication	Frequency	Date last used	Time last used (military)	
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___

24. IOP determination

	Right Eye	Left Eye
a. First IOP reading (mmHg)	_____	_____
b. Second IOP reading (mmHg)	_____	_____
c. Difference of two readings	_____	_____
d. Third IOP reading (if difference ≥ 3mm Hg)	_____	_____
e. Consensus IOP (mean of 2 readings or median of 3 readings)	_____	_____
f. Time of IOP measurement (military)	___ ___: ___ ___	

25. Gonioscopy (Shaffer grade: 0, 0.5, 1, 2, 3, 4)

	Right Eye	Left Eye
a. Angle grade (of preponderance of the angle)	_____	_____
b. Other finding (list): _____	_____	_____

26. Dilated examination of the fundus (other than ONH)

	Right Eye	Left Eye
a. Macular degeneration	_____	_____
b. Diabetic retinopathy	_____	_____
c. Other positive finding (list):_____	_____	_____

Diagnostic Impression

27. Glaucoma-related diagnosis (Y=yes, N=no)

	Right Eye	Left Eye
a. Primary open-angle glaucoma	_____	_____
b. Pigmentary glaucoma	_____	_____
c. Pseudoexfoliation glaucoma	_____	_____
d. Narrow-angle glaucoma	_____	_____
e. Secondary glaucoma	_____	_____

28. Other diagnosis based on examination? (Y=yes, N=no)

	Right Eye	Left Eye
a. Cataract	_____	_____
b. Diabetic retinopathy	_____	_____
c. Macular degeneration	_____	_____
d. Optic neuropathy	_____	_____
e. Other eye diseases (list):_____	_____	_____

Ancillary Tests and Vital Signs

	Right Eye	Left Eye
29. Central corneal thickness (microns)	_____	_____
30. Axial eye length (mm)	_____	_____

_____   _____
Investigator's signature   Date

AIGS Clinical Data Form, Follow-up Visit

1. Patient name code (4 letters) ___ ___ ___ ___   **2.** Study ID ___ ___ ___ ___

3. Date of visit (mm/dd/yy) ___ ___-___ ___-___ ___   **4.** Visit code:_____

Technician:_____   Investigator:_____

Medical / Ophthalmic History
5. List new medical condition or surgery since last visit:

_____

_____

Medication
6. List change in medication since last visit:

_____

_____

7. Is the patient using eye medication(s) (Y=yes, N=no)

	Right Eye	Left Eye
a. β-Blocker	_____	_____
b. Prostaglandin	_____	_____
c. α-2 Agonist	_____	_____
d. Oral or Topical CAI	_____	_____
e. Nonselective Adrenergic Agonist	_____	_____
f. Miotic Agent	_____	_____
g. Others (list):_____	_____	_____

8. Has the patient had ocular surgery or laser treatment since last visit? (Y=yes, N=no)

	Right Eye	Left Eye
a. Cataract extraction & PC-IOL	_____	_____
b. Corneal refractive surgery (LASIK/PRK/RK)	_____	_____
c. Trabeculectomy	_____	_____
d. Laser trabeculoplasty	_____	_____
e. Glaucoma drainage device	_____	_____
f. Laser iridotomy	_____	_____
g. Other procedure (list):_____	_____	_____

Eye Examination

	Right Eye	Left Eye
9. Afferent pupillary defect? (Y=yes, N=no)	_____	_____

10. Slit-lamp examination (Grade 0-4, 0.5 increment)

	Right Eye	Left Eye
a. Corneal epitheliopathy	_____	_____
b. Central corneal opacity	_____	_____
c. Cortical cataract	_____	_____
d. Nuclear sclerosis cataract	_____	_____
e. Posterior cortical cataract	_____	_____
f. Posterior subcapsular cataract	_____	_____
g. Other positive finding (list):_____	_____	_____

11. Last use of medications affecting IOP

			OD	OS
Medication	Frequency	Date last used	Time last used (military)	
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___
_____	_____	_____	___:___	___:___

12. IOP determination

	Right Eye	Left Eye
a. First IOP reading (mm Hg)	_____	_____
b. Second IOP reading (mm Hg)	_____	_____
c. Difference of two readings	_____	_____
d. Third IOP reading (if difference ≥ 3mm Hg)	_____	_____
e. Consensus IOP (mean of 2 readings or median of 3 readings)	_____	_____
f. Time of IOP measurement (military)	___ ___:___ ___	

13. Dilated examination of the fundus (other than ONH)

	Right Eye	Left Eye
a. Macular degeneration	_____	_____
b. Diabetic retinopathy	_____	_____
c. Other positive finding (list):_____	_____	_____

Impression

	Right Eye	Left Eye
14. Is the eye still eligible for AIGS? (Y=yes, N=no)	_____	_____
15. Group assignment (N/GSPPG/PG)	_____	_____
16. New diagnosis based on examination?	_____	_____

_____

_____

_____   _____
Investigator's signature   Date

AIGS OPTIC DISC EXAM FORM

ONH/RNFL biomicroscopy or ophthalmoscopy

Subject Study ID: _____   Investigator: _____

Visit Code: _____   Coordinator: _____

_____   Exam Date: _____

Progression Of Glaucomatous Optic Neuropathy	OD		OS	
Decreased Rim	No	Yes	No	Yes
Increased RNFL defect	No	Yes	No	Yes
Progression of Rim or RNFL defect	No	Yes	No	Yes
Disc or RNFL hemorrhage	No	Yes	No	Yes

Examine for the progression indicators above in comparison with baseline disc photographs.
If any of the above answer is "Yes" then protocol optic disc photographs should be taken.

AIGS Personnel Certification

Name (please print):_____

Personnel Duties: ☐ **Technician** ☐ **Photographer** ☐ **Ultrasonographer**

Clinical Center: _____
Phone:_____

____ **Refraction**	____ **Central pachymetry**
____ **Visual acuity measurement**	____ **Afferent pupillary defect**
____ **Tonometry**	____ **Axial eye length measurement**

____ **Visual Field (attach both standard and progression printouts)**

____ **Stratus OCT (printout and data collection form attached)**

____ **RTVue FD OCT (printout)**

____ **GDX-ECC (printout and data collection form attached)**

____ **HRT2 (printout and data collection form attached)**

____ **Disc photography (slides attached)**

I certify that the above named person has demonstrated competency in one or more of the checked tests.

_____   _____
Principal Investigator's Signature   **Date**

- -

To be completed by Coordinating Center
Received By: _____ Date Received:_____

____ Met certification requirements & is certified

____ Has met provisional certification

____ Has NOT met certification & is NOT certified

Comments_____

_____

_____

_____   _____
Director, AIGS Coordinating Center Signature   Date

7   Treatment Regimen

7.1   Introduction

The AIGS is not an interventional trial. Participating clinical investigators and patients are not constrained in their choice of glaucoma treatment options. The treatment regimens described in this chapter are those commonly accepted in the treatment of glaucoma. They only serve as a reference.

7.2   Glaucoma Medical Regimen

Glaucoma medications are generally to be used before laser or surgery on patients with glaucoma or patients with ocular hypertension who are deemed to require intraocular pressure (IOP) lowering by the treating ophthalmologist. Any one or more of the glaucoma medications currently approved by the U.S. FDA can be used. The following list classifies the medications by their mechanism of action.

1. β-blockers:
timolol 0.25%, 0.5% (Betimol®, Timoptic®)
carteolol 1% (Ocupress®)
levobunolol 0.25%, 0.5% (Betagan®)
metipranolol 0.3% (Optipranolol®, MetiPranolol®)
betaxolol 0.25%, 0.5% (Betoptic®)

2. α-ardrenergic agonists:
brimonidine 0.15%, 0.2% (Alphagan P®)
apraclonidine 0.5% for laser use (Iopidine®)

3. non-selective adrenergic agonists:
dipivefrin 0.1% (Propine®)
epinephrine 0.5%, 1% (Epifrin®)

4. topical carbonic anhydrase inhibitors:
brinzolamide 1% (Azopt®)
dorzolamide 2% (Trusopt®)

5. oral carbonic anhydrase inhibitors:
acetazolamide 250 mg, 500 mg (Diamox®)
dichlorphenamide 50 mg (Daranide®)
methazolamide 25mg, 50 mg (Neptazane®)

6. prostaglandin agents:
bimatoprost 0.3% (Lumigan®)
latanoprost 0.005% (Xalatan®)
travoprost 0.004% (Travatan®)
unoprostone 0.15% (Rescula®)

7. cholinergic (miotic) agents:
pilocarpine 1%, 2%, 4%, 6% (Isopto Carpine®, Pilocar®)
carbachol 0.75%, 1.5%, 3% (Isopto Carbachol®)

8. combination medication:
timolol maleate 0.5%/dorzolamide 2% fixed combination (Cosopt®)

7.3   Laser Trabeculoplasty

Laser trabeculoplasty (argon, diode or selective) can be performed for medically uncontrolled IOP or in place of glaucoma medication if deemed appropriate by the treating ophthalmologist.

7.4   Surgical Therapy

Glaucoma filtering surgery, usually trabeculectomy or non-penetrating glaucoma filtering surgery, may become necessary for patients with uncontrolled IOP. Glaucoma drainage devices are also used in cases where trabeculectomy has relatively low success rates.

7.5   Laser Iridotomy

If progressive angle narrowing or angle closure develops over time, laser peripheral iridotomy should be performed.

7.6   Post-Operative Subject Eligibility

Subjects who receive glaucoma surgery will remain in the AIGS but their data will be analyzed separately. The subjects will have no study measurements in the first 3 months postoperative period. New axial length, VF and optic disc baselines will be obtained between 3 and 6 months after trabeculectomy

8   Study Organization

Version 8.3

8.1   Introduction

The organizational structure of the Advanced Imaging for Glaucoma Study (AIGS) links the following resource centers together in a network:

- Clinical Centers
- Coordinating Center
- Study Chairman's Office

The AIGS is guided by the Steering committee.

In addition to the clinical study, the AIG grant from the NIH supports the development of novel advanced imaging technologies at several Engineering and Basic Science Centers. These technologies will be added to the clinical studies at the appropriate times.

8.2   Clinical Centers

Each Clinical Center is responsible for following participants according to the protocol until the termination of the trial. Each Clinical Center has at least one AIGS-certified principal investigator, one certified photographer, one certified visual field technician and one certified clinic coordinator. Each position, except for the principal investigator, requires a back-up person, although an individual can serve more than one role and can back-up more than one position.

8.3   Coordinating Center

The Coordinating Center is responsible for:

- Overall coordination of the clinical trial.
- Development and implementation of the study design.
- Receiving, editing, processing, analyzing and storing study data.
- Coordinating activities of the Clinical Centers.
- Implementing and maintaining quality assurance procedures.
- Contributing to statistical and operational methodology of multi-center clinical trials.
- Preparing reports, presentations and publications.
- Assisting in the organization of the Steering Committee and Clinic Coordinators' Group.
- Certifying study personnel.

The Coordinating Center personnel include a director, central coordinator and a database manager.

8.4   Study Chairman's Office

The Study Chairman's Office is responsible for:

- Overall scientific conduct of the trial.
- Maintaining the study organization as an effective collaborative group.
- Establishing committees, appointing committee members and dissolving committees that have completed their charges.
- Public relations and dissemination of information to health professionals and the public.
- Participant relations, education and retention.
- Quality control and troubleshooting.
- Organizing meetings of the Executive/Steering Committee and Clinical Coordinator's Group.

The staff of the Chairman's Office consists of the Study Chairman and a project manager.

8.5   Steering Committee

The Executive/Steering Committee has overall responsibility for directing AIG activities and formulating policy for the study.

8.5.1 Steering Committee Membership

The following individuals are members of the Steering Committee:
- David Huang, M.D., Ph.D., Chairperson
- Joel S. Schuman, M.D.
- David S. Greenfield, M.D.
- Rohit Varma, MD
- Brian Francis, M.D., Visual Field Reading Center

The Study Chairman may appoint other individuals to the committee as he deems necessary. All members must file statements with the Study Chairman describing any potential conflict of interest.

8.5.2 Steering Committee Functions

The specific functions of the Steering Committee include:

- Direct all activities of the AIGS.
- Formulate all policy decisions related to the design and conduct of the AIGS, except for those protocol changes based on assessment of accumulating data which are the responsibility of the DSMC.
- Assist the Study Chairman with the scientific administration of the study.
- Recommend to the Study Chairman and DSMC major changes to the study protocol judged necessary or desirable.

- Ratify major changes to the Manual of Procedures.
- Review and approve all ancillary studies.
- Monitor the performance of all Clinical Centers and to take corrective action as necessary.
- Establish writing committees for principal papers to review all written and oral reports for publication and presentation, including those from the ancillary studies.
- Appoint subcommittees as required for special study functions.
- Dissolve subcommittees and technical committees when their functions have been fulfilled.

8.5.3 Steering Committee Meetings

The Steering Committee meets in person or by telephone at least twice a year for the duration of AIG. Meetings are called by the Study Chairman.

8.6   Engineering and Basic Science Centers

The AIG project include three engineering centers and one basic science center whose mission is to develop novel advanced imaging technologies for glaucoma. Phase 2 participating centers are:

- Oregon Health & Science University, Casey Eye Institute, Novel OCT scan patterns and image processing.

- Massachusetts Institute of Technology, Department of Electrical Engineering and Computer Science and Research Lab of Electronics.

Phase 1 previously participating centers through year 5 (no longer active).

- Case Western Reserve University, Department of Biomedical Engineering Multi-angle OCT.

- Duke University, Department of Biomedical Engineering: Advanced OCT with ultra-high resolution, speed and birefringence sensing.

- University of Miami Bascom Palmer Eye Institute: In-vitro retinal reflectometry.

8.7   AIG Address List

For the AIGS contact information, please refer to the following URL:

http://www.aigstudy.net/index.php?id=11

9   Policy Matters

Appendix: Application for Proposal for Publication

9.1 IRB Approval

The principal investigator of each Clinical Center is responsible for obtaining local IRB approval for the AIGS and its informed consent form. A copy of each Clinical Center's approved informed consent form and documentation of IRB approval must be submitted to the Coordinating Center before participants are enrolled in the AIGS. Current Clinical Center IRB approval is kept on file at the Coordinating Center.

9.2 Participant Consent

The AIGS requires that written informed consent be obtained from each participant prior to enrollment. The participant is asked to sign the informed consent form only after information about study goals, risks and benefits of participation, and study tests and measures are provided. The signed informed consent form is kept with the study records in the Clinical Center and a copy is given to the participant. (See Chapter 4 for details on informed consent.)

9.3 Publicity

All press releases should be submitted to the Study Chairman for approval at least two (2) weeks prior to release. Press releases should not include pre-publication data from the study unless specifically approved by the Steering Committee.

When individual investigators speak to local or national press, the information given out should be accurate and should reflect the general policy and views of the study. The Study Chairman should be informed of all local presentations to the press and provided with a copy of the material published.

The principal investigator of each Clinical Center will have a packet of press release material prepared by the Chairman's Office and approved by the Steering Committee. This material is adequate for most public relations needs. If there is any question about press releases, the investigator should call the Study Chairman's Office.

9.4 Publications and Presentations Policy

All publications and presentations of unpublished data relating to the AIGS and its Ancillary Studies must have prior approval by the Steering Committee.

9.5 Editorial Policy

9.5.1 Publication of Trial Design, Methods and Findings

The Steering Committee will establish writing committees for all papers. A representative of the Coordinating Center will be appointed to writing committees for papers or presentations requiring study data. Investigators may volunteer for writing assignments and suggest additional topics for papers.

The lead author should submit an abstract to the Study Chair, including a short description of the proposed paper, possible co-authors, data to be reported and timeline for drafts and submission. The Steering Committee is responsible for reviewing the scientific merit of the proposed paper and deciding if it should be an AIGS publication. This review process is intended to ensure the quality of study publications and may require refinement of the proposal. The Steering Committee is responsible for setting priorities (timeline and order of preparation) of proposed papers/presentations.

The Coordinating Center is responsible for maintaining a database that tracks proposed and approved study publications. A list of approved study publications will be distributed to all AIGS investigators on a regular basis. Interested AIGS investigators are invited to contact the lead author to participate in the writing group.

The Steering Committee resolves conflicts regarding authorship. General guidelines for authorship are: active participation in formulating the question, analyzing data and producing the manuscript. If the timeline for a paper has expired with no substantial progress, authorship rights are assumed to have expired. The Study Chair will contact the lead author and leadership of the paper will be negotiated. The Steering Committee will be informed of changes in lead authorship. An individual may be given an acknowledgement for reading and providing critical comments on a manuscript. An investigator at the Coordinating Center will be added to the author list on all papers that require statistical input.

Should the workload associated with the preparation of papers exceed the resources of the Coordinating Center, it will be the responsibility of the Steering Committee to establish priorities. It will be the responsibility of the Coordinating Center to contact lead authors when timelines are not met. Major problems in the preparation of manuscripts are referred to the Steering Committee.

The lead author is responsible for coordinating all activities related to the writing and submission of papers and abstracts. This includes arranging conference calls, discussing analytic plans with the Coordinating Center, assigning writing responsibilities to co-authors, maintaining timeliness, determining the order of authorship and circulating drafts to co-authors. The Coordinating Center is responsible for circulating final drafts to the Steering Committee. Upon circulation of the draft, there will be up to a two-week period during which committee members can make comments about the paper.

If the focus of the paper changes as it moves from the abstract to the manuscript stage, the lead author will notify the Study Chairman in writing. The Study Chairman will be responsible for ensuring that the revised proposal receives appropriate review.

The Steering Committee will review all papers prepared for publication. All reports from the AIGS will list the Advanced Imaging for Glaucoma Study Group as an author. Publications will list the lead author and co-authors and the Advanced Imaging for Glaucoma Study Group. All professional participants of AIGS, including those at the central units and Clinical Centers, will be listed at the end of each paper as indicated and are considered as authors or contributors. In major papers, all study personnel, past and present, will be listed with the approval of the principal investigator for whom they have worked.

Each publication must acknowledge the following supporting entities of AIGS:

> "This study was supported by grant R01 EY013516 from the National Eye Institute, National Institutes of Health, Bethesda, MD, USA. Material support was also received from Carl Zeiss Meditec, Inc., Dublin, CA, USA, and Heidelberg Engineering Gmbh, Heidelberg, Germany."

Copies of major papers from AIGS are sent (before publication) to all principal investigators, to all members of the Steering Committee. Reprints of major published papers are mailed to each Clinical Center for distribution among the staff. Ten reprints of each paper are sent to the Coordinating Center for the AIGS library.

The Study Chairman will send a letter of approval with all manuscripts when they are submitted for publication. Some journals require that all individuals listed as members of the study group sign the copyright waiver form. If so, the writing committee will enlist the assistance of the Study Chairman's Office to obtain these signatures.

9.5.2 Presentations

Oral presentations and abstracts to be printed must be approved in advance by the Steering Committee. No unpublished study results may be used for oral presentations, local or otherwise, unless a specific exception is granted by the Steering Committee. Study results include all data collected for AIGS, whether descriptive or comparative in nature. The above restrictions do not apply to local presentations on the design of AIGS, provided these presentations contain no unpublished study results.

9.5.3 Publications from Ancillary Studies

Manuscripts from ancillary studies carried out in conjunction with the AIGS must be sent to the Steering Committee for review before submission for publication. **No investigator at any AIGS center can publish results on AIGS participants that were obtained as part of the study without permission from the Steering Committee.**

9.6 Ancillary Studies

Ancillary studies will greatly enhance the value of the AIGS and ensure the continued interest of all investigators. However, to protect the integrity of the study, ancillary studies must be reviewed and approved by the Steering Committee prior to inception, whether or not they involve the need for supplemental funds. AIGS participants cannot be enrolled in other ocular studies without authorization from the Steering Committee.

9.6.1 Definition of an Ancillary Study

An ancillary study is a research study that requires either:

- Supplemental observations or procedures to be performed upon all or a subgroup of the AIGS participants according to a predefined protocol, or

- Additional work to be done by or information to be obtained from the Coordinating Center.

An ancillary study is typically initiated by an investigator on a topic outside of the expected regular reports and statistical analysis from the AIGS data.

9.6.2 Rationale for the Approval Process

Everyone concerned with AIGS is entitled to the assurance that no ancillary study will:

- Complicate the interpretation of AIGS results.
- Adversely affect participant cooperation or retention.
- Jeopardize the public image of the AIGS.
- Create a serious diversion of study resources locally, at the Coordinating Center or at any other of the central units serving the AIGS research group.

9.6.3 Preparation of a Request for Approval of an Ancillary Study

The request for approval of an ancillary study should be made on the AIGS "Application for Proposal for Publication" (appended). It should contain a brief description of the objectives, methods and significance of the study. Full details should be given concerning any procedures to be carried out on AIGS participants, such as laboratory tests, interviews, psychological testing, etc. Detailed discussion must be provided regarding the additional participant burden imposed by the ancillary study (informed consent procedure, extra time, extra visits, etc.). If access to AIGS study data is required, the investigator must specify what data are needed, for whom it is needed and the timetable for access to such data.

9.6.4 Procedures for Obtaining Ancillary Study Approval

The investigator proposing an ancillary study should send a written request to the Study Chairman. The Study Chairman is responsible for distributing copies to all members of the Steering Committee. Within a reasonable time, the Chairman will summarize any

questions and/or objections raised by members of the Steering Committee and send this summary to the applicant to permit amplification, clarification and/or withdrawal of the request. The members of the Steering Committee will review the request again and the Chairman will then prepare a statement of the Steering Committee consensus, including any remaining reservations or objections. This statement is forwarded to the investigator who requested approval for the ancillary study.

9.6.5 Funding of Ancillary Studies

If no additional funds are required, the investigator may proceed with the ancillary study as soon as it has been approved by the Steering Committee. If additional funds are needed, the investigator may prepare and submit a research grant application to the potential sponsor for review in the same manner as any other new research grant application. Copies of the grant application are sent to the Chairman and Coordinating Center. The investigator may not submit the grant or activate the ancillary study until approval has been received from the AIGS Steering Committee.

9.6.6 Publication of Ancillary Study Results

All manuscripts or presentations based on ancillary study data must be reviewed and approved by the AIGS Steering Committee before publication or presentation. Such review pertains to impact on AIGS objectives and to scientific merit.

After publication, 10 reprints or photocopies of the ancillary study report should be sent to the Study Chairman's Office for distribution to the Steering Committee and to the Coordinating Center for the AIGS library.

9.6.7 Progress Reports

The principal investigator of each ancillary study is expected to report to the Study Chairman at six-month intervals on the progress of the ancillary study. This report may be prepared as a letter. The Study Chairman reports on the status of all ancillary studies to the Steering Committee at each meeting.

9.7 Access to Study Information

9.7.1 Study Documents

The Manual of Procedures and copies of the data collection forms used in the AIGS will be placed in a suitable repository on the Internet, after approval by the Steering Committee. These documents may be referenced without prior approval once they have been placed in the repository. The Coordinating Center Director replaces documents in the archives with updated copies whenever substantive changes are made in the AIGS procedures or methods.

In general, the following documents are considered proprietary and may not be released to any group or individual outside the AIGS Research Group:

- Minutes of study meetings.
- Performance monitoring reports for AIGS Clinical Centers and Resource Centers.

9.7.2 Study Data

Access to study data for individual participants is prohibited to unauthorized individuals, whether these data are on file at a Clinical Center or at the Coordinating Center. The identity of individual AIGS participants may not be implied or revealed in any public report or presentation.

9.8 Participation of Women and Minority Groups

A goal of the study is that all groups in the population be well represented in the study sample. This is done for the sake of fairness and also to protect the validity of the study. It is generally accepted that glaucoma occurs with equal frequency in men and women. Given the age entry criteria (40-80 years), it is anticipated that women will form a slight majority of the participants. It is generally accepted that glaucoma is more common and more severe in African-Americans than others. Furthermore, many Clinical Centers are located in medical facilities in major metropolitan areas. Thus, it is anticipated that African-Americans will be over-represented compared to the general population. All Clinical Centers must be accessible to handicapped people.

9.9 Protection of Human Subjects Certification

The NIH has adopted a policy entitled "Protection of Human Subjects Certification." This policy requires that all investigators and coordinators involved in NIH studies be certified as having passed a course on protection of human subjects. This includes all investigators and coordinators at clinics, satellites, resource centers and ancillary studies. Verification that study personnel have completed the certification process is done by the IRB at the local level.

10　Clinical Center Procedures

Version 8.3

10.1 Clinical Center Responsibilities

The responsibilities of AIG Clinical Centers include the following:

- To provide each participant with AIGS educational materials.

- To enroll participants in the AIGS through written informed consent.

- To manage each participant in accord with the instructions in the MOP.

- To examine each participant enrolled in the AIGS using the study protocol and the schedule.

- To complete the proper forms and obtain visual fields and optic disc photographs required at each visit.

- To transmit data to the Coordinating Center according to protocol. This includes data entry on the Internet-based AIGS Central Database and shipping of OCT data via digital media.

- To respond promptly to additional requests for data and audits from the Coordinating Center.

- To maintain participant records for AIGS in an easily accessible but confidential manner. It is vital to follow the HIPAA standard rule to protect the rights of the enrolled subjects and all documentation, including digital files, must be HIPAA compliant.

- To maintain complete and current residency and employment information on each AIGS participant.

- To maintain current informed consent documents that meet AIGS standards and the standards of the local Institutional Review Board.

- To maintain all equipment and supplies required for the AIGS.

- To promote participant satisfaction, commitment and retention to the AIGS through reminder systems, good rapport, newsletters and regular reports on their examinations.

- To help train new study personnel as needed.

10.2 Clinical Center Personnel

Each Clinical Center will have one principal investigator and one or more clinical investigators. Also, each Clinical Center must employ the following certified personnel:

- Clinic coordinator
- Technician
- Photographer

For each position, there must be a back-up person, although this does not necessarily require six people, i.e., the coordinator could back-up the technician and the photographer, if appropriately trained and certified. Certification is maintained for all certified personnel and new personnel are certified as needed.

10.2.1 Responsibilities of the Principal Investigator

- To lead and direct the overall conduct of the trial in the Clinical Center.

- To train, supervise and help certify Clinical Center personnel.

- To submit and maintain current IRB approval and consent from the clinic's local IRB office.

10.2.2 Responsibilities of the Clinical Investigators

- To provide participant education, enroll participants in the AIGS after informed consent and provide follow-up care for participants.

- To determine the therapy for each participant.

- To aid participant retention through good rapport.

- To perform clinical examinations including slit-lamp examination, gonioscopy and ophthalmoscopy.

- To supervise the measurements and tests performed by the technicians and ensure their accuracy.

- To review study for eligibility determination, VF interpretation, disc photography reading, and advance imaging data quality control and interpretation.

10.2.3 Responsibilities of the Clinic Coordinator

- To coordinate the Clinical Center activities related to the AIGS.

- To have a thorough understanding of AIGS design and details.

- To coordinate activities between the participants, Clinical Center, Coordinating Center and the Chairman's Office.

- To provide a resource for other Clinical Center personnel concerning the study protocol.

- To schedule participant visits and arrange participant transportation.

- To maintain participant interest in the study by contacts during scheduled visits and by expressing concern for the participant's welfare and problems.

- To maintain study documentation including a current MOP, appointment notebooks, participant log book, copies of current study forms, log books of visual fields and imaging tests and current addresses and employment information about participants.

- To review all forms and information for accuracy and to assure that copies of all forms are retained in the AIGS files at the Clinical Center. The coordinator should review all data collection forms and printouts to ensure that the technicians and photographers entered information correctly and completely. The coordinator should fill out the identifying data on the forms. The coordinator should prepare the data for review by the clinical investigators for review and make sure that proper masking procedures are followed.

- To enter data into the AIGS Central Database.

- To respond to queries from the Coordinating Center.

- To notify the Coordinating Center about personnel changes.

- To inform the principal investigator and the Coordinating Center of any problems evaluating, treating or following AIGS participants.

10.2.4 Responsibilities of the Technician

- To learn correct AIGS procedures.

- To obtain patient history.

- To perform refraction and visual acuity measurements.

- To evaluate afferent pupillary defect.

- To perform applanation tonometry.

- To perform central pachymetry.

- To perform Humphrey visual field tests.

- To label Humphrey visual fields for proper filing.

- To perform axial eye length measurement.

- To enter the above information into appropriate data collection forms.

10.2.5 Responsibilities of the Photographer/Imager

- To learn correct AIGS photography and imaging protocols, including the appropriate data forms.

- To take stereoscopic optic disc photographs, scanning laser polarimetry (GDx-ECC), Heidelberg Retina Tomography (HRT2) and Optical Coherence Tomography (OCT).

- To fill in the quality assurance items in the data collection forms associated with the photographs and advanced imaging tests.

- To label the photographs and images for review and storage.

10.3 Study Documents

Each Clinical Center must have available the following:

- A current copy of the AIGS Manual of Procedures (AIGS-MOP).

- A current copy of all study IRB approval and informed consent forms.

- Copies of the AIGS study forms for data collection, clinic management and study management.

- Batch edits received at the Clinical Center requiring data corrections should be filed in the appropriate AIGS participant file. Log books for participant visual field test and optic disc photographs.

- Other clinic and participant management aids, such as participant appointment schedules and visit reminders.

- AIGS certificates for the coordinators, technicians and photographers.

When study forms are revised, the clinic coordinator is responsible for seeing that all old versions are destroyed. Under no circumstances should outdated forms be used. The clinic coordinator is responsible for explaining to the clinic staff any changes in procedures that are required by form revisions.

10.4 Scheduling and Coordination of Participant Visits

The clinic coordinator plays a major role in scheduling and data recording. Therefore, it is important the clinic coordinator have a thorough understanding of the required procedures for each visit, the sequence in which these are best performed and the contents of the data collection and other forms to be completed. The schedule of visits is detailed in Chapter 5 of the MOP.

10.5 Data Collection Forms and AIGS Central Database

The coordinator should review the data collection forms (DCF) from each visit for completeness and accuracy. The relevant data from the DCFs and printouts should be entered into the AIGS Central Database via the Internet within one month of the visit. The coordinator is responsible for responding to audit requests from the Coordinating Center.

10.5.1 Completeness

All required items in the DCFs and Central Database must be answered within the proper time frame. If any missing or questionable item is found upon review, the coordinator should determine how the missing answer should be supplied by asking the original datataker and consulting the MOP, the clinical investigator and/or the Coordinating Center. Items that require confirmatory testing (such as VF progression) should be entered within one month of the confirmatory test.

10.5.2 Legibility

Write-in responses should be printed or typed in black ink so they are clearly legible. Check marks should be placed precisely so there is no possibility of confusion regarding the response intended.

10.5.3 Edits and Corrections

The Coordinating Center will review data entered in the Central Database and, when there is a question regarding the answer to one or more items, issue an edit statement to the coordinator at the Clinical Center. The edit statement gives AIGS identifying information about the participant and visit and lists the item number(s) and the original answer ("old value") entered in the Central Database. There is space for writing in a corrected response in the "corrected value" column. An explanation of the nature of the problem follows the list of items. The Coordinating Center may require copies of printouts, photographs, DCFs and explanation regarding specific problems.

When an edit statement is received, the clinic coordinator should obtain the participant's record from the files and determine the correct answer for each item listed. The original datataker and/or the clinical investigator may need to be consulted. After completing the edit statement, the clinic coordinator should make each correction directly on the clinic

copy of the participant's visit form and should initial and date this notation. The completed edit statement and supporting material must be returned to the Coordinating Center within one month from the time it was received.

10.5.4 Annual Audits

The Coordinating Center will perform annual audits by requesting copies of printouts, DCFs, photographs and other documents to the clinical coordinators at the Clinical Centers. The clinical coordinators are responsible for supplying the required materials within a month of the audit requests.

10.6 Assuring Completeness of Follow-up

One of the most important duties of the Clinical Center is maintaining good rapport with all AIGS participants to ensure that each remains in the study. The clinic coordinator should be thoroughly familiar with the materials pertaining to missed visits, participant contact between visits and procedures for inactive or transfer participants

10.7 Preparing for Return Visits

The following tasks should be done prior to a scheduled participant visit. The clinical coordinator has the primary responsibility for tracking these tasks and arranging for their performance.

- Remind the participant of the scheduled appointment by telephone and/or by mail in advance of the date.

- Retrieve the participant's AIGS file and make sure all VFs, disc photographs and advanced imaging tests since the last visit have been read.

- Place the participant's AIGS number and the clinic's site number on all forms pertinent to the scheduled visit.

- Refer to the most recent refraction in obtaining best-corrected visual acuity. Do not refer to the visual acuity measurements from the previous examination.

- Schedule appointments for Humphrey perimetry, disc photography and advanced imaging procedures as needed.

10.8 Wrap-up After a Visit

The following tasks should be done after a scheduled participant visit. The clinical coordinator has the primary responsibility for tracking these tasks and arranging for their performance.

- Review study forms and printouts to make sure all examinations, tests and measurements mandated by the study protocol have been performed and the data are properly recorded.

- The treating clinical investigator should have reviewed the VF during the visit for clinical decision-making.

- If the advanced imaging tests meet the unmasking condition, they should also be reviewed by the treating clinical investigator during the visit for clinical decision-making.

- Schedule subsequent visits, including the next regular follow-up visit and any repeat visit needed to obtain missing or confirmatory tests.

- Prepare VFs, disc photographs and advanced imaging tests data for formal masked review by the clinical investigator within one month of their performance. The results of the review should be recorded on the data collection forms. The investigator should review the data and determine if the subject should stay in the assigned study group, switch groups or be discontinued from the study.

- Study data should be entered into the AIGS Central Database within one month.

10.9   Certification of AIGS Clinical Coordinator

The clinical coordinator(s) at each clinical center must be certified. The principal investigator at each clinical center will submit the names of the coordinator to the director of the Coordinating Center. The director of the Coordinating Center will certify the coordinator after an interview to assess the knowledge of the coordinator. The interview may be in person or by telephone.

The clinical coordinator should demonstrate knowledge of the AIGS:
- Purpose of the study
- Design of the study
- Enrollment eligibility criteria
- Visit schedule for study subjects
- Tests to be performed at the study visits

- Steps to prepare for a study visit
- Steps to wrap up a study visit
- Procedure for filing and processing VFs
- Procedure for filing and processing disc photographs
- Procedure for filing and processing advanced imaging tests (including masking criteria)
- Familiarity with AIGS forms

The director of the coordinating center should issue certification to the coordinator once the above knowledge has been demonstrated satisfactorily.

11   Time- Domain OCT (Stratus) Procedures

Appendix: OCT Data Collection Form

11.1 Stratus OCT Image Acquisition Procedure

Optical coherence tomography (OCT) is capable of cross-sectional and three-dimensional imaging of the retina and optic nerve with higher axial resolution than other imaging modalities. The high axial resolution is achieved by using low-coherence interferometry to measure the time-of-flight delay of the reflected probe beam and determine the depth of reflection. OCT imaging of the optic nerve head (ONH), retinal nerve fiber layer (NFL) and macula is a major part of the AIGS.

The Stratus OCT system (Carl Zeiss Meditec, Inc., Dublin, CA, USA) will be used in the AIGS throughout the clinical trial. Stratus OCT is the latest version of retinal OCT scanner from Zeiss at the start of the AIGS. It is capable of axial resolution of 9-10 micron full-width-half-maximum (FWHM) in tissue and acquires data at a rate of 400 axial scans per second. The higher scan rate allows us to use newer complex scan patterns that generate a three-dimensional dataset. Software Version 5.0 is used at the current time.

Other advanced OCT systems will be developed by the engineering centers in the AIG consortium and added to the clinical study protocol at a later time.

11.1.1 Patient Setup

1. All examinations must be completed by certified personnel.

2. Image right eye first, then left eye.

3. Reduce the lighting in the room to a minimal level.

4. Imaging should be performed without pharmacologic pupil dilation unless the pupil is too small to permit imaging. For this reason, imaging should generally be performed prior to dilated fundus examination and disc photography. If dilating drops have already been applied for another advanced imaging test, go ahead and perform OCT under the dilated condition. If pharmacologic pupil dilation is required, use one drop each of tropicamide 1% and phenylephrine 2.5% and wait at least 20 minutes before imaging. Record if pharmacologic pupil dilation if used. If it is, subsequent examinations should also use the same dilation procedure.

5. Corrective lenses including contact lenses should be removed for the OCT examination and an unpreserved artificial tear drop should be administered to each eye to prevent drying.

6. Enter patient's name, ID number and date of birth in the OCT database. The spherical equivalent should be used to initially focus the objective lens.

7. Position the patient. The instrument, chair and chin rest heights should be adjusted so the patient is comfortable and stable, the forehead is placed against the forehead rest and the eyes are aligned with the eye-position markers.

11.1.2 Macular Scans

1. Under the scan tab, select **Fast Macular Thickness Map.**

2. Using the live video image, center the instrument on the pupil and instruct the patient to fixate on the internal fixation target (flashing green light). Guide the instrument closer to the eye of interest and adjust the horizontal and vertical position of the scanning instrument until the macula comes into view on the video display. Adjust the instrument until the retinal image moves into the OCT display and the instrument makes a "beep" sound indicating proper positioning for scan acquisition.

3. After the patient is properly positioned, adjust the Z-offset to center the image and optimize the polarization. The adjustment can be achieved by clicking **Optimize Z-offset** and **Optimize Polarization** on the **Scan Parameter** tab.

4. Ensure that the layers of the retina and choroid are not cropped by the upper and lower borders of the scan and the layers have minimal vertical undulation. Make sure that the scan is centered on the fovea and that the foveal pit appears in the scan.

5. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (red) in both the RPE/choriocapillaris and RNFL.

6. Select the **Scan Mode** button to prepare for image acquisition.

7. Instruct the patient to blink several times and then to hold the eye open and still. Wait for all six scans to be uniform and then select **Freeze with Flash** and then select **Save**.

11.1.3 Retinal Nerve Fiber Layer Scans

1. Under the scan tab, select **Fast RNFL Thickness (3.4).**

2. Using the live video image, center the instrument on the pupil and instruct the patient to fixate on the internal fixation target (flashing green light). Guide the instrument closer to the eye of interest and adjust the horizontal and vertical position of the scanning instrument until the optic disc comes into view on the video display. Adjust the instrument until the retinal image moves into the OCT display and the instrument makes a "beep" sound indicating proper positioning for scan acquisition.

3. After the patient is fixating on the fixation target, the optic disk should be in view. Manually center the scan circle around the optic disk. The RNFL scanning circle should not be cropped by the upper and lower borders of the video image.

4. To make sure that scans are of the highest quality, adjust both the Z-offset and the polarization after the patient is positioned correctly. The adjustment can be achieved by clicking **Optimize Z-offset** and **Optimize Polarization** on the **Scan Parameter** tab. Ensure that the scanning image is centered vertically.

5. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (white/red) in both the RPE and RNFL. Adjust the vertical and horizontal position of the OCT system until the RPE layer is as flat as possible.

6. Select the **Scan Mode** button to prepare for image acquisition.

7. Instruct the patient to blink several times and then hold the eye open and still. Wait for all three scans to be uniform and then select **Freeze with Flash** and then select **Save**.

11.1.4 Summary of scan patterns

Pattern	Group		
	Normal	**GSPPG**	**PG**
Fast Macular Thickness Map	Yes	Yes	Yes
Fast RNFL Thickness (3.4)	Yes	Yes	Yes
Fast Optic Disc	Yes	Yes	Yes

The scan patterns are performed twice during the baseline visit and twice during the follow up visits.

11.2 Quality Control and Data Analysis

11.2.4 Common Scan Quality Criteria

Each OCT scan should be checked to ensure high quality. The cross-sectional images should be inspected individually.

Check the OCT and CCD images to make sure the scan is properly positioned. The CCD image should show that the scan is properly centered on the optic disc or the fovea, as appropriate to the scan pattern. Radial scans across the disc should show both edges of the disc's RPE margin in the OCT images. Radial scans across the macula should show the foveal depression at the center. The upper and lower boundaries of the image frame should not crop off any part of the retina, RPE or the optic disc signal. Poorly positioned scans should be rejected.

A sudden jump in the retinal contour indicates a saccadic eye movement has occurred during the scan, unless the discontinuity is reproducible. Saccadic motion artifact disqualifies the scan. Small continuous changes in the scan contour due to the cardiac cycle and other slow movements are unavoidable and acceptable.

The signal level should be good all across the image. There should be pixels of strong signal in each axial scan, which commonly arise in the inner retina/disc or RPE. The presence of axial scans with weak or no signal indicates that the OCT beam has been blocked by the iris or other media opacity. A possible exception is the highly sloped area in the cup of the optic disc, where the oblique beam incidence angle can normally lead to weaker reflected signal. Besides qualitative inspection, Zeiss also recommends that 95% of the a-scans be judged acceptable by the image processing algorithm (available for some scan types). Focal signal loss would disqualify the scan. The scan should be repeated with better positioning of the OCT system. Rarely, pupil dilation may be necessary.

The overall signal level should be high. A uniformly weak signal usually means the beam is out of focus or the polarization is not optimized. The SNR parameter is available for some types of scan analysis and they are specified below. For software Version 3.1 and before, Zeiss recommends that the (maximum) SNR (signal-to-noise ratio) for the image should be ≥ 35 dB. For software Version 4.0 and after, Zeiss recommends that the *Signal Strength* parameter (scale 0-10) be ≥ 8. Rescan the eye once if the signal strength is below 8 in any required Stratus scan. If the signal strength is 6 or higher in the second acquisition and the segmentation error is acceptable (i.e. the border line fits the retina), record the scan in the central database. If a high quality scan cannot be obtained, a failed scan should be recorded.

Segmentation failure was defined as obvious deviation of the segmented borders from the subjectively perceived borders. Consecutive 15% or cumulative 20% segmentation failure within an image was labeled as poor analysis quality frame and discarded from the study.

The above quality criteria should be checked for all scan types. Specific procedures for each scan type follows. The OCT Data Collection Form (OCT-DCF) should be used to facilitate the scan quality review.

11.2.4 Fast Macular Thickness Map

1. When the image acquisition is completed, select the **Fast Macular Thickness** scan group from the scan list under the desired eye. **Retinal Thickness (single eye)** under the analyze tab should then be selected.

2. Select **Analyze**.

3. Use the scroll bar to view all six radial scans sequentially. Make sure there is no saccadic motion artifact and the signal level is uniform and adequate. If these quality criteria are not met, the scan should be deleted from the OCT system and a replacement scan should be performed.

4. Check if the borders of the retina are drawn correctly by the Stratus computer algorithm. If the borders are not identified correctly, the image should be rejected and a repeat scan should be obtained. The algorithm will usually work on a repeat image where the signal level is stronger and more uniform. Keep track of the number of images that are rejected due to poor border delineation by the algorithm and record it on the OCT-DCF.

5. Select **Retinal Thickness/Vol Tabular** under the analyze tab, and then **Analyze.**

6. Print the report.

11.2.4 Fast RNFL Thickness (3.4)

1. When the image acquisition is completed, select the **Fast RNFL** Thickness scan group from the scan list under the desired eye.

2. Select **Retinal Nerve Fiber Layer (single eye)** under the analyze tab.

3. Use the scroll bar to view the three circular scans sequentially. Make sure there is no saccadic motion artifact and the signal level is uniform and adequate. If these quality criteria are not met, the scan should be deleted from the OCT system and a replacement scan should be performed.

4. Check if the borders of the retina are drawn correctly by the Stratus computer algorithm. If the borders are not identified correctly, the image should be rejected and a repeat scan should be obtained. The algorithm will usually work on a repeat image where the signal level is stronger and more uniform. Keep track of the number of images that are rejected due to poor border delineation by the algorithm and record it on the OCT-DCF.

5. After analyzing and ensuring the quality of RNFL scans for both eyes, select both scan groups (OD and OS) from the scan list and then select **RNFL Thickness Average (OU)** under the analyze tab.

6. Select **Analyze** and print the report.

11.2.4 Fast Optic Disc

1. When the image acquisition is completed, select the **Fast Optic Disc** scan group from the scan list under the desired eye. **Optic Nerve Head (Single Eye)** under the analyze tab should then be selected.

2. Select **Analyze**.

3. Use the scroll bar to view all six radial scans sequentially. Make sure there is no saccadic motion artifact and the signal level is uniform and adequate. If these quality criteria are not met, the scan should be deleted from the OCT system and a replacement scan should be performed.

4. Check that the disk border as delineated by the termination of the highly reflective RPE/choroids/sclera edge is correctly positioned by the Stratus computer algorithm. Also check that the inner surface of the disc is drawn correctly by the algorithm. If the borders are not identified correctly despite adequate image quality, indicate this on the OCT-DCF. Because this algorithm fails in a large percentage of cases due to blocking of RPE signal by overlying blood vessels, repeating the scan is usually not helpful. Therefore the scan does not need to be repeated for algorithm failure in border identification. Do not modify the borders manually as we wish to evaluate the automated algorithm's performance.

5. Print the report with the scroll bar at the top so the vertical scan image is showing.

11.3 Data Review and Interpretation

11.3.4 Masked Review
For quality-control purposes, all advanced imaging data will be presented to a designated clinical investigator by the study coordinator with masking of the identity and disease status of the study subject. The coordinator will review the accuracy of the demographic data and the investigator will review the image quality and confirm the classification of the data as normal or abnormal. The review should occur within a month of scan acquisition.

Advanced imaging data obtained as part of the AIGS is not available for clinical decision making until the eye has reached VF endpoint, the subject has exited the study, or the study has ended. Please refer to Chapters 2 and 14 for endpoint determination.

11.3.4 Definition of Abnormality on OCT
An OCT NFL scan is considered abnormal if the average NFL thickness over the overall circle or any of the quadrants is abnormal at the $p < 1\%$ level.

Definitions of abnormality have not yet been established for OCT scans of the ONH and macula.

11.4 Management of OCT Data Files

11.4.4 Logbook
All images will be obtained using the subject name and study ID number. The technician or photographer performing the imaging, "the operator", should keep a bound logbook containing the subject's study ID, date of exam, the operator's name and type of visit. The entries should be made in chronological order.

11.4.4 Paper Files
The operator will fill out the AIGS OCT Data Collection Form (OCT-DCF). If more than one OCT scan of same type has been performed on the same day, the scan repetition number (i.e. #1, #2) should be marked on the printouts and OCT-DCFs to uniquely identify them. The OCT-DCF and scan printouts are given to the clinical coordinator for review and filing. The coordinator should record the interpretation of the OCT test (abnormality, progression) on the patient tracking form.

11.4.4 Central Database
Data from the printouts and the OCT-DCF should be entered into the AIGS Central Database via the Internet. The Central Database will record whether each scan is considered normal or abnormal, and whether progression has taken place. The Central Database will also include the peripapillary RNFL and macular retinal thickness parameters.

11.4.4 Transfer of Data to Coordinating Center

Transfer of OCT imaging data to the Coordinating Center for the development of novel image analysis and diagnostic algorithms is planned. The data transfer protocol is yet to be determined. The protocol will be established once all Clinical Centers and the Coordinating Center transition to Stratus OCT software 4.0 and Stratus OCT Reader software 4.0.

11.4.4 Data Archival

The OCT manual suggests that scans be archived each day the operator has saved new scans. To properly archive OCT scans, the following steps should be completed.

1. Insert a formatted DVD disk cartridge into the OCT drive.
2. From the main OCT window, select **Archive** from the **Data** menu to view the OCT Browser. A list of the patients who have exams that have not yet been archived will appear in the browser. There will be an empty checkbox beside the name of each patient.
3. Select the checkboxes next to the patients whose exams you wish to archive.
4. Select **File > Archive**. Insert a DVD and type in a label and select **OK**.
5. A progress dialog box will appear to show archive progress. When the archiving is complete, the progress box will disappear.

11.4.4 Handling of Missing Data

When OCT is not performed on a visit specified in the AIGS protocol, this is considered missing data and the scanning must be performed within 3 months of the scheduled visit.

11.5 Personnel

Two operators at each site will be trained and certified for obtaining OCT images. The operators will be responsible for performing OCT imaging, filling out the OCT Data Collection Form (OCT-DCF), printing out OCT data for reading per protocol and archiving data on the Stratus OCT system.

The clinical coordinator at the clinical center is responsible for maintaining a complete file of OCT printouts and OCT-DCFs, setting up the data for review by the clinical investigator(s), transferring data to the coordinating center, entering data into the AIGS Central Database and keeping track of masking status of OCT data.

The clinical investigator(s) at the clinical centers are responsible reviewing all OCT printouts and DCF for quality control and to make appropriate clinical decisions based on unmasked OCT data.

11.6 Certification of Operators

The operator desiring certification for OCT procedures should read this chapter and be familiar with the overall AIGS design and goals. The operator should read the relevant

information in the Stratus OCT Manual of Operations and demonstrate knowledge of the Stratus OCT design features and the specific examination procedure.

The certification has the following components.

11.6.4 Basic Qualification
The operator must be a qualified ophthalmic technician (COA, COT or COMT), ophthalmic photographer or medical doctor.

11.6.4 Demonstration of Practical Competency
The principal investigator of the clinical center should verify that the operator has demonstrated competency in the following:

- Adjusting the comfort features for the patient, such as the chin rest and chair
- Entering patient data
- Operating the OCT system; proper acquisition of all scan types (Macula, RNFL and ONH)
- Identifying image quality problems e.g. framing, blinks, poor fixation
- Adhering to the quality guidelines of all scan types
- Saving the image data, archiving images and making back-ups of the database
- Completing OCT-DCFs

11.6.4 Certification Request
The principal investigator of the clinical center should submit an AIGS Personnel Certification form (Chapter 6, Appendix 4) to the AIGS Coordinating Center for certification of an OCT operator. The request should be accompanied by OCT scans (using all five study scan patterns) on three eyes of three non-study subjects. The operator should fill out practice OCT-DCFs on these scans. The Director of the Coordinating Center will designate an investigator to review the scans for quality, accuracy and completeness of the OCT-DCF. Satisfactory test performance will result in certification.

AIGS OCT Data Collection Form | One for each scan set -(Optional) |

Study ID: _____

Visit Code: _____

Scan Date: _____

Review Date: _____

Operator Initials: _____

Coordinator Initial: _____

Investigator Initials: _____

Scan repetition #: _____

Patient Information	OD		OS
Pupil dilation	YES NO		YES NO
Corrective lens used (Sphere)	_____ D		_____ D
Patient able to fixate	YES NO		YES NO

Scans by Pattern	OD		OS
Fast RNFL Thickness (3.4)			
Signal strength > 7*	YES NO		YES NO
	1 2 1 2		1 2 1 2
Free of qualitative image defects**	YES NO		YES NO
	1 2 1 2		1 2 1 2
Correct RNFL boundary detection	YES NO		YES NO
	1 2 1 2		1 2 1 2
Fast Macular Thickness Map			
Signal strength > 7*	YES NO		YES NO
	1 2 1 2		1 2 1 2
Free of qualitative image defects**	YES NO		YES NO
	1 2 1 2		1 2 1 2
Correct retinal boundary detection	YES NO		YES NO
	1 2 1 2		1 2 1 2
Fast Optic Disc			
Signal strength > 7*	YES NO		YES NO
	1 2 1 2		1 2 1 2
Free of qualitative image defects**	YES NO		YES NO
	1 2 1 2		1 2 1 2
Correct disc boundary detection	YES NO		YES NO
	1 2 1 2		1 2 1 2

*Signal strength should be preferably > 7 and absolutely > 4.

* *Motion artifact, low signal in any part of image, poor centration.

1 2 refer to the 2 OCT Scan Sets. 1=first, 2=second (or use 1 form for each scan se

Baseline visit: 2 scan sets.   Follow up visit: 2 scan sets.

12   GDx Procedures

Appendix: GDx-ECC Data Collection Form

Version 8.3

NOTE: GDx will not be performed at the OHSU clinical center.
The GDx is a scanning laser polarimetry system made by Laser Diagnostic Technologies, Inc. (San Diego, CA, USA). The AIGS will use the GDx- system for measurement of retinal nerve fiber layer (RNFL) birefringence as part of the longitudinal clinical study. We will discontinue the entry of GDx-ECC NFI in the central database due to the new software upgrade to GDx-ECC 6.0.

12.1 Corneal Compensation Algorithm

The enhanced corneal compensation (ECC) algorithm has been tested and is now the replacement for the standard algorithm on the GDx system.

12.2 Handling of Missing Data

When GDx-ECC is not performed on a visit specified in the AIGS protocol, this is considered missing data and must be performed within three months of the scheduled visit.

12.3 Image Acquisition Steps

1. All examinations must be completed by certified personnel.

2. Image right eye first, then left eye.

3. Imaging should be performed without pharmacologic dilation unless the pupil is too small to permit imaging. For this reason, imaging should generally be performed prior to dilated fundus examination and disc photography. Use dilation if it was required for VF testing or another advanced imaging test. If pharmacologic pupil dilation is required, use one drop each of tropicamide 1% and phenylephrine 2.5% and wait at least 20 minutes before imaging. Record if pharmacologic pupil dilation is used. If it is, subsequent examinations should also use the same dilation procedure.

4. Reduce the lighting in the room to a minimal level.

5. Corrective lenses including contact lenses should be removed for GDx imaging. For eyes with refractive error $> \pm 2.0$ D, the spherical equivalent should be used.

6. Enter patient information accurately. Enter the diagnosis as normal, glaucoma or glaucoma suspect based on each individual case.

7. Position the patient. Make sure that the patient's forehead and cheeks are centered, gently and evenly touching the mask, and the patient is comfortable.

8. Confirm that the patient is looking at the fixation target on the left or right side (for right and left eyes, respectively) as a series of short bright blinking lights.

9. Ensure that the pupil is centered on the yellow crosshairs and the red line is centered on the focus dot. Otherwise, the scan may not pass the image quality check and will need to be repeated.

10. For each eye, one set of corneal and three sets of retinal nerve fiber layer (RNFL) retardation images should be acquired at the initial session and three sets of RNFL images should be acquired at the follow-up sessions. The corneal scans need to be acquired only on the first exam. The corneal compensation value for each eye is stored in the database and will then be used for all subsequent exams for that eye. However, if a patient undergoes corneal or cataract surgery, the corneal measurement should be repeated.

11. Following a corneal scan, the accurate positioning of the corneal measurement ellipse should be verified. To modify the Cornea Measurement Ellipse position, select **Set Position**. Four positioning buttons will be activated for right, left, up and down movement. Press the proper positioning buttons to center the Cornea Measurement Ellipse over the macula. The ellipse size should not be modified.

12. For the RNFL image, the ellipse size should correspond to the size of the ONH and be well-centered. The size of the ellipse should be constant for successive exams.

13. The default corneal compensation algorithm for the current software is referred to as VCC (variable corneal compensation). To activate RNFL image acquisition using the ECC (enhanced corneal compensation) algorithm, press the button for enhanced compensation. When using the ECC mode, the operator will also need to check the placement of the macular circle as well as placing the ellipse around the ONH. The ECC method creates an intentional bias in the compensation method, and to accurately remove this bias, the operator must make sure the circle is in the center of the macula, even for RNFL scans. The center of the macula will coincide with the center of the "bow-tie" pattern.

14. When image acquisition (cornea or RNFL) is completed, the system will automatically proceed to the Image Check screen. A good image is one that has a scan quality score of 8-10 and OKs for: *Alignment, Fixation, Refraction* and *Other*. In some cases and for some eyes, it will not be possible to achieve the recommended score value. In those cases, accept the best scan that can be obtained.

15. Before accepting the RNFL image, proceed to Image check screen and then press modify ellipse button for each eye. Inspect the fundus image for the presence of a residual bowtie to indicate incomplete neutralization of corneal birefringence. Press corneal calculation button and note the retardance to determine the magnitude of residual birefringence in the Image Acquisition Log. If residual birefringence is > 21 nm, repeat the scans, making sure that the pupil is centered on the yellow crosshairs and the red line is centered on the focus dot. Also refer to the GDx-ECC Data Collection Form (GDx-DCF) for quality criteria.

16. Save the image and export the corneal and RNFL scans to a PC.

17. Print out the RNFL scan analyses.

18. Complete the GDx-ECC data collection form.

12.4 Internal Quality Control System

To automate these controls as much as possible, several checks are built into the computer programs used in processing the GDx data. The following internal quality control checks will be performed on all scans. [The GDx program provides several automatic checks on the quality of the data.]

1. The operator should check the automated quality grading scores that are generated on the computer screen and select the best scans according to the image acquisition procedure above.
2. The Clinical Center Coordinator will review the following:
    (a) accuracy of the demographic information on the scan printout and GDx-DCF
    (b) appropriateness of the lens correction
3. The clinical investigator will then review the printouts and the GDx-DCF according to the following criteria for assessing quality:
    (a) centration of the optic nerve head
    (b) clarity and illumination of the fundus image
    (c) presence of blinks
    (d) eye movement during scan acquisition
    (e) automated scan quality score
    (f) residual birefringence in the compensated images

Also, refer to the GDx- ECC Data Collection Form (GDx-DCF) for quality criteria.

12.5 Data Review and Interpretation

12.5.1 Masked Review

For quality-control purposes, all advanced imaging data will be presented to a designated clinical investigator by the study coordinator with masking of the identity and disease status of the study subject. The coordinator will review the accuracy of the demographic data and the investigator will review the image quality and confirm the classification of the data as normal or abnormal. The review should occur within a month of scan acquisition.

Advanced imaging data obtained as part of the AIGS is not available for clinical decision making until the eye has reached VF endpoint, the subject has exited the study, or the study has ended. Please refer to Chapters 2 and 14 for endpoint determination.

12.5.2 Definition of Abnormality on the GDx-ECC

Definite abnormality using GDx-ECC will be defined as any one of the following RNFL retardation parameters outside of 99% normal limit: TSNIT average, superior average, inferior average, TSNIT standard deviation and Nerve Fiber Index (NFI). The NFI cut off for 95% specificity is 28 and the cut-off for 99% specificity is 40. (Personal communication, Qienyuan Zhou, PhD, Senior Manager of Advanced Development, Carl Zeiss, Meditec Inc.). For each set of three GDx scans, the set is considered to be abnormal if at least two scans meet the criteria for abnormality.

12.6 Management of GDx-ECC Data Files

12.6.1 Logbook

All images will be obtained using the subject name and study ID number. The technician or photographer performing the imaging, "the operator," should keep a bound logbook containing the subject's study ID, date of exam, the operator's name and type of visit. The entries should be made in a chronological order.

12.6.2 GDx Printout

The operator should obtain enough RNFL scans on each eye to have three scans that are of sufficient quality to be accepted as AIGS data. Each accepted scan should be printed out using the standard analysis software on the GDx-ECC system. GDX GPA is on the printout and will be recorded in the database.

12.6.3 GDx Data Collection Form (GDx-DCF)

The operator will fill out the AIGS GDx-ECC Data Collection Form (GDx-DCF) provided in the appendix of this chapter, except for the masking status. One form is filled out for each set of three scans.

12.7 Data Entry and Filing

12.7.1 Paper Files

The operator should provide the printouts and the GDx-DCF to the study coordinator at the Clinical Center. The coordinator should file the printouts and GDx-DCF in the study binder.

12.7.2 Central Database

Data from the printout and the GDx-DCF should be entered into the AIGS Central Database via the internet. The Central Database will record whether each scan is considered normal or abnormal, and whether conversion or progression has taken place.

12.7.3 Data Archival

The GDx system saves data to both a primary and a back-up hard disk drive for data safety. If one of the hard drives fails, it has to be replaced. If data was saved when the system contained only one functioning hard drive, the system will update the replaced hard drive with the data acquired while it was absent. When the second hard drive is reinstalled and GDx- is powered up, the presence of both drives is sensed and the back-ups are enabled automatically. Sync Disks can be used to make the back-up drive identical to the master drive. This includes databases, application files, and operating system. Everything on the back-up drive will be overwritten such that it contains identical information as the main drive.

To further enhance data back-up safety, a second back-up hard disk will be updated on a monthly basis by one of the GDx operators. The secondary back-up hard disk should be swapped into the slot for the back-up hard disk and the Sync Disks routine should be performed. The secondary back-up hard disk is swapped out and stored in the clinical coordinator's office. The monthly archival should be recorded in the GDx Logbook.

12.8 Personnel

Two operators at each site will be trained and certified for obtaining GDx images. The operators will be responsible for performing GDx imaging, filling out most of the GDx Data Collection Form (GDx DCF) and printing out GDx data for reading per protocol.

The clinical coordinator at the clinical center is responsible for maintaining a complete file of GDx printouts, archiving data, setting up the data for review by the clinical investigator(s) and entering data into the AIGS Central Database.

The clinical investigator(s) at the clinical centers are responsible for reviewing all GDx printouts and DCF for quality control and to make appropriate clinical decisions based on unmasked GDx data.

12.8.1 Certification of GDx Operators

Only individuals who are certified will perform functions for collection of GDx study data.

The operator desiring certification for GDx procedures should read this chapter of the AIGS MOP and be familiar with the overall AIGS design and goals. The operator should read the relevant information in the GDx Manual of Operations and demonstrate knowledge of the GDx design features and the specific examination procedure.

The certification has the following components.

12.8.2 Basic Qualification

The operator must be a qualified ophthalmic technician (COA, COT or COMT), ophthalmic photographer or medical doctor.

12.8.3 Demonstration of Practical Competency

The principal investigator of the clinical center should verify that the operator has demonstrated competency in the following:

- Adjusting the comfort features for the patient, such as the chin rest and chair
- Entering patient data
- Operating the GDx; proper centration of the pupil on the yellow crosshairs and the red line through the focus dot, appropriate centration of the ellipse on the macular bowtie in the corneal scans, accurate size and centration of the ellipse on the optic nerve head, ensuring the use of a constant size of the ellipse in successive scans, checking for adequacy of compensation and the magnitude of residual birefringence in the compensated scans.
- Adhering to suggestions made by the quality control software

- Identifying image quality problems, e.g. framing, blinks, poor fixation
- Saving the image data, archiving images and making back-ups of the database
- Completing GDX-DCF

12.8.4 Certification Request

The principal investigator of the clinical center should submit an AIGS Personnel Certification form (Chapter 6, Appendix 4) to the AIGS Coordinating Center for certification of a GDx operator. The request should be accompanied by sets of three GDx scans on three eyes of three non-study subjects. The operator should fill out practice GDx-DCFs on these scans.

The director of the coordinating center will designate an investigator to review the scans for quality, accuracy and completeness of the GDX-DCF. Satisfactory test performance will result in certification.

AIGS GDx Data Collection Form

<table>
<tr><td>for each set of 3 RNFL images</td></tr>
</table>

Study ID: _____   Operator Initials: _____

Visit Code: _____   Coordinator Initial: _____

Scan Date: _____   Investigator Initials: _____

Review Date: _____

Corneal Compensation Algorithm: Enhanced (ECC)

Patient Information	OD	OS
Pupil dilation	Yes No	Yes No
Corrective lens used (Sphere)	____ D	____ D
Patient able to fixate	YES NO	YES NO

Quality Control	OD	OS
Optic nerve centered (<1/4 of disc outside of target circle)	YES NO 1 2 3 1 2 3	YES NO 1 2 3 1 2 3
Eye movement minimal	YES NO 1 2 3 1 2 3	YES NO 1 2 3 1 2 3
Free of floaters over optic disk	YES NO 1 2 3 1 2 3	YES NO 1 2 3 1 2 3
Image clear and without black-border artifact	YES NO 1 2 3 1 2 3	YES NO 1 2 3 1 2 3
Quality score > 8	YES NO 1 2 3 1 2 3	YES NO 1 2 3 1 2 3
GPA	YES NO	YES NO

1 2 3 refer to the 3 RNFL images - 1 is the first image, 2 the second, 3 is the third

13   HRT II or III Procedures

Appendix: HRT Data Collection Form

Image Acquisition Procedure

Scanning laser tomography (SLT) uses a scanning laser beam and confocal imaging to obtain high quality three-dimensional imaging data in the optic nerve head (ONH) and retina. SLT has been used to obtain highly repeatable measurements of cupping and rim in the ONH. Other studies have already shown it is capable of detecting glaucoma progression prior to VF change.

The Heidelberg Retina Tomograph II (HRT II) system (Heidelberg Engineering, Heidelberg, Germany) will be used throughout the AIGS. The HRT II is the most recent generation of SLT made by Heidelberg Engineering. It has sophisticated software to measure the ONH and track changes. If available, the upgrade HRT III is used.

The Retina Module of the HRT II was previously included in the AIGS for measurement of the macula. However, this item was removed by the Steering Committee after brief initial experience with this new feature due to lack of internal fixation and analysis software.

13.1 Patient Set-up

1. All examinations must be completed by certified personnel.

2. Image right eye first, then left eye.

3. Reduce the lighting in the room to a minimal level.

4. Imaging should be performed without pharmacologic dilation unless the pupil is too small to permit imaging. For this reason, imaging should generally be performed prior to dilated fundus examination and disc photography. Use dilation if it was required for VF testing or another advanced imaging test. In the presence of media opacity, dilation of the pupil will improve image quality. If pharmacologic pupil dilation is required, use one drop each of tropicamide 1% and phenylephrine 2.5% and wait at least 20 minutes before imaging. Record if pharmacologic pupil dilation is used. If it is, subsequent examinations should also use the same dilation procedure.

5. Corrective lenses, including contact lenses, should be removed for HRT examination. For eyes with cylinder magnitude < 1.00 D, the spherical equivalent should be used as a starting position to adjust the objective lens. For eyes with astigmatism magnitude > 1.00 D, a cylinder lens should be applied to compensate for the astigmatism. A set of magnetic astigmatic corrective lenses are included with all HRT II systems shipped after January 2002. A magnetic add-on service kit is available from Heidelberg Engineering for instruments shipped prior to 2002.

6. For new patients: Enter patient data including patient's name, D.O.B, ancestry, operator initials, and study. Click **OK** to start a new examination. For follow-up examination, select the patient file from the Database Window and right-click select **New Examination**.

7. Position the patient. Make sure that the patient's forehead is centered and resting against the forehead rest. The patient should be comfortable and stable.

ONH Scan
1. In the **Examination Data** dialog box, select **Heidelberg Retina Tomograph – ONH** in the **Device Type** menu. Enter remaining examination data: Enter C-Curve Info OU (corneal curvature; average of horizontal and vertical in mm); update only after invasive surgery. Enter manifest refraction information; sphere, cylinder and axis. Enter corrective lens information **ONLY** if patient is wearing corrective lenses while image is being acquired. This field should be used if patient has astigmatism greater than 1.0 D and magnetic lenses are used to correct for astigmatism. Left click **OK**.
2. The camera will switch to "on" and initiate **live image mode** automatically.
3. Position the camera/scanning head to within 10 mm of patient's eye (just outside the eyelashes).
4. Adjust the camera to the eye so the laser beam is directly centered on the pupil and instruct the patient to fixate on the internal green flashing fixation light. The optic nerve head should be centered within the imaging window.
5. Optimize the image quality by adjusting the camera position and objective lens. Adjust the focus/objective lens until image appears brightest over the entire retinal surface (if overall image darkens when focus is adjusted, the focus is not optimal). Evenly distribute light across the retinal surface (not just the center of image) by adjusting the laser through the center of the pupil. Monitor the blue quality control bars (the more blue bars, the better the image quality). Monitor the sensitivity (keep this number as small as possible, normally between 65% and 85%).
6. Instruct the patient to blink two more times. Use the foot switch to initiate image acquisition. This automatically acquires a series of at least three images.
7. Review the images and save if satisfactory.

13.2 Data Analysis and Quality Control

13.2.1   Quality Control Criteria
The quality of the images is assessed with the aid of HRT software and by the experience of the observer. A good quality scan is sharply focused, has a well-centered optic nerve, minimal eye movement and even illumination. Floaters should not be present on ONH. Review the movie after image is acquired. Inspect the movie for minimal eye movement. Eye movements greater than 1/4 frame should be retaken. Retake if there are rapid eye movements, as opposed to slow drifts. An image with abnormal edges to the blood vessels or with black borders larger than 1/4 inch indicates excessive eye movement and is unacceptable. The vertical and horizontal cross-sectional outlines of the ONH should be smooth; a jagged curve indicates poor image quality. The HRT Data Collection Form (HRT-DCF) should be used by the operator to aid in quality assurance. In some cases, it may not be possible to achieve the recommended scan quality, in which case the best scan can be accepted.

13.2.2   Analysis of ONH Images

1. Define the optic disk margin. For details on features available on HRT II to define the contour line, see the separate booklet entitled "Definition of the optic disc margin." It is recommended to begin with four contour points. Place a contour point nasally, temporally, superiorly and inferiorly. Add contour points between each of two already marked points to refine the contour line. Starting from these initial eight points, the contour line can be refined and adapted by adding additional points or repositioning points as needed.

2. The analysis will continue automatically and compute the HRT parameters and classifications.

3. Click on the **Print** tab and select both options on the print menu: **Standard Report** and **Moorfields**.

4. Complete the HRT data collection form.

13.3 Data Review and Interpretation

Masked Review
For quality-control purposes, all advanced imaging data will be presented to a designated clinical investigator by the study coordinator with masking of the identity and disease status of the study subject. The coordinator will review the accuracy of the demographic data and the investigator will review the image quality and confirm the classification of the data as normal or abnormal. The review should occur within a month of scan acquisition.

Advanced imaging data obtained as part of the AIGS is not available for clinical decision making until the eye has reached VF endpoint, the subject has exited the study, or the study has ended. Please refer to Chapters 2 and 14 for endpoint determination.

13.3.1   Definition of Abnormality on the HRT
A scan is considered abnormal if Moorfields Regression Analysis (MRA) is abnormal (if any of the six sectors is abnormal at the $p < 1\%$ level). This approach has a specificity of 96% and sensitivity of 58% in an independent comparative test of various HRT analysis tools.

13.3.2   Topographic Change Analysis (TCA)
The TCA overview window can be opened from the menu Progression in the Analysis Center. In each examination with HRT, three 3-D image series are acquired from which the software computes the corresponding topography images. Groups of 4x4 adjacent pixels are combined to create so-called super pixels. Measurements in each super pixel are used to perform an F test to compare the "within variability" of the baseline and the follow-up examinations with the "pooled variability" of all baseline and follow-up examinations. The result is the so-called probability map. It shows the error probability of the F-test. Super pixels with an error probability of less than 5% indicate a significant

change at the corresponding location. In the software window, red pixels indicate significant surface depression, while green and white indicate surface elevation or no significant change. A region of at least 20 super pixels with significant changes in surface height that are connected to each other is called a *cluster* change. If *cluster* surface height loss appears within the ONH contour on 3 consecutive visits compared against baseline, the patient is declared to have significant TCA progression and should be labeled "Yes" in the TCA field of the HRT-DCF.

13.4   Management of Data Files

13.4.1   Logbook
All images will be obtained using the subject name and study ID number. The technician or photographer performing the imaging, "the operator," should keep a bound logbook containing the subject's study ID, date of exam, the operator's name and type of visit. The entries should be made in a chronological order.

13.4.2   Paper Files
The operator will fill out the AIGS HRT II & III Data Collection Form (HRT-DCF). If more than one HRT scan of the same type has been performed on the same day, the scan repetition number (i.e. #1, #2) should be marked on the printouts and HRT-DCFs to uniquely identify them.   In order to complete the HRT DCF either of the below printouts may be used:

- HRT follow up report: The parameter to be used is called *Topography Std. Dev.* and it is available in the table, the third line from the bottom;
- The OU report: The parameter is available on top left of each eye's image and is called *Quality: (SD);*

After reviewing one or both of the reports mentioned above, the HRT DCF field *Topography Standard Deviation < 40* should be completed by circling either "Yes" or "No" for the appropriate scan (1 or 2).

The HRT-DCF and scan printouts are then given to the clinical coordinator for review and filing. The coordinator should record the interpretation of the HRT test (abnormality, progression and topographic change analysis) on the patient tracking form.

13.4.3   Central Database
Data from the printout and the HRT-DCF should be entered into the AIGS Central Database via the internet. The Central Database will record whether each scan is considered normal or abnormal and whether progression has taken place. In addition, the global stereometric ONH analysis parameters, sector rim areas, and Moorfield classifications will be entered. The result of topographic change analysis (TCA) will be recorded as Yes or No in the database.

13.4.4   Data Archival
An external 120GB hard drive is provided with the HRTII system for archival/back-up purposes. Data should be archived at the end of each day by selecting the **Database** menu

and then selecting **Archive Images**. Select the default archive disk drive and proceed to back up the image data to the external drive.

13.4.5   Handling of Missing Data
When HRT is not performed on a visit specified in the AIGS protocol, this is considered missing data and must be performed within three months of the scheduled visit.

13.5 Personnel

Two operators at each site will be trained and certified for obtaining HRT images. The operators will be responsible for performing HRT imaging, filling out most of the HRT Data Collection Form (HRT-DCF) and obtaining the printout of HRT data for reading per protocol.

The clinical coordinator at the clinical center is responsible for maintaining a complete file of HRT printouts, archiving data, setting up data for review by the clinical investigator(s), entering data into the AIGS Central Database, and tracking the masking status of HRT data.

The clinical investigator(s) at the clinical centers is responsible for reviewing all HRT printouts and DCF for quality control and for making appropriate clinical decisions based on unmasked HRT data.

13.5.1   Certification of Operators
The operator desiring certification for HRT II procedures should read this chapter and be familiar with the overall AIGS design and goals. The operator should read the relevant information in the Stratus HRT II Manual of Operations and demonstrate knowledge of the Stratus HRT II design features and the specific examination procedure.

The certification has the following components.

13.5.2   Basic Qualification
The operator must be a qualified ophthalmic technician (COA, COT, or COMT), ophthalmic photographer, or medical doctor.

13.5.3   Demonstration of Practical Competency
The principal investigator of the clinical center should verify that the operator has demonstrated competency in the following:

- Adjusting the comfort features for the patient, such as the chin rest and chair
- Entering patient data
- Operating the HRT; obtaining quality scans; defining the optic disk margin
- Identifying image quality problems
- Saving the image data and archiving the HRT database

- Completing HRT-DCF.

13.5.4   Certification Request

The principal investigator should submit a request to the AIGS Coordinating Center for certification of an HRT operator. The requesting letter should identify the name of the operator and state that the principal investigator has observed the operator demonstrate practical competency in the operation of the HRT system according to AIGS protocol. The request should be accompanied by HRT scans of the ONH on three eyes of three non-study subjects. The operator should fill out practice HRT-DCFs on these scans. The Director of the Coordinating Center will designate an investigator to review the scans for quality, accuracy and completeness of the HRT-DCF. Satisfactory test performance will result in certification.

Scan Date: _____   Investigator Initials: _____

Review Date: _____   Repetition #: _____

Patient Information	OD	OS
Pupil dilation	YES NO	YES NO
Corrective lens used (Sphere)	_____	_____
Patient able to fixate	YES NO	YES NO

Quality Control	OD	OS
Scan sharply focused	YES NO 1 2 | 1 2	YES NO 1 2 | 1 2
Well-centered optic nerve	YES NO 1 2 | 1 2	YES NO 1 2 | 1 2
Eye movement minimal and even illumination	YES NO 1 2 | 1 2	YES NO 1 2 | 1 2
Vertical and horizontal cross-sectional outlines of the ONH are smooth	YES NO 1 2 | 1 2	YES NO 1 2 | 1 2
Topography Standard Deviation < 40	YES NO 1 2 | 1 2	YES NO 1 2 | 1 2

Comments	OD	OS

1 2 refer to each scan set. 1=first, 2=2nd (or use 1 form for each scan set).

14   Visual Field Testing and Interpretation

Appendix: VF Data Collection Form

14.1 Equipment and Setting

All AIGS visual field (VF) tests will be performed with the Humphrey Field Analyzer II (HFA-II) Model 750 or later, equipped with the Swedish Interactive Threshold Algorithm (SITA) and Humphrey Glaucoma Progression Analysis (GPA) software. Program 24-2 with the SITA Standard algorithm will be used for all visual field (VF) testing.

14.2 Technique of Testing

VF testing should be performed after manifest refraction and measurement of visual acuity.

14.2.1 Testing Algorithm

The HFA-II is to be set for the 24-2 threshold test, size III white stimulus and the SITA Standard algorithm. The SITA Fast algorithm is not permitted. The foveal threshold test must be turned on for all VF tests.

14.2.2 Refractive Correction

Depending on the age of the patient, the refraction used at the bowl may be quite different from the patient's best distance correction. Take the current distance correction and add the amount of sphere indicated by Goldmann's Table below (use the patient's birth date to determine the patient's age, not the age on the Humphrey visual field printout). The only exception is if the eye was dilated with cycloplegic eye drops. In this case, use the full near correction (see table below). If the trial lens set does not contain the exact lens, round up to the nearest 0.25 D. Astigmatic errors of 1.00 D or more must be corrected with the appropriate lens. However, drop cylinders of 0.75 D or 0.50 D, and add 0.25 D to the spherical correction as a spherical equivalent instead. Finally, spheres and cylinders of ±0.25 D should simply be dropped for the test.

If the sphere required for the test is greater than ±6.00 D, have the patient wear soft contact lenses, if possible. If a patient is already wearing contact lenses that correct his or her vision to 20/20 or better, you may leave them in for the test. However, you must still enter the best-corrected distance correction as well as the "naked eye" correction used for the test (i.e., the combined correction of the contact lens and the trial lens) into the patient data (see Entering Patient Data).

GOLDMANN'S TABLE

Age	Add
40 - 44	+1.50 D
45 - 49	+2.00 D
50 - 54	+2.50 D
55 and older	+3.00 D
Patient dilated with tropicamide or cyclopentolate	+3.00 D

Examples:

1. Best-corrected distance Rx (41-year-old): OD -2.00 +2.00 x 120
                                                OS -3.25 +0.75 x 090

    Use: OD -0.50 +2.00 x 120
          OS -1.50 D sphere

2. Best-corrected distance Rx (53-year-old): OD +1.00 DS +0.25 +065
                                                OS Plano +1.50 x 090

    Use: OD +3.50 D sphere
          OS +2.50 +1.50 x 090

14.2.3   Pupil Measurement and Dilation

Measure the patient's pupils to the nearest 0.5 mm. If the pupils are less than 3 mm in diameter, dilate them with 2.5% phenylephrine drops, unless contraindicated. If this is ineffective, dilate with tropicamide 1% and wait at least 20 minutes before starting the test. **If using tropicamide, use the full near correction.**

14.2.4   Patient Setup

Occlude the eye not being tested. If the brow is heavy or the upper lid is drooping, tape accordingly. Allow the patient to adapt to the bowl luminance for three minutes. During this time, familiarize the patient with the testing procedure (see Figure 1).

Figure 1
HUMPHREY PATIENT INSTRUCTIONS

- keep at your perimeter -

> *"Always look straight ahead at the steady yellow light. Other lights will flash one at a time at other positions around the center light. Some may be bright and others will be dim. Press the button whenever you see one of these flashes. You are not expected to see all of them. The best time to blink is just as you press the button."*

Adjust the chin rest and table height to align the pupil in the center of the eye monitor. Make sure the patient's forehead is against the head rest and that he or she is comfortable. Move the trial lens holder close to the patient's eye; however, make sure the patient's lashes do not touch the lens. Check again to see that the pupil is at the center of the lens. It is extremely important to reduce the possibility of trial lens rim artifact by having the lens as close to the patient's eye as possible (see Figure 2) and by aligning the pupil in the center of the lens.
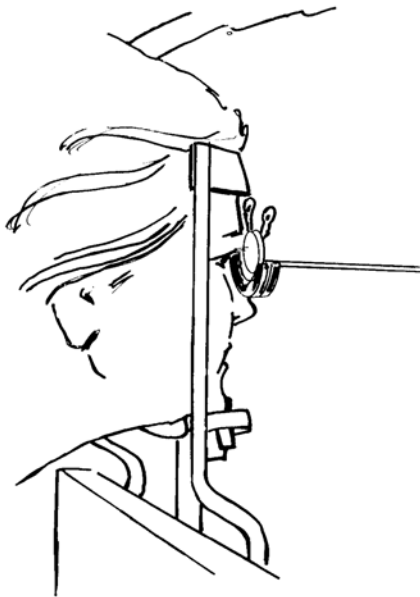
Proper Trial Lens Position
Figure 2

14.2.5   Entering Patient Data

Enter patient data as follows:

Humphrey Screen	Information Entered
ID	Leave Blank
BIRTHDATE	MM-DD-YYYY
PUPIL DIAMETER……	RE: e.g., _4_ mm LE:
NAME	[2]Patient ID, Best-corrected Distance Rx
VISUAL ACUITY……	RE: e.g., _20/20_ LE:
RX USED…………….	RE: [3](+ or -) _._ _ DS (+ or -) _._ _ DCX _ _ _ DEG LE: (+ or -) _._ _ DS (+ or -) _._ _ DCX _ _ _ DEG
COMMENTS…………	Tech Initials

14.2.6   Proceeding with the Test

Follow the instructions shown on the HFA testing screen. It is permissible to encourage the patient occasionally if the patient seems to be fatigued or losing concentration and to allow the patient to pause and rest if necessary. If you allow a pause, it should be between 30 seconds and 2 minutes long. The object is to avoid changing the subject's criteria for response during the course of the test but to remain alert to problems that develop.

If the "gaze tracking initialization" is unsuccessful, choose to either "re-try to initialize" or "turn off gaze tracking." The latter will turn off the gaze tracking, but the blind spot monitor will remain on. DO NOT TURN OFF ALL FIXATION MONITORING, AS THIS ALSO TURNS OFF THE BLIND SPOT MONITORING. It is imperative that the blind spot monitor be left on so that reliability and unreliability can be accurately judged.

If, during the test, the fixation monitor detects fixation losses three or more times out of the first six or fewer checks, try again to locate the blind spot and remind the patient to fixate at the target. If excessive fixation losses are again detected after the second try to locate the blind spot, just allow the patient to continue through to the end of the testing program.

The patient should be given five to 15 minutes to rest between the testing of each eye on the Humphrey Field Analyzer. The second (i.e., left) eye should be tested in a fashion similar to the above. **DO NOT forget to edit the best-corrected distance correction in the Name field of the patient data before the start of the second test.**

14.2.7   Repeating Unreliable VF Tests

After printing the VFs, check the reliability indices (i.e., fixation losses, false positive errors and false negative errors) to see if the test results are reliable. A VF examination with ≥15% fixation losses, ≥33% false positive errors or ≥33% false negative errors is considered to be unreliable and must be repeated. The retest VF should be scheduled for any time up to 3 months of the unreliable VF. Up to two tests per eye may be performed on any one day.

If a patient is unable to complete VF testing within a study visit time window due to any reason (e.g., stroke or other neurological, psychological or physical defect), the clinical investigator should be notified and a decision should be made regarding whether the subject should continue in the study.

14.2.8   Files at Clinical Centers

One copy of the test results must be saved on a diskette labeled with the patient's study ID number and test date. In addition, print out the test results at the completion of each test and print out a copy of the Glaucoma Progression Analysis if baseline VFs are available for comparison. A copy of the printouts should be in the patient's regular clinic chart and a separate copy should be made for the patient's AIGS file. Both the printouts and the diskette will be kept in the patient's study file at the Clinical Center. The coordinator will transfer the digital file to the hard disk of the study computer at least monthly. The files should be organized by subject study number, eye (OD/OS) and date. If more than one VF is performed on the same eye during the same day, the VF should be labeled by sequential order (#1, #2, etc) so each VF has unique identification.

14.2.9   Central Database

The coordinator will enter VF data into the AIGS Central Database via the internet. These include the important STATPAC parameters Mean Deviation (MD), Corrected Pattern Standard Deviation (CPSD) and Glaucoma Hemifield Test (GHT). In addition, VF status will be classified as normal, abnormal (glaucomatous) or borderline. Unreliable VFs are not recorded in the Central Database. The interval VF change will be entered as unchanged, conversion or progression. For the GSPPG and PG groups, the visual field index (VFI) number, the VFI regression slope number and the confidence interval number from 24 month visits and onward will be entered. The VFI numbers are obtained from the VF progression print out. The CIGTS score will also be recorded when the scoring software becomes available.

14.2.10 Handling of Missing Data

For purposes of data analysis, missing VF data will be entered into the database as using the code defining missing data from the statistical software. This will result in the data point being dropped from the analysis of the VF results.

14.3 Reading of VF

The reliability of VF should be assessed by the technician during the visit so that retesting, if needed, may be performed during visit or scheduled in a timely manner.

After a reliable VF is obtained, the coordinator should arrange for a formal masked reading of the VF by an AIG clinical investigator within one month. The VF should be read independent of other clinical data to avoid bias. Therefore the clinical chart and the name of the subject should be withheld at the time of reading. The VF reading form (see appendix) should be used to record the results of the reading.

VFs obtained to confirm progression should be read in comparison with the most recent baseline VFs. All other VFs should be read independently.

After the masked reading is performed, the results should be recorded in the AIGS Central Database. In the Normal and GSPPG groups for follow up visual field testing, conversion analysis should be performed by an investigator with the aid of a study coordinator. The results of the masked reading and the VF should be available to the clinical investigator and other treating physicians at any time. The masking procedure for VF is used to improve the reliability of study data and should not interfere with availability of test results for routine clinical care.

14.4 VF Eligibility Criteria

14.4.1   VF Reliability
One reliable VF must be obtained in each eye within three attempts during the qualifying visit(s). If not, the subject is not eligible for enrollment in the AIGS.

14.4.2   Use of Pre-Study VF
Pre-study VF taken within 6 months of the last qualifying visit can be used to determine eligibility and serve as a qualifying VF. The clinical investigator should determine that the pre-study VF is of adequate quality and reliability. The coordinator should copy and file it as part of the qualifying VF set.

14.4.3   Classification of VF Abnormality
-*Normal VF*: A VF is classified as normal if the MD and PSD are within 95% limits of normal reference, and GHT is within normal limits (97%).

-*Abnormal VF*: A VF is classified as abnormal if Pattern Standard Deviation (PSD) is outside of normal limits ($p < 0.05$), or GHT is outside of normal limits ($p < 0.01$).

-*Borderline:* A VF is classified as borderline if it does not meet the criteria of normal or abnormal VF.

14.4.4   Perimetric Glaucoma Group

Eyes in the perimetric glaucoma (PG) group must have two reliable qualifying VFs that are abnormal. The VF defects on the two abnormal fields must be consistent in location as judged by the reader.

Eyes with one abnormal qualifying VF and one borderline or normal qualifying VF should be reassigned to the GSPPG Group.

14.4.5   Normal Group

Patients enrolled in the normal (N) group must have at least one normal reliable qualifying VF. If the patient has had cataract surgery since their initial baseline/qualifying visit or their last follow up visit, then the patient should have repeat baseline visual fields done.

14.4.6   Glaucoma Suspect & Pre-Perimetric Glaucoma Group

Eyes in the glaucoma suspect & pre-perimetric glaucoma (GSPPG) group must have 2 reliable VF at the time of enrollment. At least one of the VF must be either normal or borderline (satisfying neither normal nor abnormal conditions). Eyes with two reliable VF's that are inconsistently abnormal (satisfying conditions of abnormality on one field but not the other) are assigned to this group.

14.4.7   Post Cataract Surgery VF:

For all groups, if the patient has had cataract surgery since their initial baseline/qualifying visit or their last follow up visit, then the patient should have new baseline visual fields done."

14.5 VF Conversion

The primary end point for subjects in the N and GSPPG groups is conversion to confirmed abnormal VF.

Conversion to abnormal VF is suspected when a regular follow-up VF meets the criteria for abnormality (see 14.4.3 for definitions). Confirmation of conversion of the VF is required before a conversion end point is considered to have taken place.

The investigator should first examine the record of most recent eye examinations to see if cataract, macular disease or other non-glaucoma conditions might have affected the VF. The clinical investigator may order additional examination or tests if necessary. A visually significant cataract might be treated by extraction and intraocular lens implantation. These and other correctable confounding conditions are treated and followed by a series of two VFs to serve as new baseline. Uncorrectable confounding conditions that significantly affect the VF will disqualify the patient from the study.

If the investigator determines that a confounding condition is unlikely to have caused the VF change, one confirmatory VF test is scheduled within three months. The confirmatory VF test may be scheduled and performed on the same day if the patient is not fatigued or on two separate days within the three months. No more than 2 VF tests should be should be administered to the same eye of a participant within the same day. If it is beyond three months, then the confirmatory visual field should be done on the next regular visit. If the confirmatory test is normal or borderline, stop. If it is abnormal then do the 2nd confirmatory test. In the case of confirmed conversion, the eye has reached an endpoint. Alert the treating physician investigator to review the clinical data and make an end point determination. The advanced imaging data can be unmasked if the end point has been reached.

14.6 Visual Field Progression

Visual field progression is confirmed when an eye in the PG or GSPPG group is found to have 3 consecutive follow-up VF's that show consistent focal deepening of defects compared to the baseline VF's. The determination is made with the aid of the Humphrey Glaucoma Progression Analysis (GPA) software. The use of this software is described in 14.6.1.

A confirmed VF progression is the primary end point for participants in the PG group and secondary end point for participants in the GSPPG group. When the GPA indicates confirmed progression, alert the treating physician investigator so the overall clinical picture can be assessed. Before determining that an end point has been reached, the investigator should examine the record of most recent eye examinations to see if cataract, macular disease or other non-glaucoma conditions might have affected the VF. The clinical investigator may order additional examination or tests if necessary. A visually significant cataract might be treated by extraction and intraocular lens implantation. These and other correctable confounding conditions are treated and followed by a series of two VFs to serve as new baseline. Uncorrectable confounding conditions that significantly affect the VF will disqualify the patient from the study. If the investigator does not find any significant confounding condition, then he or she should make a determination that the end point has been reached. Once the end point has been reached, the participant should continue to be followed, but the advanced imaging data can be unmasked to the investigators and new baseline VF's are designated for the purpose of detecting future progression beyond the end point.

14.6.1   Humphrey Glaucoma Progression Analysis

The Glaucoma Progression Analysis (GPA) software should be installed at all AIGS clinical centers. The GPA program should be run for follow up VF tests in the PG and GSPPG group at the second (12 month) and subsequent follow-up visits. It is not necessary to run GPA at the first (6 month) follow-up visit.

To run the GPA for AIG study, the proper baseline VF's must be selected. For eyes without previous progression, the VF's obtained at the enrollment or baseline visits should be used. The investigator could designate a VF obtained shortly before enrollment as baseline within the MOP guideline. Careful attention is required because the software automatically recommends the earliest recorded VF's in the hard disk as the baseline. For eyes with previous progression, the new baseline visual field should be the first two of three VF's that defined the last progression event. The third visual field could be used if one of the first two visual fields has a low test reliability.

To avoid the possibility that the wrong baseline VF's are chosen by the GPA program by default, coordinators should preferably use VF diskettes saved in each study patient's file to select the VF's used in the GPA. Use the following method: Run the GPA using the study visual field diskette. From the Main Menu select Print Functions. At the Option Menu, select Floppy. Enter the subject name or study number. Select the follow up visual field. From the print Menu select Glaucoma Progression Analysis and close the Exam Selection button. The visual field directory from the diskette will show on the screen. Select the baseline visual fields (marked with asterisks) and the current follow up visual field and the previous two follow up visual fields.

Progression of VF loss in glaucoma patients is based upon the Glaucoma Change Analysis algorithm which uses the first two test results to define a baseline. Worsening at a test location that falls below the 5th percentile for expected variability among stable glaucoma patients is flagged in the change analysis printout. Worsening that occurred on only on follow-up VF is shown as an open triangle on the GPA printout. Half-filled triangles represent worsening on 2 consecutive follow-up VF's. Completely filled (black) triangles indicate worsening on 3 consecutive follow-up VF's.

The 4 possible outputs for the GPA are discussed below.

No progression: less than 3 open triangles. No further VF testing is needed for the visit.

Progression is confirmed if three black triangles are present. No further VF testing is needed for the visit. Ask the investigator to review the clinical examination and make an endpoint determination.

Progression is unconfirmed if three white triangles are present. No further VF testing is needed for the visit.

Progression is possible if at least three half-filled triangles are seen on the current VF. If so, one more VF should be obtained within three months to confirm. The confirmatory VF could be performed on the same day if the participant is not overly fatigued. No more than 2 VF tests should be administered to the same eye of a participant within the same day. Run the GPA again after obtaining the confirmatory VF. If it confirms progression, ask the investigator to review the clinical examination and make an endpoint determination. If not, wait for the next regular visit to obtain the next VF. Only one confirmatory VF is needed.

14.7 VF Quality Control

The technician administering the VF test is responsible for following the proper procedure and assessing the reliability of the VF. The investigator reviewing the VF should confirm the quality of the VF.

The Coordinating Center will also conduct annual audits which include review of the VF files of randomly selected study subjects. The VF printouts and Glaucoma Progression Analysis printouts for these tests will be sent to the Coordinating Center, and will be evaluated for accuracy in detecting VF end points. In addition, the reliability indices will be checked to ensure compliance with the reliability criteria, and the date of examination will be checked to be certain that the test was performed within the appropriate time window.

14.8 Training and Certification of Technicians

Each Clinical Center should have at least two ophthalmic technicians who will be certified to perform VF testing for the AIGS. The technicians to be certified should study the VF procedures described in this chapter. The principal investigator of the clinical center should follow the following procedures in certifying the technicians.

14.8.1   Basic Qualification

The principal investigator should verify that the VF technician is a qualified ophthalmic technician (COA, COT or COMT) who routinely administers VF examinations.

14.8.2   Demonstration of Practical Competency

The principal investigator should review the protocol with the technician and observe one VF procedure performed by the technician on at least one non-study patient.

To become certified for AIGS VF testing, a technician must demonstrate competency in the following:

- Calibrating the Humphrey perimeter and formatting a floppy disk

- Measuring the pupil size

- Demonstrating knowledge of pupil dilation protocol

- Adjusting the comfort features for the patient, such as the head and chin rest and chair

- Calculating the proper lens power from the distance refraction

- Adjusting the fixation monitor and resetting the fixation monitor later during the test

- Selecting the proper test parameters and entering patient data

- Running Program SITA 24-2

- Being sensitive to patient fatigue and allowing the patient to rest during the test

- Saving and printing the test data

- Judging the reliability of the VF. Verbal demonstration of knowledge of reliability criteria

- Making a disk copy of VF files

14.8.3   Lens Correction Calculations Test

The principal investigator should administer the following test to the VF technician. If the VF technician does not obtain the correct answer initially, the test may be repeated (with change in the test refraction) after additional instructions. The test is passed when the technician is able to compute the lens corrections correctly in two cases (four eyes).

LENS CORRECTION CALCULATIONS

TECHNICIAN NAME: _____

CLINICAL CENTER: _____

PRINCIPAL INVESTIGATOR: _____

1.   59-year-old with best-corrected distance Rx of:

                    OD   -2.25 +0.50 x 180

                    OS   -2.00 +2.00 x 090

          Calculated correction:

              OD: _____

              OS: _____

2.   46-year-old with best-corrected distance Rx of:

                    OD   +1.25 DS +0.25 X120

                    OS   -0.75 +1.00 x 070

          Calculated correction:

              OD: _____

              OS: _____

14.8.4   Request for Certification

The principal investigator of the clinical center should submit an AIGS Personnel Certification form (Chapter 6, Appendix 4) to the AIGS Coordinating Center to certify a technician. The request should also include two SITA 24-2 VF printouts. After satisfactory review of the submitted letter and VF printouts, the Director of the Coordinating Center should issue a certificate in the name of the qualified VF technician.

AIGS VISUAL FIELD DATA COLLECTION FORM

Subject Study ID: _____ Name Code: _____ Visit Code: _____

VF#1 Test Date: _____ VF#2 Test Date: _____ VF#3: _____

Reliability	**OD**		**OS**	
(Circle Yes or No)				
<15% Fixation Losses				
Visual Field #1	Yes	No	Yes	No
Visual Field #2	Yes	No	Yes	No
Visual Field #3	Yes	No	Yes	No
<33% False Positives				
Visual Field #1	Yes	No	Yes	No
Visual Field #2	Yes	No	Yes	No
Visual Field #3	Yes	No	Yes	No
<33% False Negatives				
Visual Field #1	Yes	No	Yes	No
Visual Field #2	Yes	No	Yes	No
Visual Field #3	Yes	No	Yes	No

Abnormality Classification	**OD**	**OS**
Classification by PSD & GHT		
(Circle One)		
Visual Field #1	Normal / Borderline / Abnormal	Normal / Borderline / Abnormal
Visual Field #2	Normal / Borderline / Abnormal	Normal / Borderline / Abnormal
Visual Field #3	Normal / Borderline / Abnormal	Normal / Borderline / Abnormal

Definitions of Classifications

Normal: *A VF is classified as normal if the MD and PSD are within 95% limits of normal reference, and GHT is within normal limits (97%).*

Borderline: *A VF is classified as borderline if it does not meet the criteria of normal or abnormal VF.*

Abnormal: *A VF is classified as abnormal if Pattern Standard Deviation (PSD) is outside of normal limits (p < 0.05), or GHT is outside of normal limits (p < 0.01).*

GSPPG-Assessing for conversion	**OD**	**OS**

On a follow up visit, if the first VF is abnormal, conversion is assessed with 1 confirmatory test. If the 1st confirmatory test is normal or borderline, stop. If it is abnormal then do the 2nd confirmatory test. The confirmatory VF tests should be performed within 3 months of the first test. Check one box for each eye.

☐ No   ☐ Unconfirmed   ☐ No   ☐ Unconfirmed

☐ Possible   ☐ Confirmed   ☐ Possible   ☐ Confirmed

Definition of Conversion

No Conversion: *The first VF is normal or borderline. Stop. No further VF needed.*
Unconfirmed: *The first VF is abnormal. The second VF is normal or borderline.*
Possible: *The first and second VF's are abnormal. The third is normal.*
Confirmed: *The first VF is abnormal. Both confirmatory VF's are also abnormal.*

In the case of confirmed conversion, the eye has reached an endpoint. Alert the treating physician investigator. The advanced imaging data can be unmasked.

Subject Study ID: _____   Name Code: _____   Visit Code: _____

PG & GSPPG — Assessing for progression at 12-month and subsequent visits

OD	OS

One VF should be performed at the follow up visit. The Glaucoma Progression Analysis (GPA) printout should be obtained. This analyzes the current and previous two follow up visual fields against the 2 baseline VF's (make sure the AIG study baseline VF's are used – the default baseline are the 2 earliest VF's in the database, which may not be the study baseline). Look at the PROGRESSION ANALYSIS plot for the current follow up VF (bottom of the right column) to determine if progression is confirmed or suspected. Progression is confirmed if three or more filled triangles are seen (STOP). Progression is possible if at least three half-filled or filled triangles are seen on the current VF. If so, one more VF should be obtained on the same day or within 3 months to confirm. Run the GPA again after the confirmatory VF. Only one confirmatory VF is needed in the case of possible progression; no confirmatory VF is needed in all other cases. Check one box for each eye.

☐ No   ☐ Unconfirmed   ☐ No   ☐ Unconfirmed

☐ Possible ☐ Confirmed   ☐ Possible ☐ Confirmed

Definition of Progression

First VF on follow up and first GPA
No Progression: The first VF on follow up shows no progression on the first GPA plot at p<5% level. Stop. No further VF needed.

Unconfirmed: The GPA plot has at least 3 points of deterioration at the p<5% level (triangles) on the GPA plot. But less than 3 points represented consecutive deterioration (less than 3 half-filled or filled triangles).
In case of no progression or unconfirmed progression, no confirmatory VF test is needed.

Possible: The GPA plot and previous follow up VF has 3 or more points showing deterioration at the p<5% level, two consecutive times (half-filled triangles) and the GPA alert prints "Possible Progression"
In the case of possible progression, re-run the GPA after one confirmatory VF. This may be done on the same day or on a separate visit within 3 months.

Confirmed: On the GPA plot, if 3 or more points showing deterioration at p<5% level, three consecutive times (filled triangles) and the GPA alert prints "Likely Progression".
In the case of confirmed progression, the eye has reached an endpoint. Alert the treating physician investigator. The advanced imaging data can be unmasked.

* Reminder to run Visual Field Index (VFI) progression analysis from each new visit.

Reviewing Investigator:_____
(Signature)

**Review Date: ** _____

15   Optic Disc Photography

Appendix: Optic disc photography reading form

When to Take Optic Disc Photographs

1. Entry exam visit:
Stereo optic disc photographs will be taken at the entry exam visit.

2. Follow-up:
Photographs will be taken at 12-month intervals after the initial visit for the PG and GSPPG Groups. Photographs will be taken at the 48-month follow-up visit for the Normal Group.

3. Retakes:
When technical quality is poor, "retakes" may be requested. Repeat photographs must be taken within 3 months (90 days) of the request.

4. Confirmation of change detected by ophthalmoscopy:
The investigator should order disc photography any time when disc or RNFL change is detected by direct or indirect ophthalmoscopy. These photographs should be read according to AIGS protocol.

15.1   Alternative Methods

Acceptable methods include the following:
1. Sequential stereo fundus photography with color slide film.
2. Sequential stereo fundus photography with color digital imaging.
3. Nidek 3Dx simultaneous stereo fundus photography

Each clinical center should choose one of the methods and use it consistently.

15.2   Optic Disc Photography Protocol (Sequential Stereo Film)

A magnification lens providing 12-20 degrees field should be used.

15.2.1   Determine Eyepiece Setting

To ensure properly focused images, the appropriate eyepiece setting must be determined for each certified photographer. To do this, dim the room illumination and place a piece of plain white paper over the front of the fundus camera lens. Rotate the eyepiece all the way out counterclockwise. Next, look into the eyepiece with both eyes open, looking beyond the crosshairs. With smooth motions, turn the eyepiece clockwise until the crosshairs are sharp. Stop, note the setting and repeat the procedure twice more to determine the average reading. Use this reticle setting for each session.

15.2.2   Film

The following color slide films are acceptable: Ektachrome or Fujichrome 100. Use one roll of film (24 exposure) per study participant.

15.2.3   Repetition

Take at least four (4) stereo pairs of each eye to ensure the required two (2) good stereo pairs for each eye.

15.2.4   Dilation

The standard pharmacologic pupil dilation regimen is tropicamide 1% and phenylephrine 2.5%, one drop each, instilled at least 20 minutes prior to photography. The drops could be repeated up to three times total if necessary. If the eye has been previously dilated for other procedures, further dilating eye drops may not be necessary. As long as adequate dilation is obtained, protocol imaging can be performed.

15.2.5   Photography Instruction

1. Clean the headrest and chinrest before each participant and clean the lens with isopropyl alcohol disposable wipes.
2. Set the appropriate flash settings according to the photographer's experience and participant's pigmentation. Use the same settings which give the best results each time the participant is photographed.
3. At the first exposure, photograph the participant ID.
5. Photograph the right eye first, then the left.
6. Instruct the participant to follow the fixation light until the optic nerve is centered on the cross-hairs.
7. Tilt the joystick right to the 3 o'clock position just outside the pupillary crescent and take the first right stereo photograph, focusing at the junction of the RPE and the rim. After taking this photograph, tilt the joystick left to the 9 o'clock position outside the pupillary crescent, focusing at the junction of the RPE and the rim.
8. Repeat this technique to obtain two good stereo pairs of the right eye.
9. Use this technique to obtain two stereo pairs of the left eye.
10. Set the appropriate flash settings, and use the same settings, which give the best results each time the participant is photographed.

15.2.6   Developing Film

Send film for processing within two working days from exposure.

15.2.7   Labeling Slides

A permanent ink black pen (e.g. Pilot extra fine point permanent marker) for labeling slides should be used. The photographs should be labeled with the subject's study ID number, date of photography, visit code and OD or OS.

15.3   Tracking and Storage of Disc Photographs

15.3.1   Logging in Photographs

The clinical center photographer should maintain an "AIGS Disc Photography Logbook" for study participants. The logbook should be bound. Dates and photographs should be entered sequentially. A computerized logbook may be used in place of a paper version.

The logbook should contain the following information for each set of photographic slides.

1. Labeling data: the subject's study ID number, date of photography, visit code and OD or OS.
2. Relevant quality factors which may include pupil size, flash setting media clarity and the presence of photophobia. These may be useful if the quality of the photographs are not acceptable and a decision needs to be made on whether and how to retake the photographs.

15.3.2   Storage of Optic Disc Photographs

Photographic slides are stored in 8½" x 11" plastic sheets in the subject's study binder. Graded slides are stored in date-order with the AIGS reading forms in the same subfolder. Slides that have not been read are stored in a separate plastic sheet and subfolder. If the photography department require a separate filing system for the slides, they should be duplicated so one copy can be stored at both the photography department and the research coordinator's office.

15.4   Disc Photographs Prior to Initial Study Visit

Disc photographs prior to the initial study visit may be used to establish eligibility for enrollment in the AIGS.

If pre-study photographs are used to be used as baseline, they should be taken within 6 months of the last qualifying visit. This would obviate the need for a baseline photograph to be taken at the qualifying visit(s).

If pre-study photographs are used to establish progressive change, then two sets taken one year or more apart are needed. The earlier one will serve as the baseline and the second one will serve as the follow-up comparison. A disc photograph should be taken at the qualifying study visit to confirm the progression and serve as the new baseline.

The pre-study photographs used in this fashion must meet the study criteria for quality. These slides should be duplicated so a copy can be stored in the study files.

15.5   Optic Disc Reading Procedures

Disc photographs will be read by the AIGS clinical investigator at the Clinical Center with the assistance of a study coordinator to help in the masking procedure. The coordinator should fill out the information on top of the AIGS Disc Reading Form and give it to the reader along with the masked sets of slides from both eyes of the subject. The material given to the reader should not contain the name of the subject and other information that might give clues to the identity or glaucoma status of the subject. The reading will be performed in the following steps. The AIGS Disc Reading Form will be used to record the results.

15.5.1   Evaluation of Stereo and Clarity

The reader will select the best 2 stereo pairs for each eye from the set of slides. These 2 pairs will be labeled as stereo pair #1 and #2 and used for formal reading. If either pair is graded "unacceptable" for either clarity or stereo, the set of slides is returned to the photographer with a report explaining the reason and request for retake. Repeat photographs should be performed within 3 months. Sufficient photographs should be taken to ensure that 2 high quality stereo pairs are obtained for each eye. Acceptable sets are used for further grading.

15.5.2   Evaluation of Optic Nerve Damage

All optic disc photos will be read in a masked fashion by the designated clinical investigators at each site.

15.5.2.1 Non-glaucomatous Optic Nerve or Retinal Abnormality

The subject will be ineligible if there is evidence of a non-glaucomatous optic nerve or retinal disease that might produce confounding visual field defects. The reader will first look for these abnormalities.

15.5.2.2 Glaucomatous Optic Nerve Damage

Using both stereo pairs # 1 and #2, the reader will independently record the vertical and horizontal cup-to-disc ratios to the nearest 0.1 unit. The reader will then inspect the disc rim for focal and diffuse thinning and look at the peripapillary retinal nerve fiber layer (RNFL) for defects. Splinter disc hemorrhage should also be noted.

15.5.3   Progressive Disc Change

Two sets of disc photographs from two dates approximately 6 months or more apart are compared to determine if progressive disc or RNFL changes consistent with glaucoma have developed. The comparison is made in three situations: (1) comparison between two previous sets of disc photographs to satisfy enrollment eligibility in the Glaucoma or GSPPG Group, (2) comparison between follow-up disc photographs against baseline photographs. The coordinator should organize and label the slides so that the reader is not aware which type of comparison is being made.

Using stereo pairs #1 first, the coordinator should mask the stereo pairs from the 2 dates in masked plastic sheets and present them to the reader. The reader will determine if the two sets are sufficiently different to indicate progression, and identify which set of photos was taken before and after the progression. The reading is positive for progressive glaucomatous optic nerve damage only if the order is judged correctly. Progressive optic nerve damage will be defined as a visually detectable decrease in neural rim surface, as either generalized or localized thinning of the optic disc rim. Excavation of localized areas of rim tissue, a change in position of the vessels, or development of a notch are evidence of this change.

If the comparative reading of stereo pairs #1 is positive for glaucomatous progression, a confirmatory reading should be performed using stereo pairs #2 from the 2 dates. If the

confirmatory reading is again positive, then the progression is confirmed. If the 2 readings are in conflicts, then progression is not confirmed and the result should be classified as "borderline."

If the patient has confirmed glaucomatous optic nerve damage by disc photography, the progression is noted in the study database and the information is unmasked and provided to the investigator and treating physician (if not the same person) for clinical decision-making. The patient will continue in the study at the regular follow-up schedule. The slides that confirm the progression will become the new baseline for subsequent comparisons.

15.6   Optic Disc Eligibility Criteria for Study Enrollment

15.6.1   Normal Group
1.   Sufficiently clear media adequate for optic disc photography
2.   Absence of all the following confounding conditions:
- localized or diffuse pallor indicating non-glaucomatous optic nerve atrophy
- disc drusen
- congenital pit
- optic nerve coloboma
- other optic disc or macular conditions that might lead to a confounding non-glaucomatous visual field defect.
3.   Absence of the following findings that indicate glaucoma or increased risk for glaucoma:
- diffuse or localized thinning of the rim
- RNFL defect
- disc (splinter) hemorrhage
- inter-eye cup/disc ratio asymmetry greater than .2

15.6.2   Glaucoma Suspect and Preperimetric Glaucoma (GSPPG) Group
1.   Sufficiently clear media adequate for optic disc photography
2.   Absence of all the following confounding conditions:
- localized or diffuse pallor indicating non-glaucomatous optic nerve atrophy
- disc drusen
- congenital pit
- optic nerve coloboma
- other optic disc or macular conditions that might lead to a confounding non-glaucomatous visual field defect.
3.   GSPPG subjects must have at least one of the defined risk factor for glaucoma (see eligibility information in Chapter 3). Any of the following disc findings is considered a sufficient risk factor:
- diffuse or localized thinning of the rim
- RNFL defect
- disc (splinter) hemorrhage
- inter-eye cup/disc ratio asymmetry greater than .2

     - previous photographic documentation of progressive excavation of the disc, progressive thinning of the neuroretinal rim or progressive loss of RNFL.

15.6.3   Glaucoma (Perimetric) Group

1.   Sufficiently clear media adequate for optic disc photography
2.   Absence of all the following confounding conditions:
     - localized or diffuse pallor indicating non-glaucomatous optic nerve atrophy
     - disc drusen
     - congenital pit
     - optic nerve coloboma
     - other optic disc or macular conditions that might lead to a confounding non-glaucomatous visual field defect.
3.   An eye to be enrolled in the Glaucoma Group must have at least one of the following glaucomatous optic nerve head or nerve fiber layer.
     - diffuse or localized thinning of the rim
     - RNFL defect
     - vertical cup/disc ratio greater than the fellow eye by > 0.2
     - previous photographic documentation of progressive excavation of the disc, progressive thinning of the neuroretinal rim or progressive loss of RNFL.

15.7   Method of Training Optic Disc Photographers

Two experienced photographers at each site will be trained for optic disc photography. They will be responsible for archiving, labeling and submitting optic disc photographers for analysis by the investigator.

15.7.1   Certification of Optic Disc Photographers

Only certified photographers will perform functions for collection of optic disc photography study data.

The principal investigator of the Clinical Center should formally submit an AIGS Personnel Certification form (Chapter 6, Appendix 5) and work samples to the Coordinating Center for certification of the ophthalmic photographers. The principal investigator will ensure that any individual to be certified is an ophthalmic photographer with at least one year of practical work experience. The photographer must be familiar with the overall study design and goals, and demonstrate knowledge of the camera design features and the specific optic disc photographs acquisition procedure. The photographer will complete two full stereo sets, both right and left eyes, of two participants (16 slides all together), complete the photography checklist, label slides and submit them to the Director of the Coordinating Center.

The Coordinating Center will designate a clinical investigator to review the photographs for quality, accuracy and completeness of the photography checklist and labeling. If the photographs are acceptable, the Coordinating Center will certify the photographer. If the photographs are not acceptable, the reason is discussed with the photographer and additional sets of photos are requested. The review process continues until the photographs are accepted and the photographer is certified. During the course of the

study, no new individual may participate in collection of data for the study without having completed the certification process.

AIGS OPTIC DISC READING FORM

for each set of disc photographs

Subject Study ID: _____   Investigator: _____

Visit Code: _____   Coordinator: _____

Photographer: _____   Reading Date: _____

Photo Date: _____   _____

Quality of Disc Photographs

	OD		OS	
Clarity of photograph acceptable?	No	Yes	No	Yes
Stereo adequate?	No	Yes	No	Yes

Non-Glaucomatous Optic Nerve Abnormality

	OD		OS	
Pallor	No	Yes	No	Yes
Drusen	No	Yes	No	Yes
Coloboma, pit or other congenital defects	No	Yes	No	Yes
Any non-glaucomatous abnormality	No	Yes	No	Yes

Glaucomatous Optic Nerve Damage

	OD		OS	
Vertical Cup/Disc Ratio (0.1 unit) Horizontal/Cup Disc Ratio (0.1 unit)				
*RNFL defect	No	Yes	No	Yes
*Vert. or Horiz. Cup/Disc larger than fellow eye by > 0.2	No	Yes	No	Yes
*Rim Thinning (focal or diffuse)	No	Yes	No	Yes
Glaucomatous Optic Nerve or RNFL	No	Yes	No	Yes

* Defines Glaucomatous Optic Nerve/RNFL

Other Findings

	OD		OS	
Splinter Hemorrhage	No	Yes	No	Yes

Progression Of Glaucomatous Optic Neuropathy

(in comparison with baseline photographs)	OD			OS		
Decreased Rim	No	BL	Yes	No	BL	Yes
Increased RNFL defect	No	BL	Yes	No	BL	Yes
Progression of Rim or RNFL defect	No	BL	Yes	No	BL	Yes

Ver : .3

16   Central Database

Appendix: Screen Examples

16.1   Introduction

A web-based Central Database was developed to facilitate statistical analysis and quality assurance. This system records a select subset of the clinical data recorded on the completed data collection forms and printouts. The coordinators at the Clinical Centers are responsible for entering the clinical and imaging data within one month of acquisition. The Coordinating Center has access to the overall database and is responsible for querying the database for quality assurance and statistical analysis. The data is stored on a secure server maintained by the Cleveland Clinic Division of Clinical Research. Access to the system requires a user ID and password, which may be obtained with authorization by the study's principle investigator. Patient data from a given site is only enterable and viewable by users uniquely associated with that site.

The database application program may be run from anywhere on earth using any PC and a reasonably up-to-date browser (e.g. Internet Explorer 5.5 or better). The URL is

https://clinicalresearch.ccf.org/forms/frmservlet?config=aigs

Upon entering the website you will be presented with a login prompt. Enter your assigned user ID and password where indicated and press `Enter`. This will enable the main patient information screen, which may be used to enter new patient data or query (retrieve) existing patient information.

16.2   Entering a New Patient

Patients in the AIGS are identified using a compound identifier consisting of a single-digit Site Number and a 3-digit Patient Number. E.g. the ID "1234" would denote patient "234" from site "1". The program automatically manages the Site Number component based on the choice of Site from the pull-down list of sites. Before creating a new patient record in the database, it is generally a good idea to query the database to ensure that the patient does not already exist in the system. This is discussed below in the section titled *Querying Information for an Existing Patient.*

Data items are entered by either typing in the appropriate text or making a choice from a pull-down list. After entering an item, navigate to the next item either by pressing the `Enter` or `Tab` key or clicking the mouse in the next item to be entered.

The source of the Patient's page data is the AIGS CRF titled **AIGS Clinical Data Form, Qualifying Visit**. To enter a new patient:

- Choose a site from the pull-down list.
- Enter the subject's 3-digit patient ID.
- Select patient's gender, family history, and race from the pull-down lists.
- Select the patient's group assignments for each eye. If GSPPG is selected, the appropriate ancillary items will be enabled. Fill these in if appropriate.

The patient data screen is shown in Figure 1. Screen images of all online form pages are provided in the Appendix.

Figure 1. Patient Data Screen

16.3   Querying Information for an Existing Patient

To retrieve the information for an existing patient:

- Navigate to the Patients tab page (this is the initial page upon start-up).

- Press ▣ (Enter Query) or **F7** (this puts the screen in *query mode*).

- Enter search criteria into any of the Subject Information or Initial Group Assignment fields.

- Press ▤ (Execute Query), enter or **F8** (this executes the query and retrieves the requested patient records).

   Example 1: To retrieve patient # 007, press ▣, then type "007" in the Patient ID field. Then press ▤ to retrieve the data for this patient.

   Example 2: To retrieve all male patients, press ▣, then select "Male" from the gender pull-down list. Then press ▤ to retrieve the data for all male patients.

- If multiple patients are retrieved as in Example 2 above, you may navigate among patients by clicking the cursor in any of the Patient fields and using the ▶ (next record) or ◀ (previous record) buttons in the tool bar. The Down Arrow and Up Arrow keys on the keyboard also perform the Next Record and Previous Record functions.

- To exit query mode, press ▣ (cancel query)

16.4   Form Tracking Matrix

The Form Track matrix, located in the bottom half of the *Patients* page displays the progress of data collection for a single patient. As the various CRFs are completed, abnormality and changes will be indicated in the appropriate cells of the tracking matrix. Information in the Form Tracking matrix is display-only, i.e. no data is entered here.

The tracking matrix is also used to select the visit you wish to enter or view. To select a visit, double-click anywhere in any of the three rows associated with the visit you wish to retrieve. This will cause the form to retrieve the requested visit and navigate to the first page of visit information, *Visit Page 1*.

16.5   Visit Specific Information

The source for information entered on *Visit Page 1* and *Visit Page 2* are the AIGS CRFs titled **AIGS Clinical Data Form, Qualifying Visit** and **AIGS Clinical Data Form, Follow-Up Visit.** Enter data from the paper form. As with the patient specific data, not all items on the paper form are collected in the database. Be sure to enter the Visit Date, the first item on *Visit Page 1*. Only fields with white backgrounds are enterable. Gray items are either display-only or are programmatically disabled when inappropriate for the current visit type or contingent on values of previous items.

To navigate to *Visit Page 2*, click on the tab so labeled near the top of the screen.

16.6   Diagnostic Test Pages

The diagnostic tests (Visual Field, Disc Photo, etc.) are performed one, two, or three times (see the MOP for details). To enter the results of any diagnostic test:

- Navigate to the appropriate page by pressing the tab new the top of the screen.
- Enter the Date of Test in the indicated field. Press **Enter**.

This will create a new record in the database to record the test results and assign a sequence number from 1 to 3. Enter the results for repeated tests in the chronological order each test was performed

The GDx tests present a special case. For the GDx test, the test is always performed in sets of three repeated measurements. Each Sequence, therefore, represents a set of three tests performed on the same date. Fill in the results for a complete set of three *across* the screen. If a GDx set needs to be repeated, subsequent sets of three should be recorded

with a new test date (and automatically generated sequence number, as with the other diagnostic tests).

To add a second or third confirmatory test, navigate to the *first* page of the test by clicking on the appropriate tab (e.g. VF, OCT 1, etc.). Press the ▶ (next record) button until the cursor is in a new (empty) record. The Sequence field will be empty as well until you enter the Date of Test and save the record (press **Enter**) as described above.

16.7   Changing Your Password

Federal regulations require the database administrators to enforce periodic password changes. At present, all database passwords expire 75 days from the last password change. Users are notified via email 15 days in advance of their accounts becoming disabled. The notification message will direct the user to a standard web address. **We recommend you do <u>not</u> use this site to change your password**. Rather, please use the following technique to change your password:

- From the *Action* menu, choose *Change Password*.
- Ensure that *Logon* is selected as the *Password Type*.
- Enter your current AIGS database password where indicated.
- Enter your new AIGS database password where indicated.
- Re-enter your new AIGS database password where indicated to confirm.
- Press **Enter**.
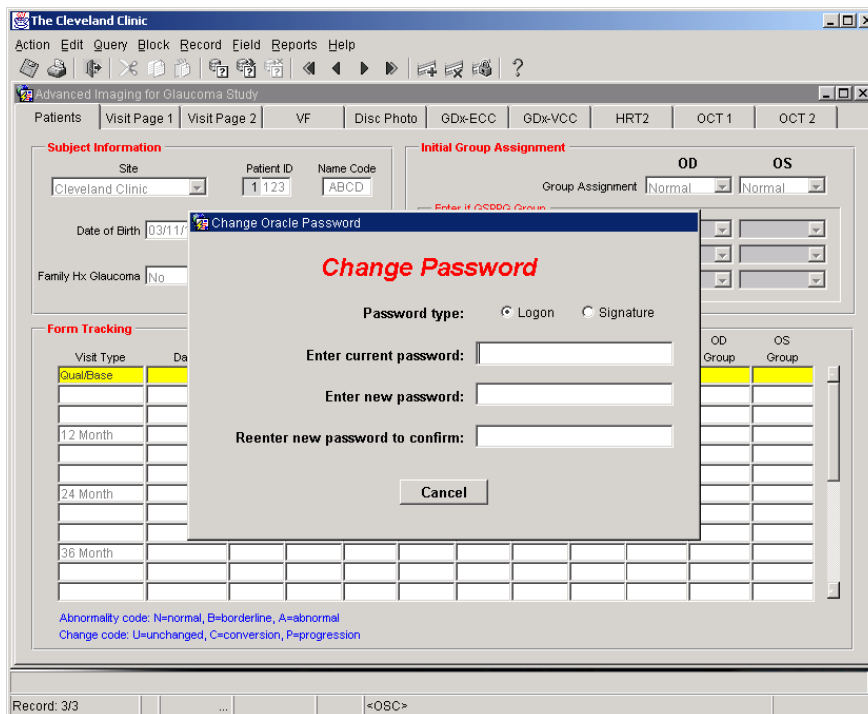
Figure 2. Password changing screen

Note that the system enforces certain rules for ensuring secure, hard-to-guess passwords. Be sure to use a new password. The system checks your new password request against a list of your previous passwords and requires that a significant number of characters have changed. Include at least one alphabetic and one numeric character in your new password.

When you're done, be sure that a message is displayed confirming that your password has been changed.

16.8   **HIPAA Compliance**

HIPAA compliance issues involve both the security of electronically stored protected health information (PHI) and the deliberate disclosure of PHI, whether electronic or physical. The discussion below will address these issues separately.

Physical and Electronic Security. The hardware on which the AIGS data is stored is located inside a locked, key-card accessible server room inside the Chester Conference Center building on the Cleveland Clinic Foundation's main campus. Access to the room is limited to system operators, database administrators, and their direct supervisors. All server room access is logged. Access to the building itself is also key-card controlled. Physical security for all Cleveland Clinic buildings is ensured by the armed Cleveland Clinic Police.

The AIGS database exists in an Oracle 8i database system. All access to the Oracle database is controlled by individually assigned user IDs and passwords. Access to the AIGS tables is limited to authorized AIGS users. Access to patient data, with the exception of the PI, is limited at the database level to users from the patient's site using Oracle's FGAC feature. All entries and changes to patient data are logged in an audit trail.

The graphical user interface used to enter and view data is built on the Oracle Forms product. This allows access to authorized users through a standard web browser such as Internet Explorer (5.5 or better) or Netscape (4.7 or better). All data communication between the user's PC and the secure web server is encrypted using 128-bit SSL technology.

PHI Disclosure. Patients in the database are identified using a single-digit site number, a 3-digit subject number, and a 4-character name code. Full names are not recorded in the database. However, since the database does include an exact date of birth and a variety of dates of clinical visits and diagnostic tests, disclosure outside the patient's provider institution must either be further de-identified or approved by the local IRB under the Limited Data Set rules under CFR 45 Parts 160 and 164.

Appendix: Data Screen Examples

The Cleveland Clinic

Action Edit Query Block Record Field Reports Help

Advanced Imaging for Glaucoma Study

| Patients | Visit Page 1 | Visit Page 2 | VF | Disc Photo | GDx-ECC | GDx-VCC | HRT2 | OCT 1 | OCT 2 |

Subject Information

Site: University of S. California   Patient ID: 4   Name Code:

Date of Birth: Gender:

American Indian/Alaska Native:
Asian:
Native Hawaiian or Other Pacific Islander:
Black or African American:
White:
Ethnicity:

☐ Disenrolled
on:

Family Hx Glaucoma:
Notes:

Enrollment Status

	OD	OS
Closed		
Disenrolled		

Initial Group Assignment

Group Assignment:

Enter if GSPPG Group
Ocular Hypertension (IOP >= 24 mmHg):
ONH/NFL defect or progression:
Perimetric Glaucoma in fellow eye:

Biometry

Axial length:
Central Corneal Thickness:

Form Tracking

Visit Type	Date	History & Eye Ex	VF	Disc	GDx-ECC	GDx-VCC	HRT2	Stratus OCT	Masking Status	OD Group	OS Group

Abnormality code: N=normal, B=borderline, A=abnormal
Change code: U=unchanged, C=conversion, P=progression

Patient Demographics eligibility, and form tracking

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Action Edit Query Block Record Field Reports Help

Advanced Imaging for Glaucoma Study

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Site-PtID 1 - 003   Visit Type Qual/Base   Date 08/23/04

IOP Determination

	OD	OS
First IOP Reading (mmHg)	32	22
Second IOP Reading (mmHg)	32	22
Difference of two readings	0	0
Third IOP Reading (mmHg)		
Mean of first 2 if 2 done or median if 3 are done.	32.0	22.0

Visual Acuity

	OD	OS
Visual Acuity Score	85	88

Refractive Correction

OD: +1.50   +.75   X   160
OS: +1.00   +1.25   X   148

Impression

	OD	OS
Primary open-angle glaucoma	Yes	No
Pigmentary glaucoma	No	No
Pseudoexfoliation glaucoma	No	No
Narrow-angle glaucoma	No	No
Secondary glaucoma	No	No
List cause		
Is the subject still eligible for AIGS		
Group Assignment		

Masking Status

Masking Status Masked

Record: 1/1   ...   <OSC>

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Advanced Imaging for Glaucoma Study

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Site-PtID 4 - 001   Visit Type Qual/Base   Date 08/05/05

Visual Field Tests

Sequence	Date of Test		OD		OS	
1	08/05/05	Abnormality Classification	Normal		Normal	
		Progression of Field Defect	No		No	
		GHT Classification	Within Normal Limits		Within Normal Limits	
		MD	1.46 dB	Normal	0.94 dB	Normal
		PSD	1.38 dB	Normal	1.30 dB	Normal
		Abnormality Classification				
		Progression of Field Defect				
		GHT Classification				
		MD	dB		dB	
		PSD	dB		dB	
		Abnormality Classification				
		Progression of Field Defect				
		GHT Classification				
		MD	dB		dB	
		PSD	dB		dB	

Conversion

Progression

Action Edit Query Block Record Field Reports Help

Advanced Imaging for Glaucoma Study

| Patients | Visit Page 1 | Visit Page 2 | VF | Disc Photo | GDx-ECC | GDx-VCC | HRT2 | OCT 1 | OCT 2 |

Site-PtID 1 - 002   Visit Type Qual/Base   Date 03/12/04

GDx-ECC

Sequence 1		1		2		3	
Date 04/07/04		OD	OS	OD	OS	OD	OS
TSNIT Average		46.46	46.69	46.73	47.89	46.50	46.34
Superior Average		59.54	62.20	60.01	65.61	58.39	62.88
Inferior Average		59.42	56.96	59.86	59.62	59.93	56.95
TSNIT Std. Dev.		24.05	22.50	24.02	24.99	23.02	23.24
Inter-Eye Symmetry		0.91		0.92		0.89	
NFI		28	23	27	21	29	23
SVM							
Quality Score		9	9	9	9	9	9

Sequence		1		2		3	
Date		OD	OS	OD	OS	OD	OS
TSNIT Average							
Superior Average							
Inferior Average							
TSNIT Std. Dev.							
Inter-Eye Symmetry							
NFI							
SVM							
Quality Score							

Record: 1/1   ...   <OSC>

Appendix: Data Screen Examples   GDx-ECC data   5

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Advanced Imaging for Glaucoma Study

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Site-PtID 1 - 003   Visit Type Qual/Base   Date 08/23/04

Heidelberg Retina Tomograph II

Sequence 1   Date of Test 09/21/04

Stereometric Analysis

	OD	OS
Disk Area	1.821	1.632
Cup Area	.606	.482
Rim Area	1.215	1.150
Cup Volume	.127	.081
Rim Volume	.180	.218
Cup/Disk Area Ratio	.333	.295
Linear Cup/Disk Ratio	.577	.543
Mean Cup Depth	.210	.193
Maximum Cup Depth	.593	.541
Cup Shape Measure	-.185	-.160
Height Variation Contour	.303	.274
Mean RNFL Thickness	.157	.136
RNFL Cross Sectional Area	.755	.614
Reference Height	.330	.187
Topography Std. Dev.	18	46

Actual Rim Area

	OD	OS
Global	1.215	1.15
Temporal	.246	.201
Temporal/Superior	.15	.144
Temporal/Inferior	.112	.122
Nasal	.375	.355
Nasal/Superior	.193	.165
Nasal/Inferior	.138	.164

Moorfield Regression Classification

	OD	OS
Global	Borderline (95-99%)	Borderline (95-99%)
Temporal	Normal (< 95%)	Borderline (95-99%)
Temporal/Superior	Borderline (95-99%)	Borderline (95-99%)
Temporal/Inferior	Borderline (95-99%)	Borderline (95-99%)
Nasal	Borderline (95-99%)	Borderline (95-99%)
Nasal/Superior	Borderline (95-99%)	Borderline (95-99%)
Nasal/Inferior	Abnormal (99-99.9%)	Borderline (95-99%)

Record: 1/?   ...   <OSC>

HRT II data

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Action Edit Query Block Field Reports Help

Advanced Imaging for Glaucoma Study

| Patients | Visit Page 1 | Visit Page 2 | VF | Disc Photo | GDx-ECC | GDx-VCC | HRT2 | OCT 1 | OCT 2 |

Site-PtID 1 - 003   Visit Type Qual/Base   Date 08/23/04

Stratus OCT

Sequence 1   Date of Test 08/23/04

RNFL Thickness Average Analysis

Sector	OD Microns	OS Microns
1	67	129
2	56	79
3	50	49
4	53	63
5	72	147
6	73	111
7	81	88
8	59	71
9	32	56
10	56	61
11	85	81
12	75	83
Superior	76	98
Nasal	53	63
Inferior	75	115
Temporal	49	63
Avg Thick	63.27	84.82
Signal Strength	8	7
Borders are detected acurately	Yes	Yes

Fast Macular Thickness Map

	OD	OS
Fovea	204	210
Temporal Inner Macula	251	261
Superior Inner Macula	264	270
Nasal Inner Macula	265	276
Inferior Inner Macula	250	281
Temporal Outer Macula	202	212
Superior Outer Macula	225	223
Nasal Outer Macula	230	246
Inferior Outer Macula	206	221
Signal Strength	8	6
Borders are detected acurately	Yes	Yes

Record: 1/?   ...   <OSC>

First page of OCT data

Appendix: Data Screen Examples

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Action Edit Query Block Record Field Reports Help

Advanced Imaging for Glaucoma Study

| Patients | Visit Page 1 | Visit Page 2 | VF | Disc Photo | GDx-ECC | GDx-VCC | HRT2 | OCT 1 | OCT 2 |

Site-PtID 1 - 003   Visit Type Qual/Base   Date 08/23/04

Stratus OCT

Optic Nerve Head Analysis

	OD	OS
Vert. Integrated Rim Area (vol.)	.102	.179
Horiz. Integrated Rim Width (Area)	1.305	1.461
Disk Area	2.43	2.264
Cup Area	1.41	.845
Rim Area	1.02	1.419
Cup/Disk Area Ratio	.58	.373
Cup/Disk Horiz. Ratio	.805	.679
Cup/Disk Vert. Ratio	.745	.546
Signal Strength	10	9
Borders are detected acurately	Yes	Yes

Record: 1/?   ...   <OSC>

Second page of OCT data

Appendix: Data Screen Examples   8

17   Transfer of Raw OCT Data to the Coordinating Center

(Procedures described in this section are considered outdated and are no longer in use)

17.1   Introduction

In order to apply novel image processing and parameter extraction software to an OCT image, it is necessary to collect the raw data for post processing. This chapter describes the procedure for exporting OCT files for shipment to the Coordinating Center. The export function of the Stratus OCT 4.0 software and import function of the Stratus OCT reader 4.0 software are used. The XML export function is not used because it is slow and not set up for all centers.

17.2   Export and Transfer of OCT Data

The Coordinating Center will specify which patients are to be included in each special study that requires collection of raw OCT data. The research coordinators at the Clinical Centers should follow the specifications from the Coordinating Center. Any question should be directed to Dr. Ou Tan, the OCT data coordinator at the Coordinating Center.

1. Compile the specified list of patient names in AIG study in your center.
2. Export the OCT data to a DVD RAM disk using export function of stratus OCT 4.0, See 17.3 for detail procedure
3. Shipped the DVD RAM disk to Ou Tan, Ph.D

17.3   Detail export procedure

1. Have Stratus OCT 4.0 and a formatted and empty and DVD RAM disk.
2. Put the DVD RAM in the DVD RAM drive of Stratus OCT machine.
3. Create three directories on the DVD RAM with explore.exe of windows:

    AIG_PG
    AIG_GSPPG
    AIG_NORM

The directories corresponding to Perimetric Glaucoma Group, Glaucoma Suspect and PrePerimetric Glaucoma Group and the Normal Group, respectively. Some special studies will not require all groups to be exported. In those cases only the included groups need to be exported.

4. From the MAIN WINDOW, select Export from the Data menu (click Data > Export) to reach the BROWSER. (If you are in the BROWSER View mode, click Data Transfer > Export.) The BROWSER appears as below. The Patients list displays every name in the patient database. Each name has an empty checkbox by it.
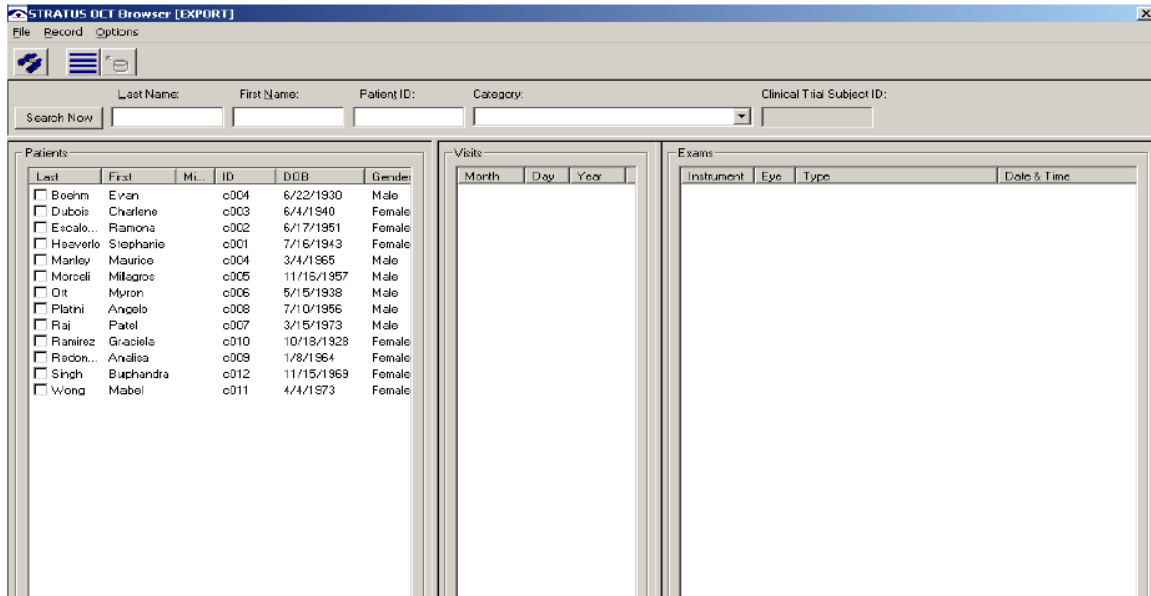
Fig 17.1 Brower interface

5. Select the checkboxes next to the patients who is in AIG study and belong to the PG Group. Use the Search Now button and fields to find and select the patients whose data you wish to export. Time interval and scan type is helpful to narrow your choice. For each selected patient, all his exams are selected by default. If there is some scan or visit is not in AIG study for this patient, deselect these Exams. See Stratus OCT 4.0 manual pp151 for how to deselect exam.

6. When you have finished making your selections, select Database Export from the File menu (click File > Database Export). The Export Options dialog box appears:
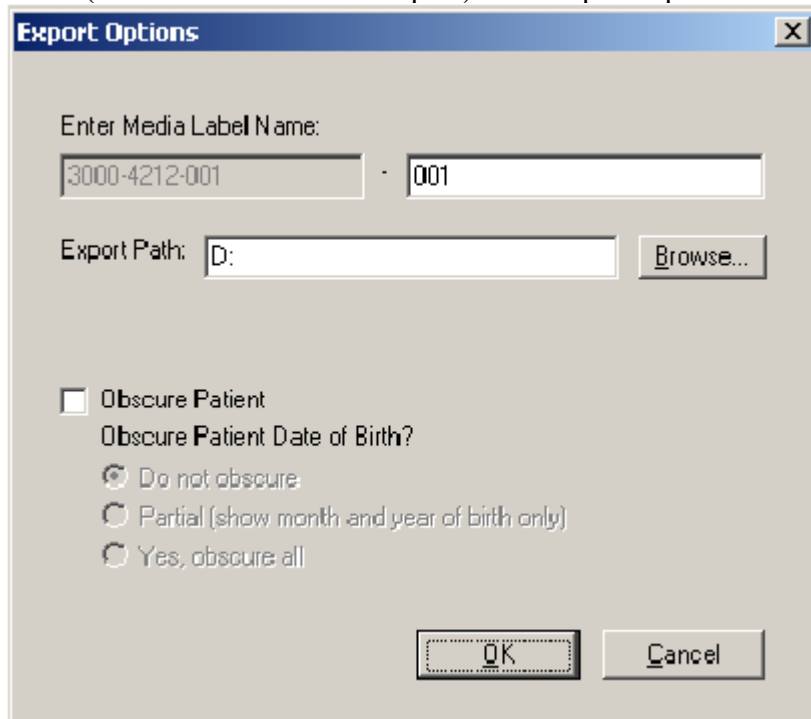
Fig. 17.2 Export Options dialog box

Push browse button, and choose d:\AIG_PG, then push OK.
Do NOT select obscure patient checkbox. If it is selected, click it to deselect. The Patient name will be the only source to compare with the central database. Push OK button to start the exporting.

7. After the export finished, repeat step 5~6 for other groups to be exported. Choose the corresponding data and directory.

8. After three groups are exported, take out the DVD RAM and label it with "AIG_Stratus_OCT"+"center name"+time interval, for example
AIG_Stratus_OCT _USC_20050112_20050313

18   Fourier Domain OCT (RTVue) Procedures

18.1 Fourier Domain OCT (RTVue) Image Acquisition Procedure

The faster Fourier Domain OCT (FD-OCT) allows high density scanning over a larger region in less time. This decreases motion artifact and provides more detailed measurements of the retinal layers that are affected in glaucoma.

The RTvue FD-OCT system (Optovue, Inc., CA, USA) has been installed at all active AIGS clinical centers as of May 2007 and will be used as a standard component of the clinical study from that time onward. The RTVue is capable of an axial resolution of 5 micron full-width-half-maximum (FWHM) in tissue (2x better resolution than Stratus OCT) and a data acquisition rate of 26,000 axial scans per second (65x faster than Stratus OCT). The higher scan rate allows us to use newer complex scan patterns that generate a three-dimensional dataset. Software Version 4.0 is used at the current time.

18.1.1 Patient Setup

1. All examinations must be completed by certified personnel.

2. Image right eye first, then left eye.

3. Reduce the lighting in the room to a minimal level.

4. Imaging should be performed without pharmacologic pupil dilation unless the pupil is too small to permit imaging. For this reason, imaging should generally be performed prior to dilated fundus examination and disc photography. If dilating drops have already been applied for another advanced imaging test, go ahead and perform OCT under the dilated condition. If pharmacologic pupil dilation is required, use one drop each of tropicamide 1% and phenylephrine 2.5% and wait at least 20 minutes before imaging. Record if pharmacologic pupil dilation if used. If it is used at baseline, subsequent examinations should also use the same dilation procedure.

5. Corrective lenses including contact lenses should be removed for the OCT examination and an unpreserved artificial tear drop should be administered to each eye to prevent drying.

6. In the **Patient** tab, if it is the first visit of this patient, push the **New Patient** button. Enter patient's last name, first name, date of birth, and select gender, in the Patient Information screen. In the **Visit Information** are on the lower half, select the name of the investigator from the pull down menu, then select the name of photographer from the pull down menu on the right. In the **Diagnosis Category** box, on the upper right, check Glaucoma, Glaucoma Suspect, or Normal. Then push the **Save** button to save the information. The information can be edited by clicking the **Edit** button. Select the patient by clicking on the patient name at patient page. Push the **New Visit** button to add a visit. Click the corresponding visit under the patient name to select it.

7. Go to **Examine** page (See Figure 1) by clicking the **Examine** tab. Select all scan patterns according to protocol. Check **OD** and **OS**. Put 3 in the **Scan Number**. Then

push the Add button to add patterns to **Examine To-do list**. Or push the **Examine protocols** button and select "AIGS normal" or "AIG GSPPG/PG" protocol and push **add** button to add the scan patterns to **Examine To-do list.**

8.   The spherical equivalent should be used to change the **Focus** value on the **scan** tab at the right-bottom of the screen.

9.   All the scans should be performed in the "vitreous mode." The checkbox to the left of "Vitreoretinal" should be checked. If "Chorioretinal" is checked, switch it back to "Vitreoretinal."

10.   Position the patient. The instrument, chair and chin rest heights should be adjusted so the patient is comfortable and stable, the forehead is placed against the forehead rest and the eyes are aligned with the eye-position markers.
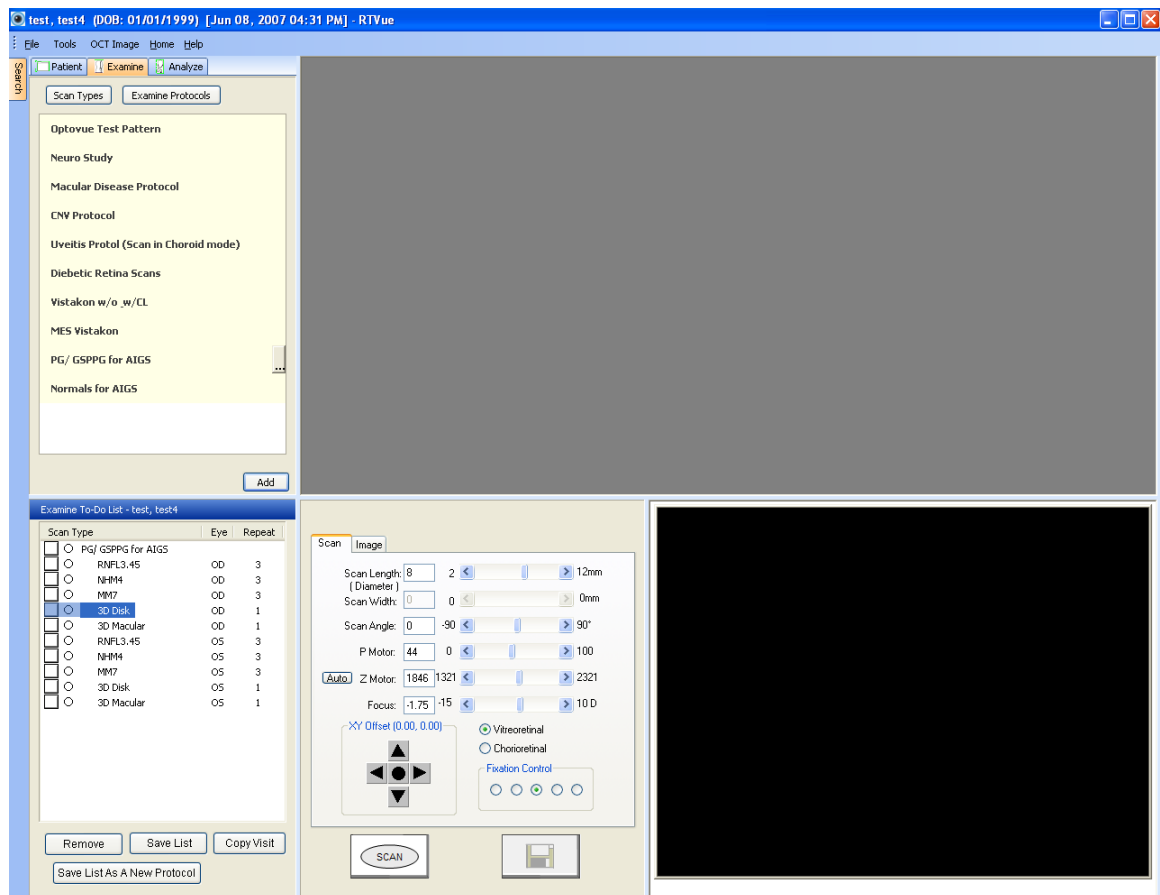
Figure 1. Examination page

18.1.2 Macular Scans

1.   Under the **Examine To-Do list**, select **GCC (Ganglion Cell Complex).** Push the **Scan** button.

2.   Using the live video image, center the instrument on the pupil and instruct the patient to fixate on the internal fixation target (blue light). Guide the instrument closer to the

eye of interest and adjust the horizontal and vertical position of the scanning instrument until the macula comes into view on the video display. Adjust the instrument's distance relative to the subject eye until the retinal image moves into the OCT display.

3. After the patient is properly positioned, adjust the **Z-motor** to center the image and adjust the polarization and focus to maximize signal. The adjustments can be performed manually or achieved by clicking the **Auto** button left to **Z-Motor** and **P Motor** on the **Scan** tab. Make sure the retina on the OCT image is not upside down (mirror image).

4. The **GCC** pattern is centered slightly temporal to the foveal center, therefore the patient will see the OCT scan pattern (red moving light) centered nasal to the fixation target (blue light). Ask the patient to concentrate on the blue light and ignore the moving red pattern. Ask the patient to verbally confirm that this is understood.

5. Ensure that the layers of the retina and choroid are not cropped by the upper and lower borders of the scan and the layers have minimal vertical undulation. The best place for the retina to be on the screen is between the two red dash lines. Make sure that the scan is centered on the fovea and that the foveal pit appears in the scan.

6. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (red) in both the RPE/choriocapillaris and RNFL.

7. Instruct the patient to take normal blinks. Then capture the image by pressing on the button on the joystick or by using the mouse to press the **Stop** on the screen.

8. The acquired OCT image will be listed on the left of screen. A bad quality image will be displayed as an inverse color map. Check that all images are good quality. If not, repeat steps 1-7 until good quality images are obtained. Push the **Save** button to save each OCT image before acquiring another image.

9. For subjects in the normal group, the EMM5 (E **Macular mapping 5mm)** pattern is also used. The procedure is similar to that for the GCC (**Ganglion Cell Complex) scan** in steps 1-8.

10. Ask the patient to concentrate on the blue light and ignore the moving red pattern. Ask the patient to verbally confirm that this is understood.

11. After the patient is properly positioned, adjust the **Z-motor** to center the image and optimize the polarization. The adjustment can be achieved by clicking the **Auto** button left to **Z-Motor** and **P Motor** on the **Scan** tab. Make sure the optic nerve on the OCT image is not upside down (mirror image).

12. Ensure that the layers of the retina and choroid are not cropped by the upper and lower borders of the scan and the layers have minimal vertical undulation.

13. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (red) in both the RPE/choriocapillaris and NFL.

14. Instruct the patient to blink several times and then to hold the eye open and still. Then select **Stop**.

15. The acquired OCT image will be listed on the left of screen. A poor quality image will be displayed as an inverse colormap. In many cases, if 1 out of the 101 scans is of poor quality, you will be asked to re-take the image. Check that all images have good quality. If not, repeat steps 11-16 until good quality images are obtained. Push the **Save** button to save the OCT images.

18.1.3 Optic Nerve and Retinal Nerve Fiber Layer Scans

1. Under the **Examine To-Do list**, select O**NH (Optic Nerve Head).** Push the **Scan** button.

2. Using the live video image, center the instrument on the pupil and instruct the patient to fixate on the internal fixation target (blue light), for OD the blue light will appear on the left, for OS the light will appear on the right. Guide the instrument closer to the eye of interest and adjust the horizontal and vertical position of the scanning instrument until the optic nerve comes into view on the video display. Center the instrument until the circular mire is centered over the optic nerve on the video display.

3. After the patient is properly positioned, adjust the **Z-motor** to center the image and optimize the polarization. The adjustment can be achieved by clicking the **Auto** button left to **Z-Motor** and **P Motor** on the **Scan** tab. Make sure that the optic nerve on the OCT image is not upside down (mirror image).

4. Ensure that the layers of the retina and choroid are not cropped by the upper and lower borders of the scan and the layers have minimal vertical undulation. The best place for the retina to be on the screen is between the two red dash lines. Make sure that the scan is centered on the optic nerve

5. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (red) in both the RPE/choriocapillaris and RNFL.

6. Instruct the patient to blink normally. Then select **Stop**.

7. The acquired OCT image will be listed on the left of the screen. A poor quality image will be displayed as an inverse colormap. Check that all images have good quality. If not, repeat steps 1-7 until good quality images are obtained. Push the **Save** button to save the OCT images.

8. To insure good quality images, make sure the SSI (signal strength index) is above 30. The SSI number will appear just above the **Scan** and **Image** tabs when in the examination mode.

9. Under the **Examine To-Do list**, select 3D **Disk.** Push the **Scan** button. This scan will be done only one time for each eye.

10. Using the live video image, center the instrument on the pupil and instruct the patient to fixate on the internal fixation target (blue light). Guide the instrument closer to the eye of interest and adjust the horizontal and vertical position of the scanning instrument until the optic nerve comes into view on the video display. Adjust the instrument until the optic nerve image moves into the OCT display.

11. After the patient is properly positioned, adjust the **Z-motor** to center the image and optimize the polarization. The adjustment can be achieved by clicking the **Auto** button left to **Z-Motor** and **P Motor** on the **Scan** tab. Make sure the optic nerve on the OCT image is not upside down (mirror image).

12. Ensure that the layers of the retina and choroid are not cropped by the upper and lower borders of the scan and the layers have minimal vertical undulation. The best place for the optic nerve to be on the screen is between the two red dashed lines.

13. Signal Strength (color saturation) should be uniform across the scan and the operator should see high signal (red) in both the RPE/choriocapillaris and RNFL.

14. Instruct the patient to blink several times and then to hold the eye open and still. Then select **Stop**.

15. The acquired OCT image will be listed on the left of the screen. A poor quality image will be displayed as an inverse colormap. In many cases, if 1 out of the 101 scans is of poor quality, you will be asked to re-take the image. Check that all images have good quality. If not, repeat steps 9-14 until good quality images are obtained. Push the **Save** button to save the OCT images.

18.1.4 Summary of Scan Patterns

Pattern	Group		
	Normal	**GSPPG**	**PG**
Ganglion Cell Complex (GCC)	3	3	3
E Macular Mapping 5mm (EMM5)	3	0	0
Optic Nerve Head (ONH)	3	3	3
3D Disk	1	1	1

The above scan patterns are performed at each visit.

18.2 *Quality Control and Data Analysis*

18.2.1 Common Scan Quality Criteria

Each OCT scan should be checked to ensure high quality. The cross-sectional images should be inspected individually.

Check the OCT and CCD images to make sure the scans are properly positioned. The CCD image should show that the scan is properly centered on the optic disc or the fovea, as appropriate to the scan pattern. Radial scans across the disc should show both edges of the disc's RPE margin in the OCT images. Radial scans across the macula should show the foveal depression at the center. The upper and lower boundaries of the image frame

should not crop off any part of the retina, RPE or the optic disc signal. Poorly positioned scans should be rejected.

The signal level should be good all across the image. There should be pixels of strong signal in each axial scan, which commonly arise in the inner retina/disc or RPE. The presence of axial scans with weak or no signal indicates that the OCT beam has been blocked by the iris or other media opacity. A possible exception is the highly sloped area in the cup of the optic disc, where the oblique beam incidence angle can normally lead to weaker reflected signal. Focal signal loss would disqualify the scan. The scan should be repeated with better positioning of the OCT system. Rarely, pupil dilation may be necessary.

The overall signal level should be high. A uniformly weak signal usually means the beam is out of focus or the polarization is not optimized. The SSI parameter is provided. Optovue recommends that the SSI parameter be ≥ 45 for macular scan patterns and ≥ 40 for all other scan patterns (around the disc). Scans with *Signal Strength* below 45 for macular scan patterns or 40 for all other scan patterns should not be accepted unless the operator is unable to get it above 45 or 40 in at least one repeat scan.

Scan SSI Minimum

	Macula	ONH
Preferred	≥ 45	≥ 40
Absolute	≥ 35	≥ 35

If the preferred minimum SSI is not met, repeat the scan once more. If the repeat scan meets the absolute minimum then keep the scan. If not, discard and record the scan as failed.

The above quality criteria should be checked for all scan types. Specific procedures for each scan type follows. The FD-OCT Data Collection Form (FD-OCT-DCF) should be used to facilitate the scan quality review.

18.2.2 Analysis

GCC, EMM5, ONH, Disc 3D can be analyzed with the current version of RTvue. Go to the Diagnosis page and click the corresponding scans to check the report at the right of the screen. Printout is not required at this stage.

An XML export of all AIG data is required at each call for raw data collection of FD-OCT, which will automatically analyze all data and export the results and raw data into XML files under the export data directory.

18.3 Data Review and Interpretation

18.3.1 Masked Review

For quality-control purposes, all advanced imaging data will be presented to a designated clinical investigator by the study coordinator with masking of the identity and disease status of the study subject. The coordinator will review the accuracy of the demographic data and the investigator will review the image quality and confirm the classification of the data as normal or abnormal. The review should occur within a month of scan acquisition.

Advanced imaging data obtained as part of the AIGS is not available for clinical decision making until the eye has reached the VF endpoint, the subject has exited the study, or the study has ended. Please refer to Chapters 2 and 14 for endpoint determination.

18.3.2 Definition of Abnormality on OCT

Abnormal features in the OCT image that are not typical for glaucoma patients, such as edema, cystoid and macular hole, should be reported. If this is a permanent condition, the patient should be placed on "closed" status from the study.

18.4 Management of OCT Data Files

18.4.1 Log Book

All images will be obtained using the subject name and study ID number. The technician or photographer performing the imaging, "the operator," should keep a bound logbook containing the subject's study ID, date of exam, the operator's name and type of visit. The entries should be made in a chronological order.

18.4.2 Paper Files

The operator will fill out the AIGS OCT Data Collection Form (FD-OCT-DCF). If more than one FD-OCT scan of same type has been performed on the same day, the scan repetition number (i.e. #1, #2) should be marked on the printouts and FD-OCT-DCFs to uniquely identify them. The FD-OCT-DCF and scan printouts are given to the clinical coordinator for review and filing. The coordinator should record the interpretation of the FD-OCT test (abnormality, progression) on the patient tracking form.

18.4.3 Central Database

Inputting results into the Central Database is currently not required.

18.4.4 Data Archiving

Archiving is currently not required.

18.4.5 Handling of Missing Data

When OCT is not performed on a visit as specified in the AIGS protocol, this is considered missing data and the scanning must be performed within 2 months of the scheduled visit.

18.5 Exporting and Uploading FD-OCT Results

18.5.1 Introduction

One major goal of AIGS is to validate the diagnostic and predictive power of different Fourier Domain Optical Coherence Tomography (FD-OCT) parameters for glaucoma. The major parameters include the nerve fiber layer thickness, ganglion cell complex and nerve head shape. We will use RTVue 6.0 (Optovue, CA) to analyze images from two scan patterns, ONH and GCC. As the analysis of ONH also requires disc boundary detection from a baseline 3D disc scan, we will collect data and results from all three scan patterns.

18.5.2 Software

RTVue 6.0 was released in October 2010. In comparison to the previous software versions, RTVue 6.0 enhances the algorithm for the retinal layers boundary detection algorithm and disc boundary detection. It also revises the interface for 3D disc scan pattern. Please contact Mike Sinai for the new version of RTVue 6.0 and RTVue viewer 6.0 if your center is not updated. You can check the version of the software by checking main menu-> help->about RTVue.

To upload the results directly to the AIGS central database, you will also need the XML export function. The function can be found under main menu->File->export. If you cannot find this menu item, try main menu->Tools->User Preference (Figure 1), and change the user interface setting (right top item) from "Clinical" to "Advanced". If the XML export is still not enabled, contact Optovue.

Figure 2. User preference dialog

For ONH scans, the RTVue provides a baseline for the disc boundary. The recommended method is to use the disc boundary defined on the 3D disc scan. You must verify that the 3D baseline option is checked under main menu->OCT Image->ONH mode before batch processing begins (Figure 2).
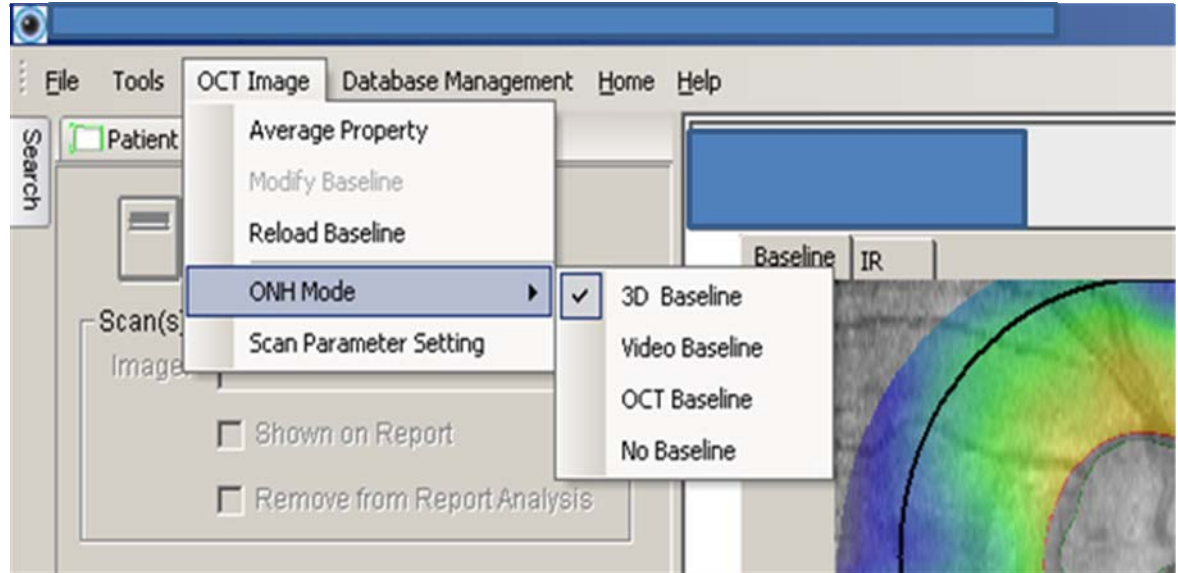
Figure 2. Choosing the ONH analysis method

18.5.3 Flowchart

You will need to export the results from the RTVue FD-OCT data of AIGS patients and then upload the results into the AIGS central database. As a first step, all old RTVue scans need to be analyzed and uploaded to the central database before Dec 31, 2010. Then you will need to analyze and export new scans every week when there is new visit recorded for a subject.

1. Define the disc boundary for the first qualified 3D disc scan as baseline for each eye among all the subject's visits. Record the visit, quality of 3D disc scan and boundary drawing of baseline in the central database.

2. Analyze the results of two scan patterns, ONH and GCC, which you will then export into an XML file for each subject using the XML export function.

3. Upload the XML file to the AIGS central database.

18.5.4 Exporting

1. De-identification of the patient data

   As required by HIPAA, the patient data needs to be de-identified before the data is transferred to the AIGS central database. This must be done prior to batch processing and export. As the XML file name is defined by the patient name, you must change the patient name to the AIGS ID before creating the XML file. This will also help to match results in the central database.

   To edit the patient name, push the edit button under the patient tab and then change both the last name and the first name to the AIGS ID. As we have multiple centers in the AIGS study, the AIGS ID is the site ID+patient ID. For example, a patient with ID 109 from the USC center would be 4109. After editing, push the save button.
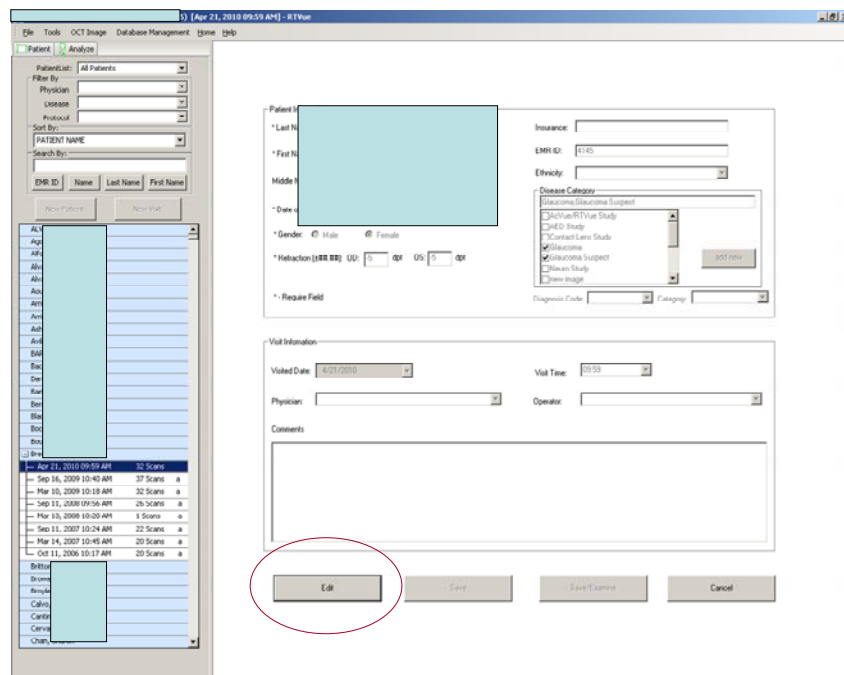
   Figure 3. Changing the patient's name to the AIGS ID for export

2. Clear the old analysis results

   In order to make sure you export the results using the RTVue 6.0 software, you need to delete the old results that used the previous software. You can do this for each subject individually or for all subjects in a batch. Figure 4 shows how to delete the

old results for all subjects at once (main menu->clean diagnosis data->All patients->ONH/GCC/3D disk). You will need to delete the results from all three scan patterns, ONH, GCC and 3D disk. Figure 5 shows how to delete the results for an individual (main menu->clean diagnosis data->Current patient->ONH/GCC/3D). You will need to delete the results from all three scan patterns, ONH, GCC and 3D disk.
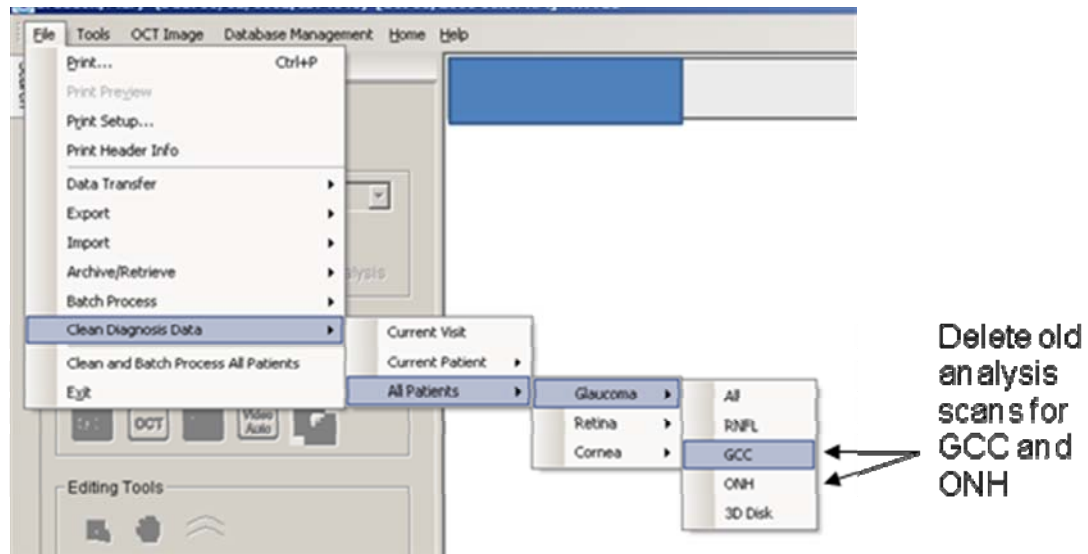
Figure 4. Deleting old results from the previous software version for all subjects
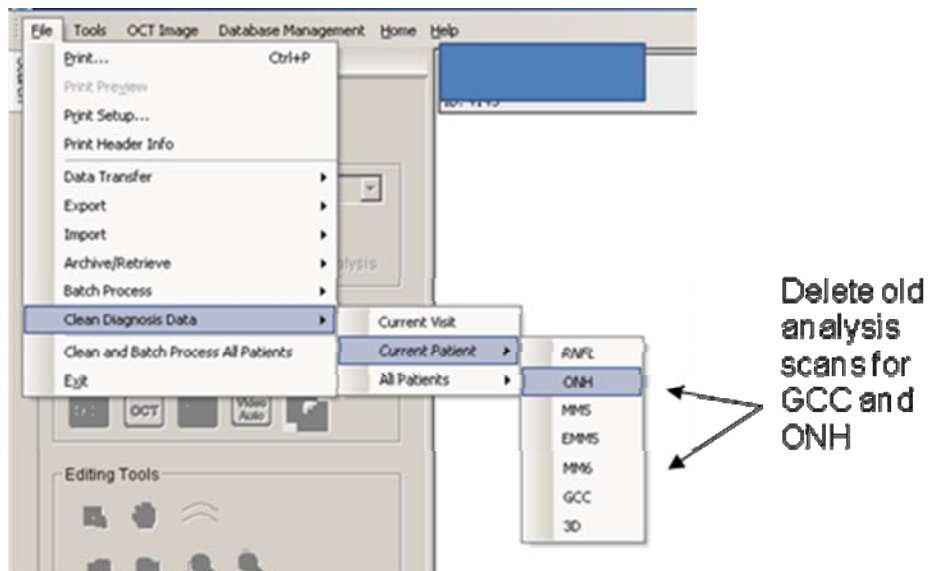
Figure 5. Deleting old results from the previous software version for a single subject

3. Draw the disc boundary on 3D scan

You will need to define the disc boundary on the 3D disc scan. There is an automatic function for detecting the disc margin in version 6.0. This automatic disc margin detection is more repeatable than the previous version for following the dark region on the center of the en face (or SLO, scanning laser ophthalmoscopy) OCT fundus image. Thus no manual editing is required. However, you will need to check that the boundary is acceptable and the image quality is OK. You will need to save the first acceptable disc drawing on qualified 3D scan among all available visits (Figure 6).
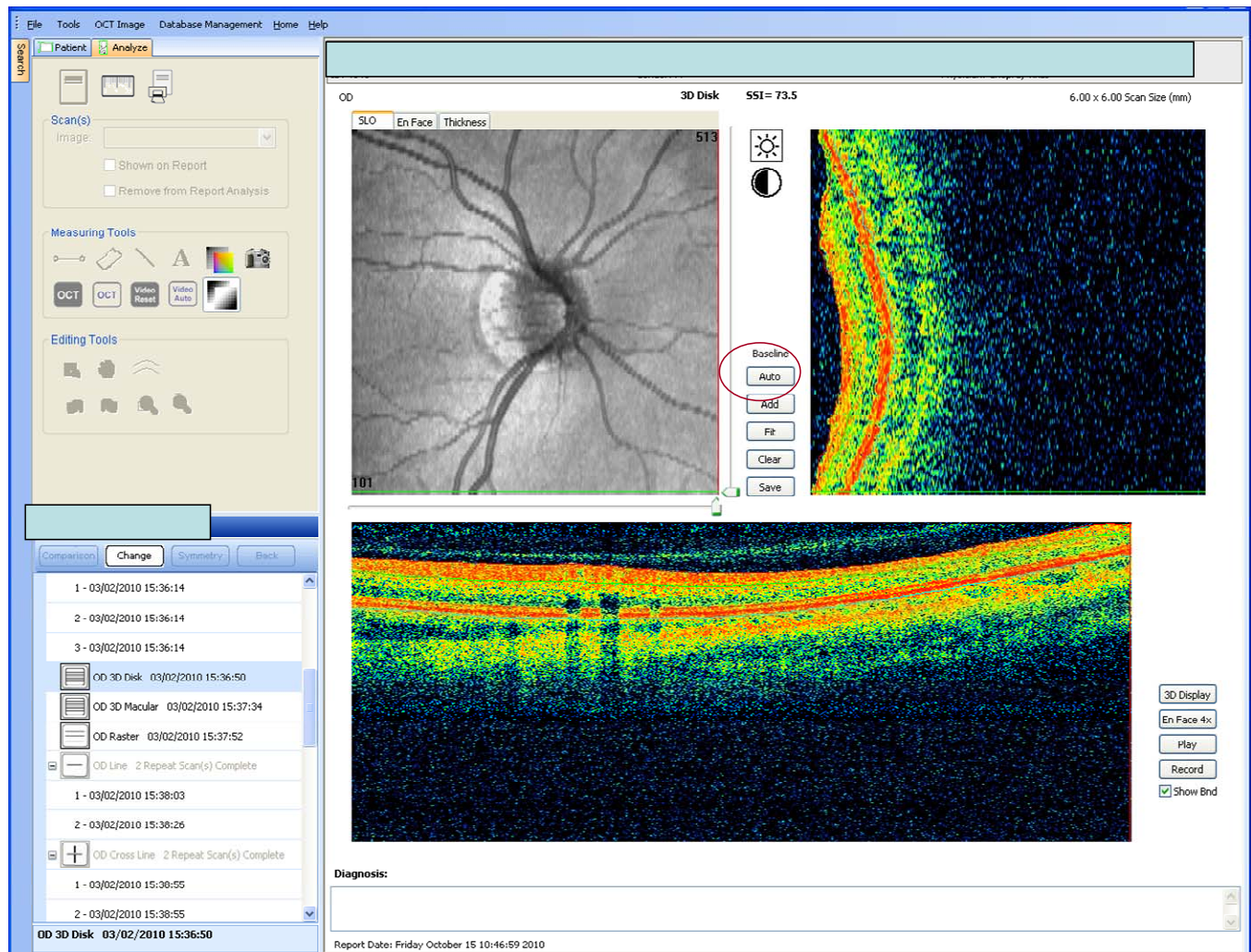
Figure 6. Analysis page of 3D scan pattern

Use the following flowchart to evaluate the disc boundary drawing:

A.   Select a 3D disc scan for the subject

If there is no valid 3D disc scan among all visits, choose the best 3D scan's result as the final. But record it as a fail and schedule another visit.

B.   Check that all of following requirements are satisfied:

–   SSI (signal strength index)>45

–   No movement artifact > 1 main vessel width within main analysis region (inscribed circle of SLO window)

–   No retina out of range in the main analysis region

–   No blink or shadows in the main analysis region

If Step B is passed, go to step C.

If Step B is failed, go back to step A.

C.   Push the Auto button to automatically create the disc boundary

D.   Visually check the automatic boundary for obvious placement errors.

If Step D is passed, go to step E.

If Step D is failed, go to step A.

E. Check the four edges of the disc boundary (right, bottom, left, top) to make sure the cross section point matches the RPE band and its extension tip. This should be done only if the automatic boundary drawing is questionable.

If Step E is passed (i.e., the automatic editing is acceptable), go to step F.

If Step E is failed, go to Step A.

F.   Push the "Save" button

Below are details of each step:

A. Find a 3D disc scan and check the image quality

You need to perform a 3D disc scan with each visit. But only one 3D disc boundary needs to be saved as the baseline. First check the 3D disc scan from the first visit (baseline visit). You will need to define the disc boundary from the other visits only if the quality of the first visit is poor or the automatically detected disc boundary is wrong. Here, poor quality means either low signal

strength (SSI<45) or a big distortion of the SLO image caused by eye movement. Figure 7 gives an example of big eye movement.

Distortion caused by eye movement
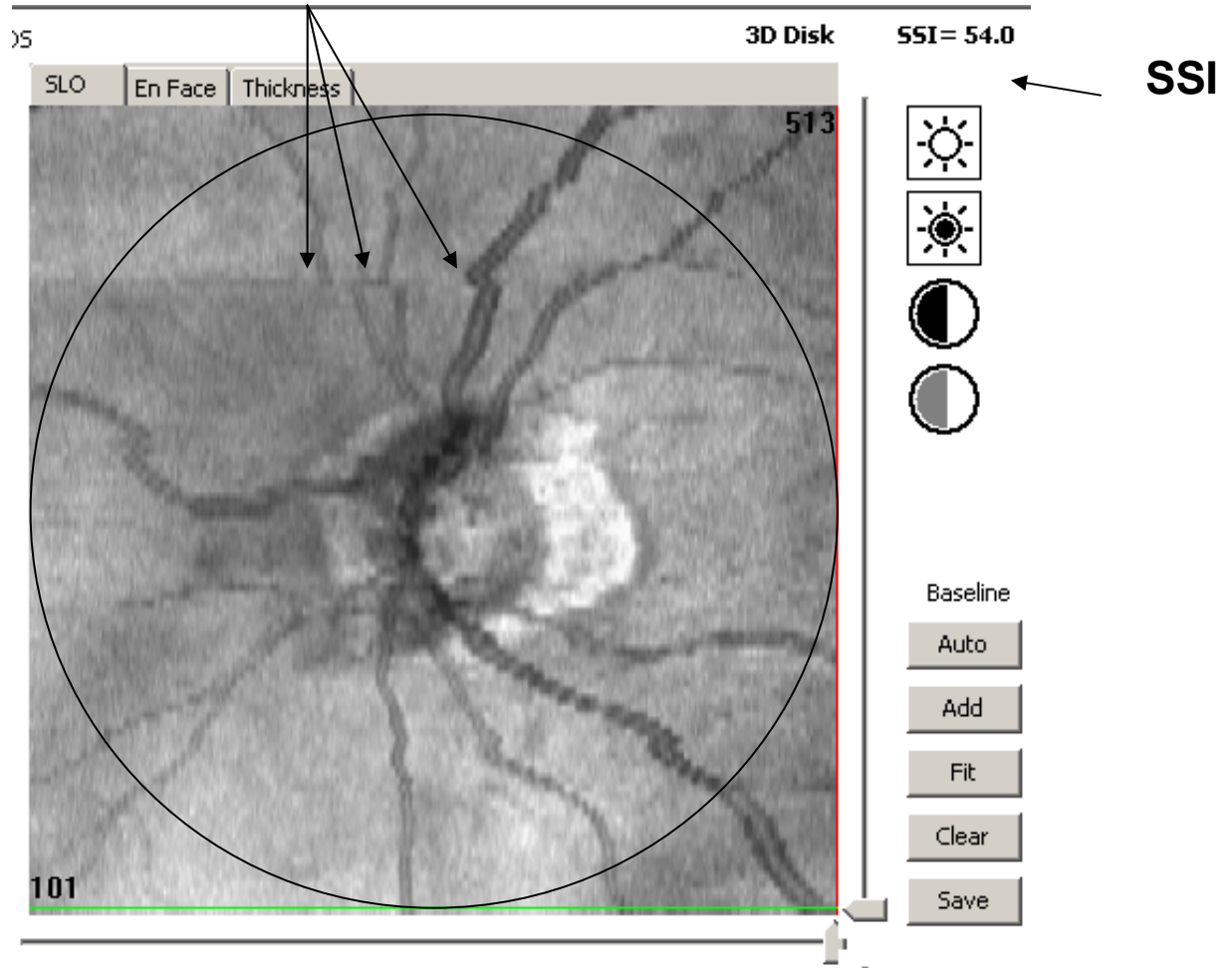
Figure 7. Distortion of SLO image caused by eye movement. The black circle shows the region you should check for eye movement, shadows and blink.

B. Automatic detection of disc boundary

As shown in Figure 6, you can push the "Auto" button in the analysis page of the 3D scan. The software will automatically create a disc boundary (Figure 8). The disc detected is usually along the dark ellipse region in the center of the SLO image, which would be an acceptable disc boundary. If there are points not along the edge, move the scan position (red and green lines on the SLO window) to that portion. Check to see that the scan position is at the end tip of the RPE band and

its extension. If the scan position is around that tip, the boundary is still acceptable. Otherwise, choose another visit and try Auto again.
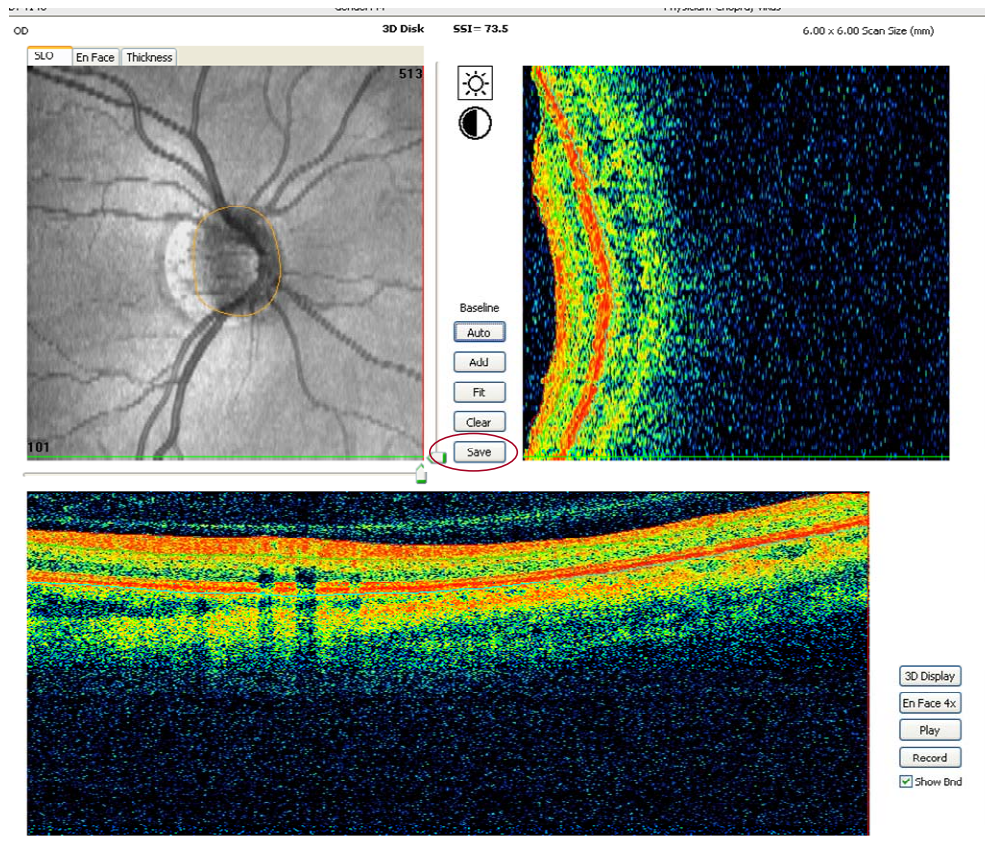
Figure 8. Automatic disc boundary detection
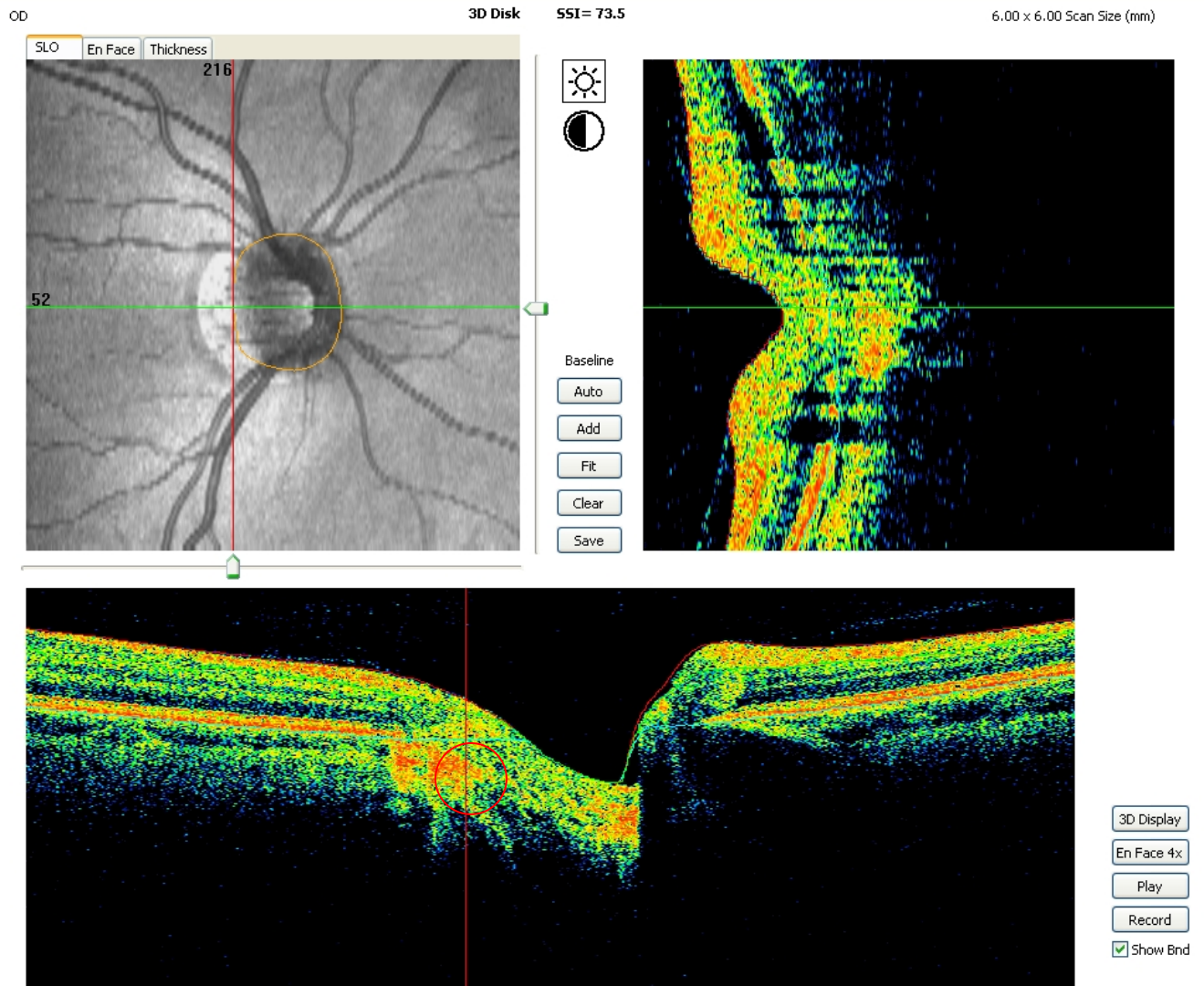
Figure 9. Check that the disc boundary is at the end of the RPE band or its extension. As long as the tip position is in the red circle, which is around the true tip, the drawing is acceptable.

(For tips and instructions on proper identification of disc boundaries, see the document "Automatic 3D Disc Boundary Detection and Validation").

C. Do the disc boundary detection (A-B) for both OD and OS. They do not have to be done in the same visit. For each eye, only one visit for OD and one visit for OS needs to be processed for disc boundary detection.

4. Analysis and Export

After the disc boundary is saved for an eye, the scan needs to be re-analyzed before export. RTvue will not automatically re-do the analysis if the analysis has been done previously.

You will first need to manually delete the old result. Then you can export using the XML function. The program will automatically process the data if the analysis has not been done previously or has been deleted.

First, clear the ExportData folder under RTVue root folder (usually c:\rtoct or c:\rtoctview):
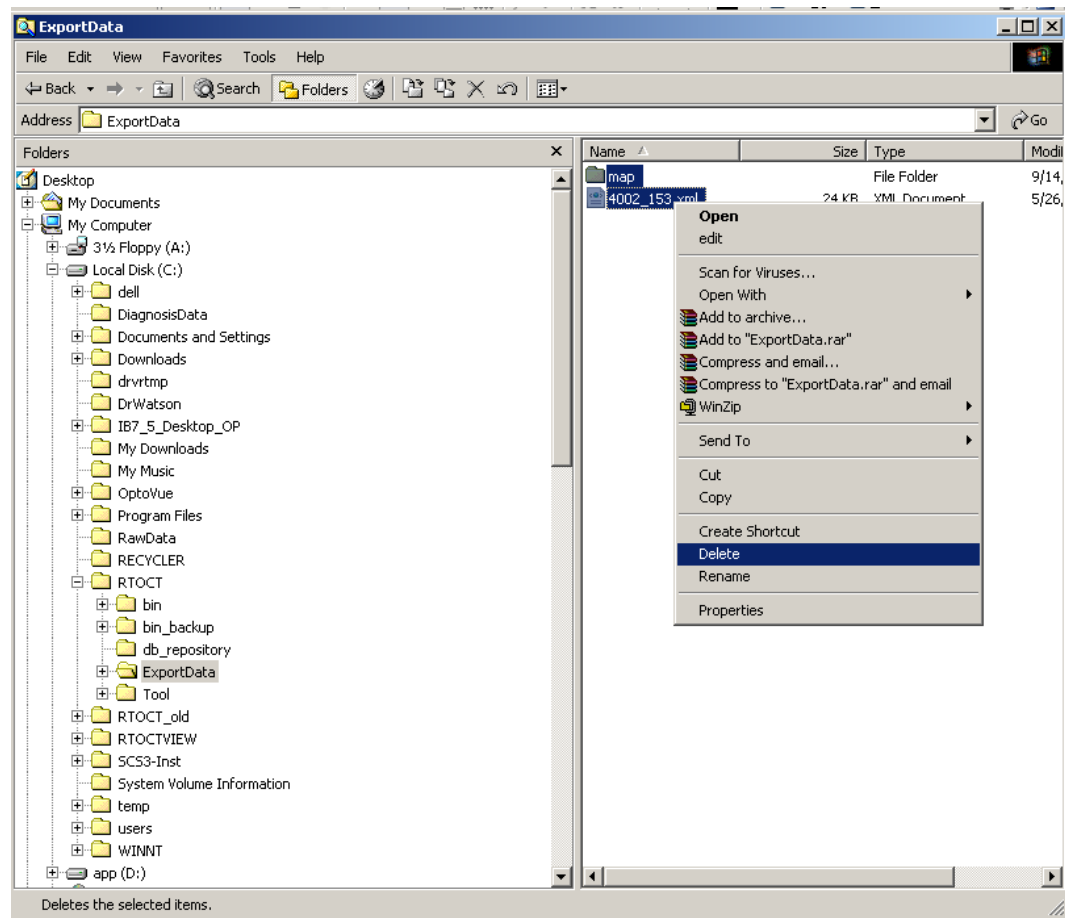
Figure 10. Clearing the ExportData folder

To begin the export, go to main menu->export->XML. This will give the XML export dialog:
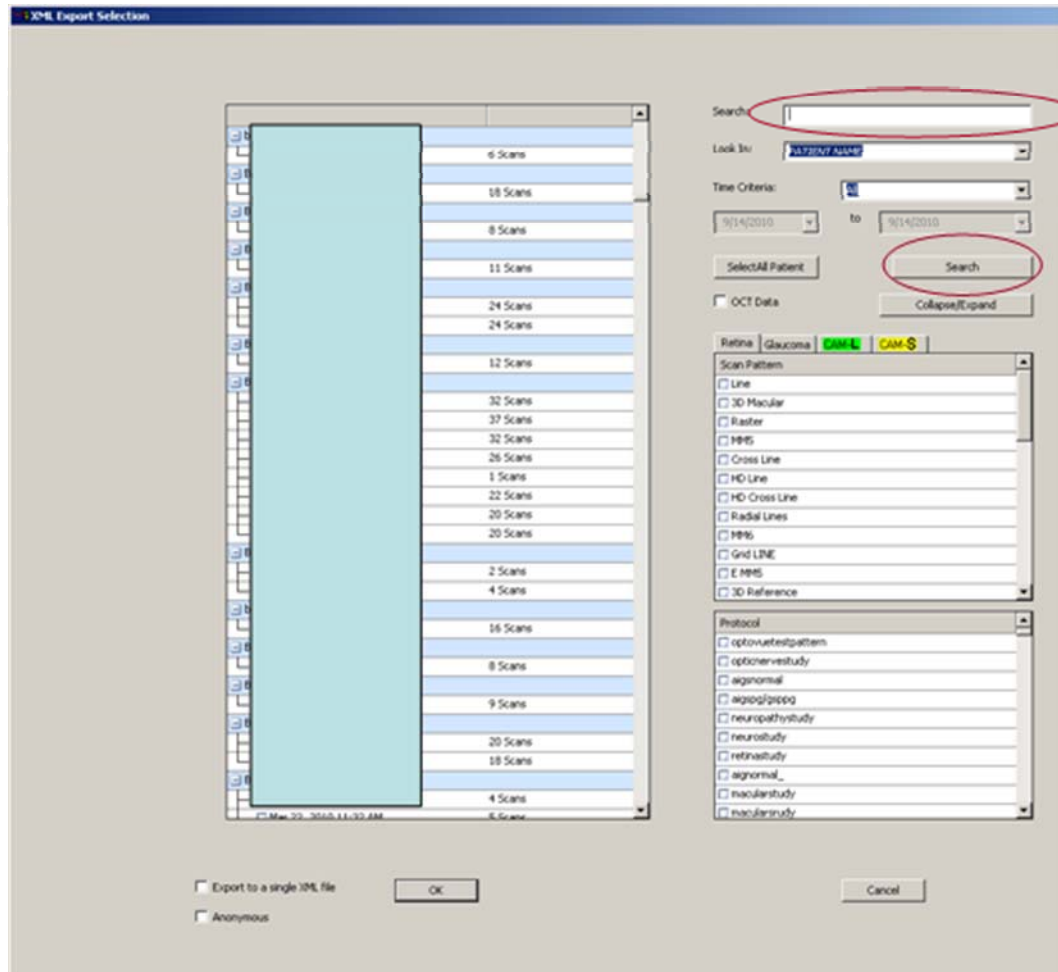
Figure 11. XML export dialog

You can select one or multiple patients and visit(s) by clicking the check boxes in the left window. You can also quickly find an individual patient by using the searching function at the right. After you select the desired visits and patients, go to the glaucoma tab at the right side and check ONH and GCC in the scan pattern selection (Figure 12). Then push the OK button to start the export. A progress bar will show up and display the progress.
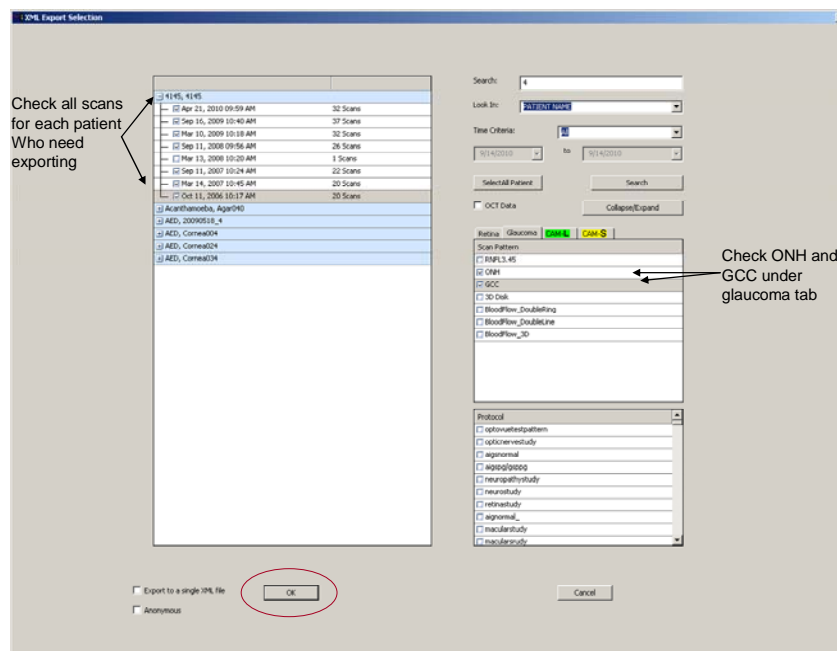
Figure 12. Selecting scans to be exported

After the export is finished, copy the XML file under RTOCT root\exportdata to an external hard disk or thumb drive.
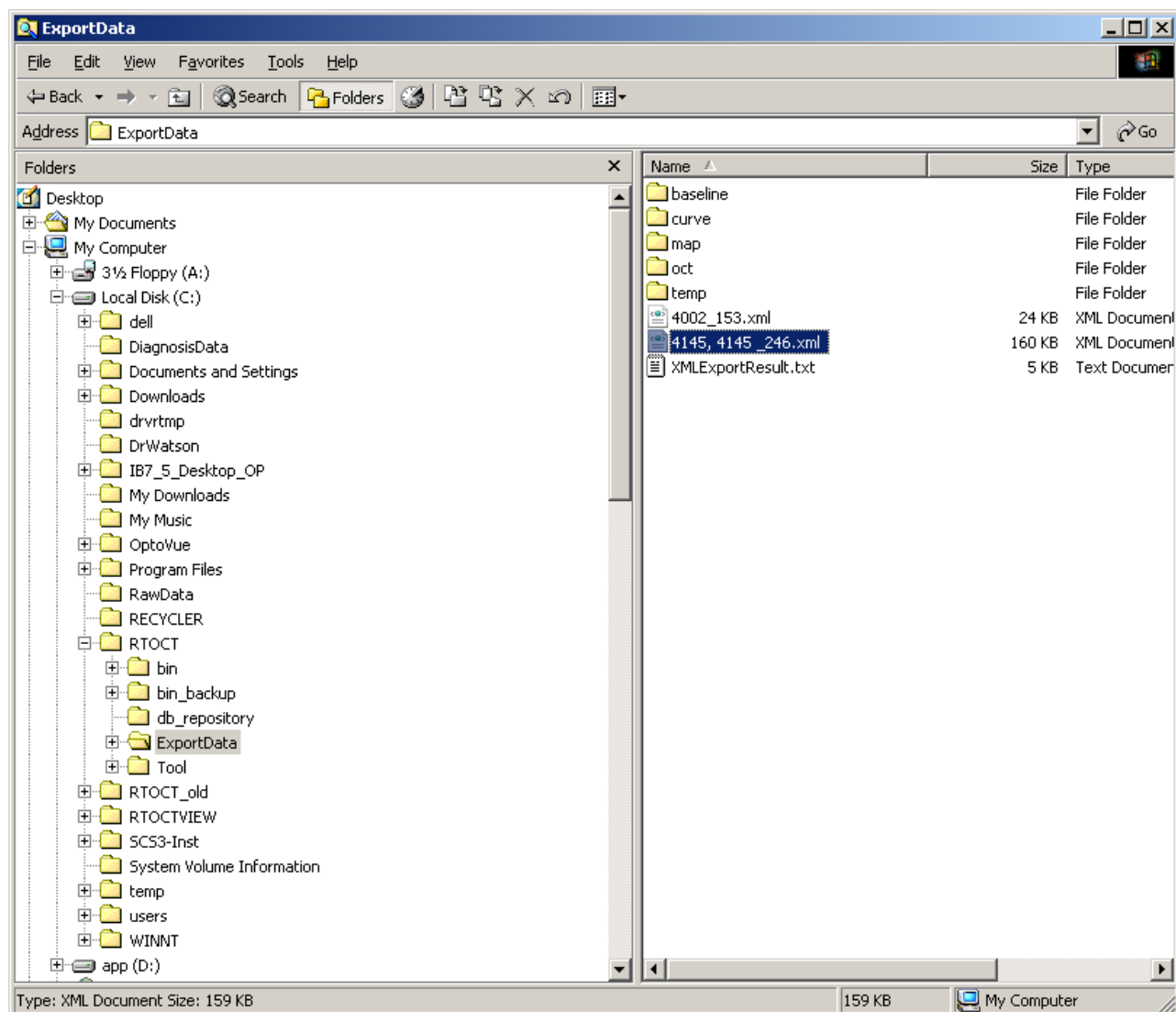
Figure 13. Copying the XML file for an individual subject

5. Batch process

   You can export data for multiple patients and visits at one time. Follow the same procedure listed in the last section, but use the procedure below to select multiple patients quickly.

   Search for the patient by starting with the site number. Since the patient names should have been converted to site ID+patient ID, searching the site ID should display all of the AIGS patients at a given center. Then you can push the 'Select All Patients" button to include all of the AIGS patients. If there are patients not belonging to the AIGS, you can de-select them by clicking the check boxes for

those patients again. Or you can select only those patient results that needed to be exported. You can also choose to export only particular visits for each patient.

18.5.5 Uploading

AIGS Central Database for FD-OCT Results

We have added two FD-OCT results pages to the AIGS central database under the tabs RTV1 and RTV2 (Figure 14). Record the quality of the baseline 3D disc boundary drawing and choose the 3D scan visit you used to draw the baseline disc boundary. Check the "Acceptable 3D Scan Image Quality" as YES if the image quality is acceptable. Check the "Successful Disc Detection" as YES if the disc boundary drawing is acceptable.

Although it is possible to input other values directly, we can upload the XML files instead to save time and eliminate transcription errors.

Figure 14. Two FD-OCT result pages in the central AIGS database

18.5.6 Uploading Procedure

After the scans are exported, save the XML files on an external hard disk or a USB thumb drive.

Record the quality of the disc drawing directly in the central database.

Email the XML files to Sharon Bi (bis@ccf.org) for uploading into the AIGS central database. Make sure to put in the subject line of the email "AIGS FDOCT analysis". Send the XML files as attachments. It is OK to attach multiple XML files within one email.

After receiving the email, Sharon will transfer the XML files into the central database using special software. She will send you a confirmation email after she has completed the transfer.

After you hear from Sharon you will need to review the newly uploaded results to ensure that no mistakes occurred during the transfer. At the same time you will need to record the quality of the disc drawing in the central database. It is also important to verify that the information for each patient visit matches the record.

18.6 Personnel

Two operators at each site will be trained and certified to obtain FD-OCT images. The operators will be responsible for performing FD-OCT imaging.

The clinical coordinator at the clinical center is responsible for maintaining a complete file of FD-OCT printouts, transferring data to the coordinating center, and keeping track of masking status of FD-OCT data.

The clinical investigator(s) at the clinical centers are responsible for reviewing all OCT data and DCF for quality control and to make appropriate clinical decisions based on unmasked OCT data.

18.7 Certification of Operators

The operator desiring certification for OCT procedures should read this chapter and be familiar with the overall AIGS design and goals. The operator should read the relevant information in the RTVue OCT Manual of Operations and demonstrate knowledge of the RTVue OCT design features and the specific examination procedure.

The certification has the following components.

18.7.1 Basic Qualifications
The operator must be a qualified ophthalmic technician (COA, COT or COMT), ophthalmic photographer or medical doctor.

18.7.2 Demonstration of Practical Competency
The principal investigator of the clinical center should verify that the operator has demonstrated competency in the following:

- Adjusting the comfort features for the patient, such as the chin rest and chair
- Entering patient data
- Operating the FD-OCT system; proper acquisition of all scan types (GCC , EMM5, ONH and 3D disk)
- Identifying image quality problems e.g. framing, blinks, poor fixation
- Adhering to the quality guidelines of all scan types
- Saving the image data, archiving images and making back-ups of the database

18.7.3 Certification Request

The principal investigator of the clinical center should submit an AIGS Personnel Certification form (Chapter 6, Appendix 4) to the AIGS Coordinating Center for certification of an OCT operator. The request should be accompanied by OCT scans (using all five study scan patterns) on one eye of one non-study subjects. The Director of the Coordinating Center will designate an investigator to review the scans for quality and accuracy. Satisfactory test performance will result in certification.

19   Doppler Fourier Domain Optical Coherence Tomography Measurement of Retinal Blood Flow

19.1 Introduction

Blood flow in the surface of retinal vessels may be useful as an early indicator for ocular disease. While measurement of the ocular blood flow has been difficult in the past, non-invasive OCT technology may be able to provide this information to assist in the diagnostic process. The process for extracting this information is called Doppler OCT.

Doppler OCT is based on the principle that moving particles, such as red blood cells inside a blood vessel, cause a Doppler frequency shift Δv to the scattered light. Given the Doppler angle α between the scanning beam and the normal direction of flow, the Doppler shift is equal to

$$\Delta v = 2V \sin(\alpha) / \lambda,$$

where λ is the center wavelength of the light source and V is the flow velocity (Figure 1). Doppler angle is measured from the difference in the vessel positions in two concentric circular scans (Figure 2). Too low a Doppler angle will cause a weak Doppler shift. On the other hand, too high a Doppler angle will cause a Doppler shift out of the detecting range of Doppler OCT. For the current RTVue Doppler OCT system e it has been found that the optimal Doppler angle to get reliable blood flow measurement is between 5 and15 degrees.
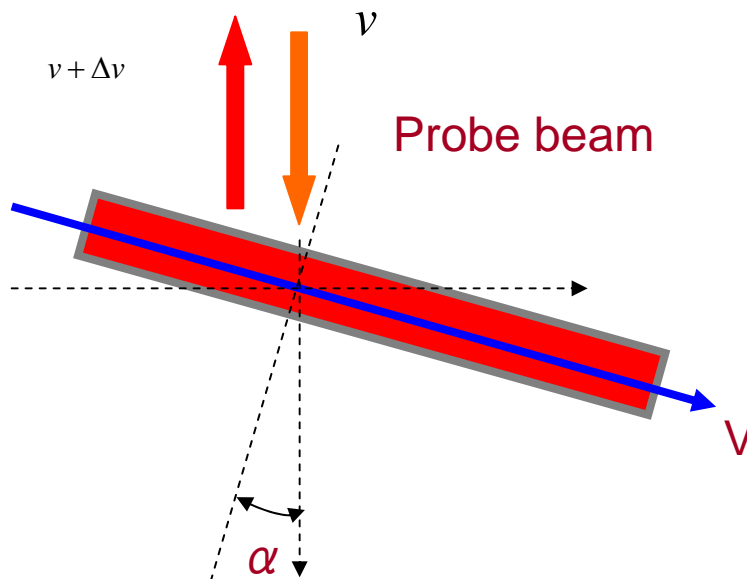

Figure 1. Measurement of both Doppler shift and Doppler angle are needed to compute flow in a vessel.

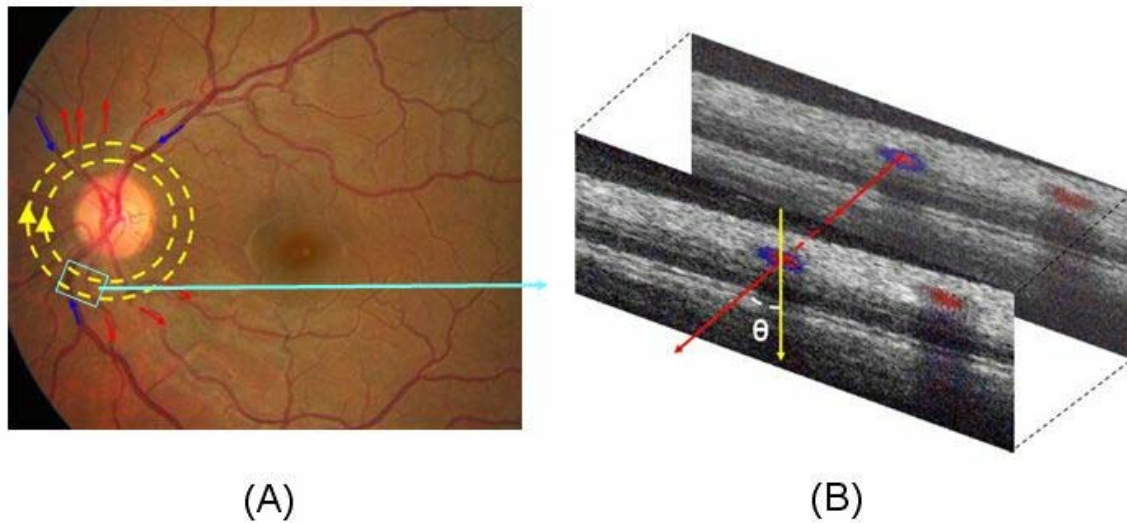(A)   (B)

Figure 2. Two concentric circular scans and Doppler angle calculation. (A) Scan pattern of two circular scans around the optic disc; (B) Doppler angle can be calculated from the vessel positions measured on the two concentric circular scans.

The Doppler angle can be controlled by adjusting the OCT beam path. Figure 3 shows that the Doppler angle of an OCT beam passing through the nasal portion of the pupil is larger than that of the OCT beam passing through the temporal portion of the pupil. Because of the variation of vessels, it is difficult to find one single beam path that optimizes Doppler measurements for all vessels. Experience shows that the optimal strategy is to perform Doppler scans using two different beam paths: one passing through the supranasal (SN) quadrant of the pupil and the other passing through the infranasal (IN) quadrants of the pupil (Figure 4). Although the operator cannot see the beam position in the pupil directly, this can be inferred from the sinusoidal variation in the vertical position of the retina in the real time display of the circular OCT scans. Use the retinal pigment epithelium (RPE) as the reference layer to assess the sinusoidal variation. When the OCT beam is in the SN quadrant of the pupil, the peak of the sinusoid is 1/8 frame to the left of center (Figure 5). When the OCT beam is in the IN quadrant of the pupil, the peak of the sinusoid is 1/8 frame to the right of center (Figure 5). For each retinal vessel, a good flow measurement can usually be obtained from at least one of the two sets of scans.
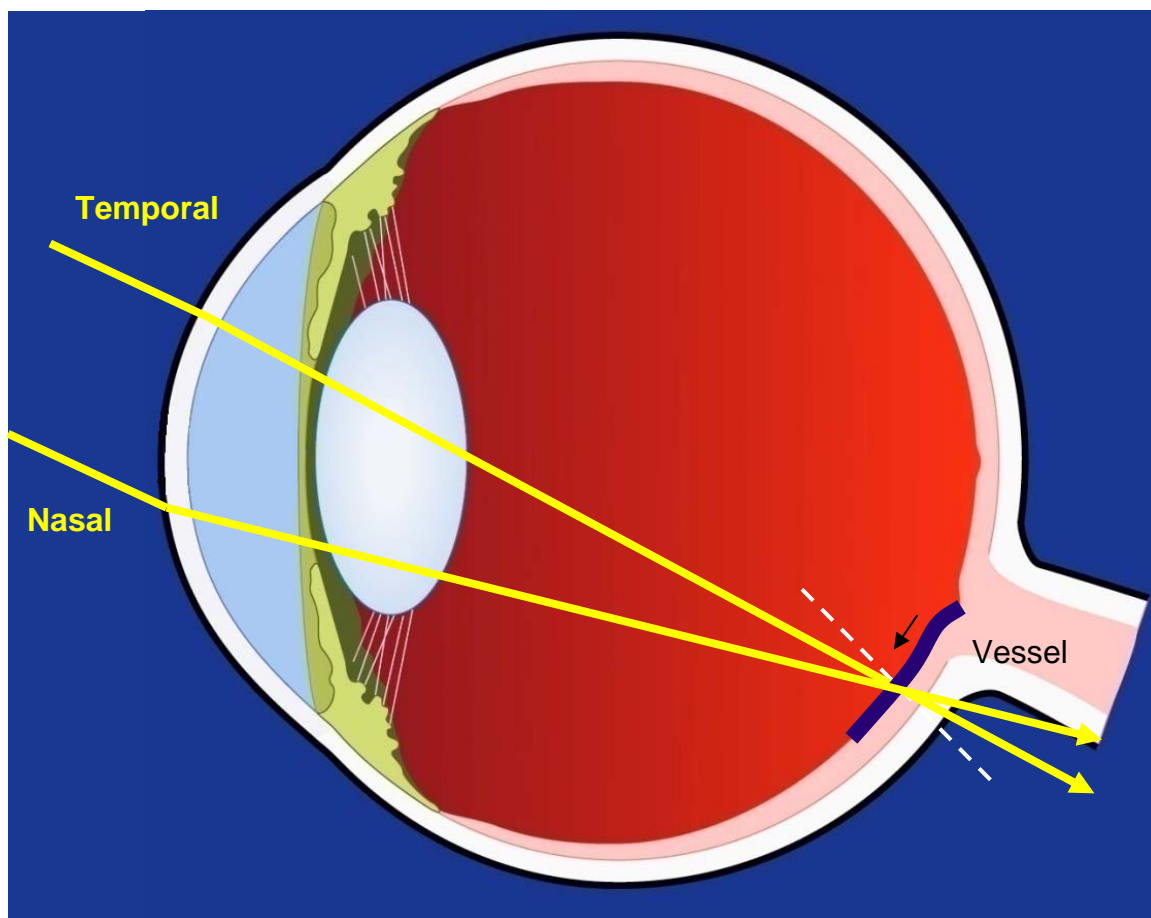
Figure 3. The OCT beam path determines the incidence angle of the blood vessel and can be adjusted to optimize the angle for Doppler shift readings.

Supranasal beam position

Nasal

Temporal
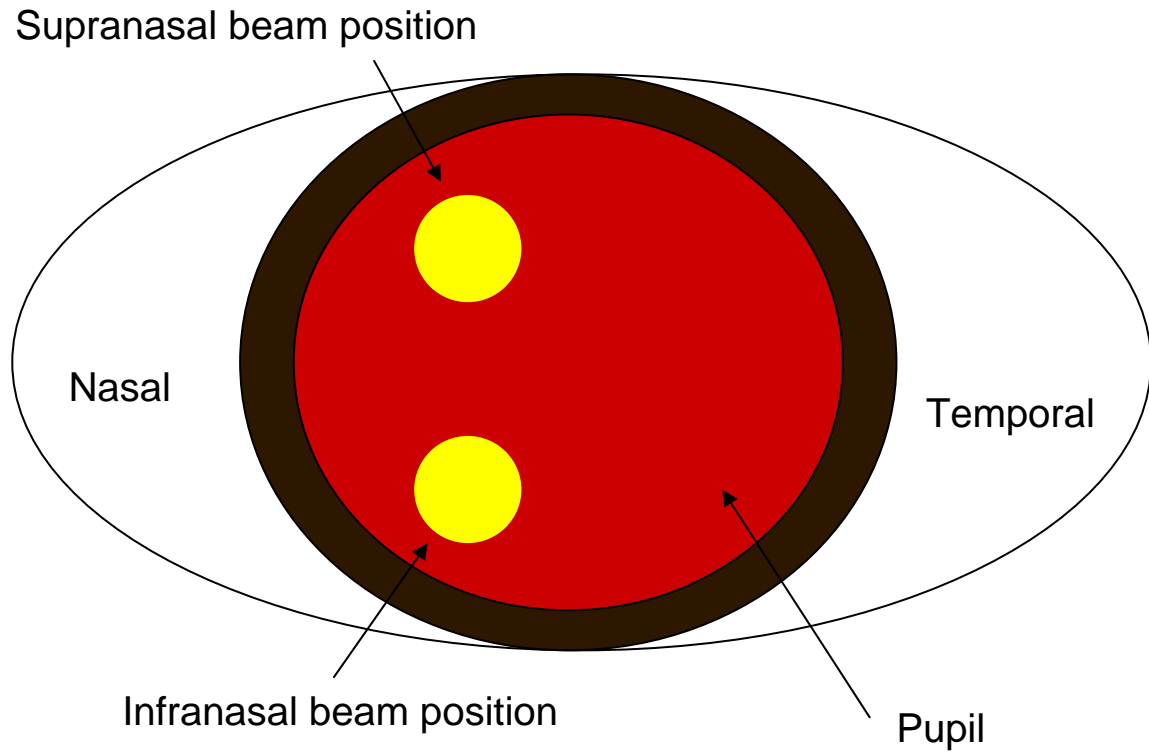
Infranasal beam position

Pupil

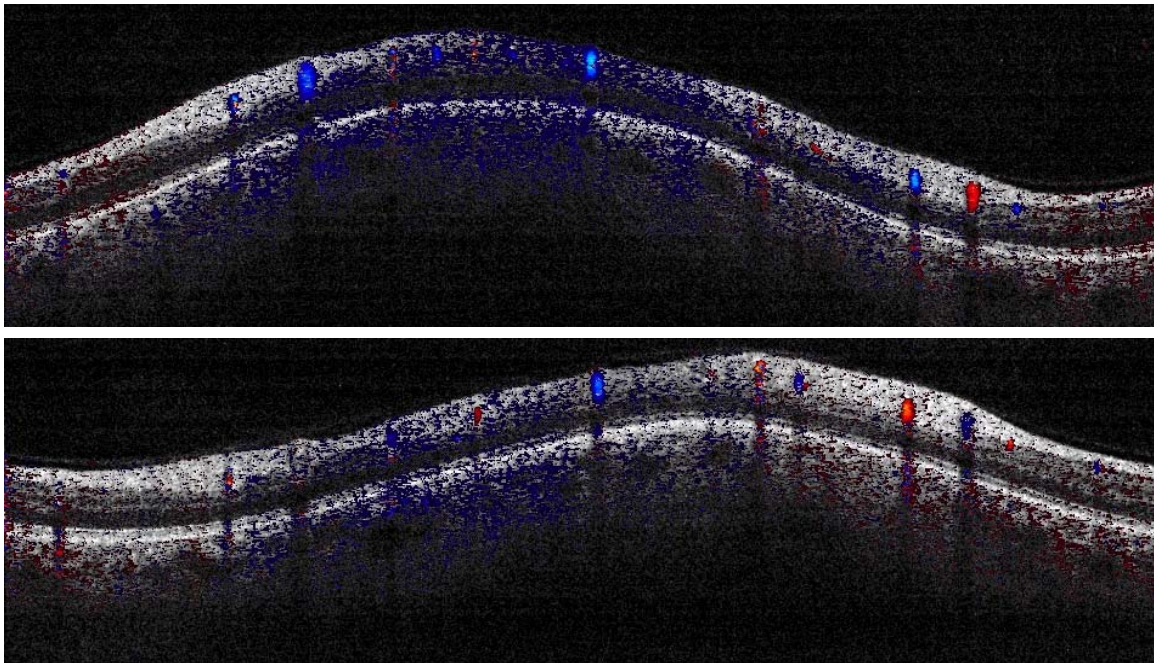Figure 4. Two optimal positions for the OCT beam in the pupil.

Figure 5. Top: OCT image for OCT beam passing through the supranasal quadrant of the pupil. Bottom: OCT image for OCT beam passing through the infranasal quadrant of the pupil.

19.2   Data Collection

19.2.1 Procedure for Obtaining Doppler OCT Scans

Six Doppler OCT scans are taken of one eye of each subject at every visit. If only one eye is suitable for imaging, then only that eye will be scanned. Otherwise, scan the right eye if the patient's study ID number is even and the left eye if the number is odd. A 3D Disk scan is also needed for blood flow measurement.

Scan Pattern	Parameter	Beam Position in Pupil	Repeat
3D Disk	6X6mm	Center	1
Double ring Blood flow	Default	Supranasal quadrant	3
Double ring Blood flow	Default	Infranasal quadrant	3

Patient Setup

1. Corrective lenses, including contact lenses, should be removed before the OCT examination and an unpreserved artificial tear drop should be administered to each eye to prevent drying.

2. Pharmacologic pupil dilation should be used on all study eyes. Use one drop each of tropicamide 1% and phenylephrine 2.5%. All Doppler OCT scanning should be done between 20 minutes and 2 hours after the dilation drops have been given. Record the use of dilation drops on the **Collection Form** for initial and subsequent visits.

3. All examinations must be completed by certified personnel.

4. Reduce the lighting in the room to a minimal level.

5. In the **patient** tab, if it is the first visit of this patient, push the **New Patient** button. On the Patient Information screen, enter the patient's last name, first name, and date of birth, and select gender. In the **Visit Information** on the lower half, select the name of the investigator from the pull down menu and then select the name of the photographer from the pull down menu on the right. In the **Diagnosis Category** box, on the upper right, check Glaucoma, Glaucoma Suspect, or Normal. Then push the **Save** button to save the information. The information can be edited by clicking the **Edit** button. Select the Patient by clicking on the patient name on the Patient page. Push the **New Visit** button to add a visit. Click the corresponding visit under the patient name to select it.

6. Go to the **Examine** page (See Figure 6) by clicking the **Examine** tab. Select all scan patterns according to the protocol. Check **OD** or **OS**. Put 3 in the **Scan Number**. Push the **Add** button twice to add patterns to **Examine To-do list**. Or push **the Examine Protocols** button and select "Blood Flow OD" or "Blood flow OS" protocol; push the **Add** button to add the scan patterns to **Examine To-do list.**

7. The spherical equivalent should be used to change the **Focus** value on the **Scan** tab at the bottom-right of the screen.

8. Position the patient. The instrument, chair and chin rest heights should be adjusted so the patient is comfortable and stable, the forehead is placed against the forehead rest, and the eyes are aligned with the eye-position markers.
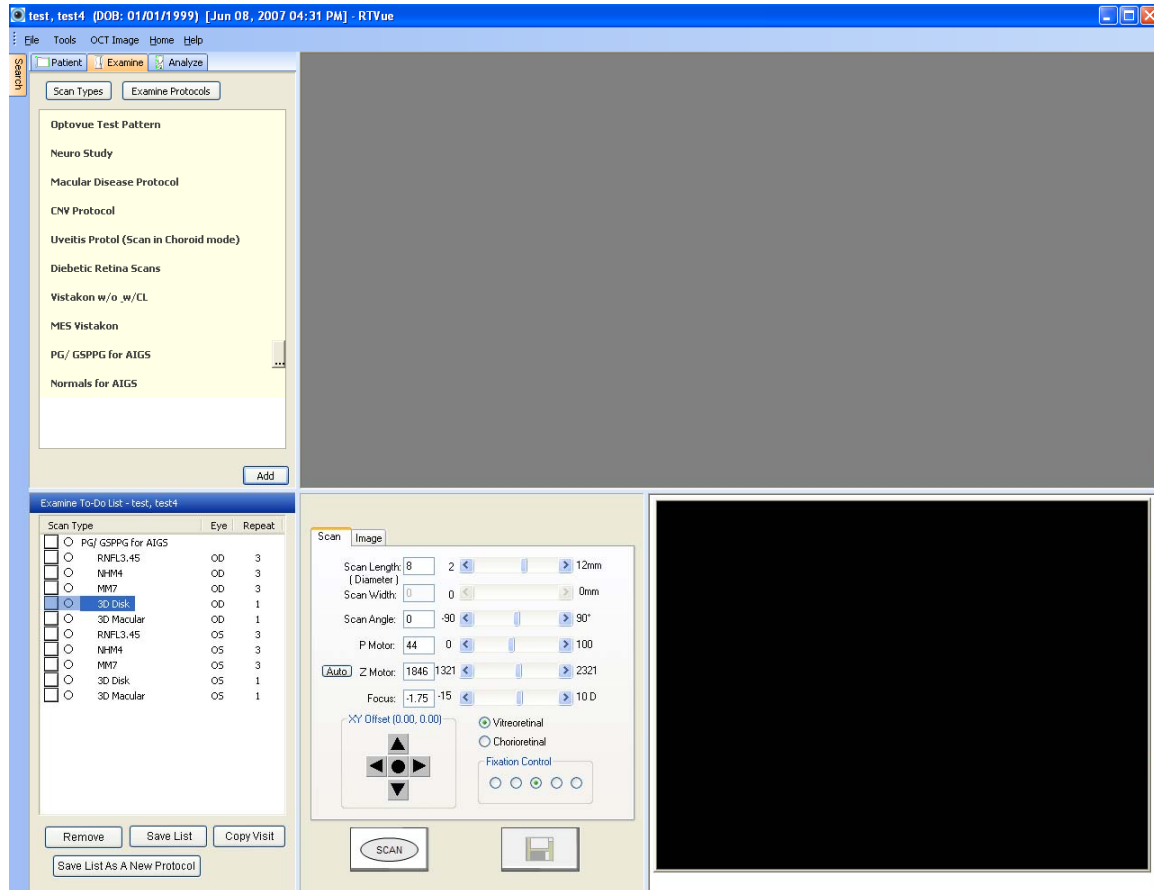

Figure 6. Examination Page

3D Disk Capture

1. Start the 3D Disk scan.

2. Always start the position process with the scan head in the farthest back position.

3. All scans should be performed in the "vitreous mode." The "Vitreoretinal" checkbox should be checked. If "Chorioretinal" is checked, change it to "Vitreoretinal".

4. Instruct the patient to look straight ahead until the blue fixation light becomes visible, then to stare at the blue fixation light. In the CCD image (lower right of the screen.), center on the patient's pupil, then move the scan head forward until the retina can be seen.

5. Press **Auto-all** to perform the Z correction, focus correction, and polarization correction.

6. The patient's optic nerve should be visible in the CCD. Double click on the center of the optic nerve to center the scan over the nerve.

7. Have the patient blink a couple of times, then ask them to hold steady and not blink.

8. While observing the CCD image, wait until the patient is stable for 3 to 4 seconds and press the **Stop** button (The OCT capture takes place PRIOR to stopping the scan.).

9. Evaluate the 3D Disk image for patient movement and save if an acceptable scan was captured.

10. Start the first Doppler Scan.

Doppler Data Sampling

1. Center the scanning circle on the optic disk by dragging the white circles in the CCD screen window (or by double clicking in the center of the disk). Then, using very small movements with the joystick, adjust the OCT scanning head towards and away from the patient and place the Doppler OCT image as close to the upper dashed line as possible, without going beyond it. The color Doppler OCT image should be seen in the OCT window as shown in Figure 7.
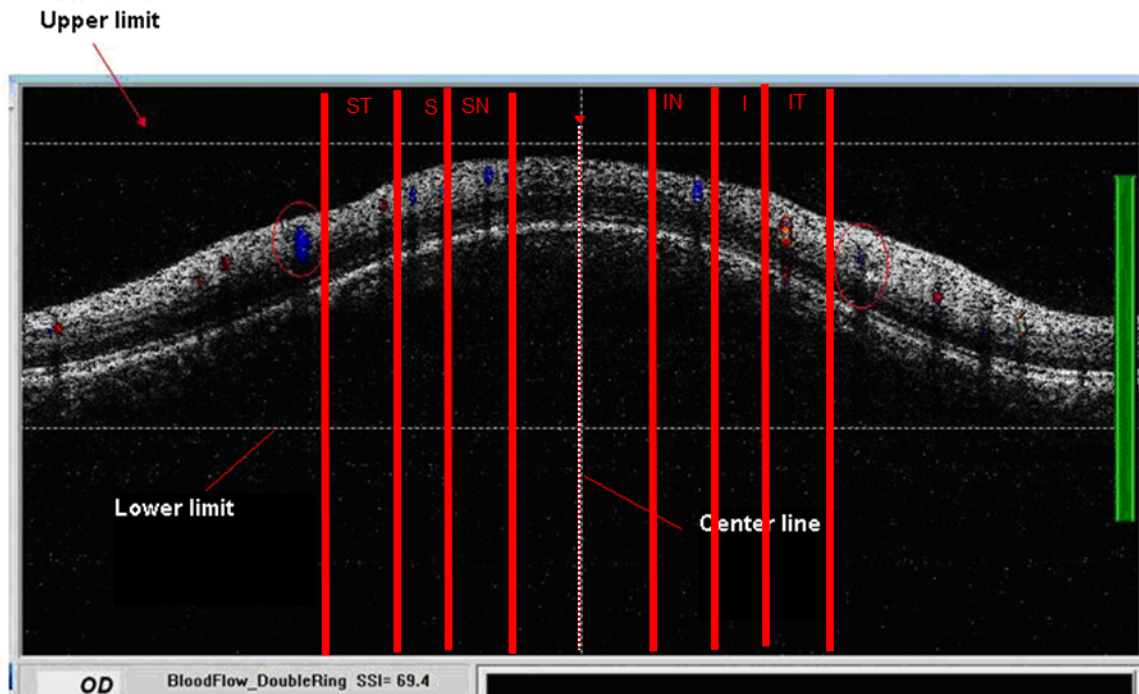

Figure 7. Scanning display window

2. Adjust the focus to maximize the OCT signal. In the auto or manual capture tabs, push the button AUTO F. The OCT system will automatically adjust the focus to maximize the OCT signal strength.

3. *Line up the retinal image with the guide lines using the method described in section 19.2.2 below. First complete three scans in the SN position and then position for and acquire three IN scans.*

4. Notice the signal strength index (SSI) during the process. The recommended value is a number above 45. The lowest acceptable SSI is 40. Shadowing is also not allowed.

5. Ask the patient to blink then hold. When the data looks stable for 3 to 4 seconds, push the **Stop** button to stop the scan by clicking the left mouse key (do not use the button on the top of the joystick to stop the scan since this may cause scan head movement and alter the captured Doppler data).

6. Check the image quality in the pop-up message box (refer to section 19.2.3 for details). If the quality check returns "Image quality: Acceptable," close the message dialog by pushing the **No** button. Then push the **Save** button to save the scan. If the quality check fails, check the reason (section 19.2.3**)**, close the message box and redo the scan by pushing the **Start** button again. Repeat steps 5-6 until Image Quality is "Acceptable" indicating that the quality check has passed.

7. If the quality test fails upon repeat (after 2 attempts) the user should abandon this scan location and try either the S location (if the SN scan failed) or the I location (if the IN failed). If the quality check fails for the S or I position again, try ST (if SN and S Failed) or IT (if IN and I failed). If all three positions fail, find the scan with the highest overall Doppler score and redo the scan with same beam position and save it anyway (Reduce the amplitude of the RPE curve to avoid weak SSI and shadow).

8. Ideally the double circular scan should be done three times with the OCT beam in the SN quadrant of the pupil and three times with the OCT beam in the IN quadrant of pupil. In the situation of step 7, one of the scan positions may vary depending on the scan that passed the quality check.

19.2.2 Doppler OCT Scan Positioning

19.2.2.1   Relationship Between the Beam Position on the Pupil and the RPE Curve

Generally, the amplitude of the RPE curve increases when the beam's position on the pupil is shifted from pupil center to pupil edge except when shifted in the temporal direction. When shifted in the temporal direction, the peak point of the RPE curve will shift to the left if the beam is moved in the superior direction and to right if the beam is moved in the inferior direction.

19.2.2.2   Guidelines for the Real Time Scanning

To help align the OCT beam to the required path, new guidelines were developed to divide the screen according the beam position on pupil (Figure 8). From left to right, the regions are Temporal (T), SupraTemportal (ST), Superior (S), SupraNasal (SN), Nasal (N), Infranasal (IN), Inferior(I) and InfraTemporal (IT). Notice the vertical guide lines are only correct if the beam position is not close to pupil center.
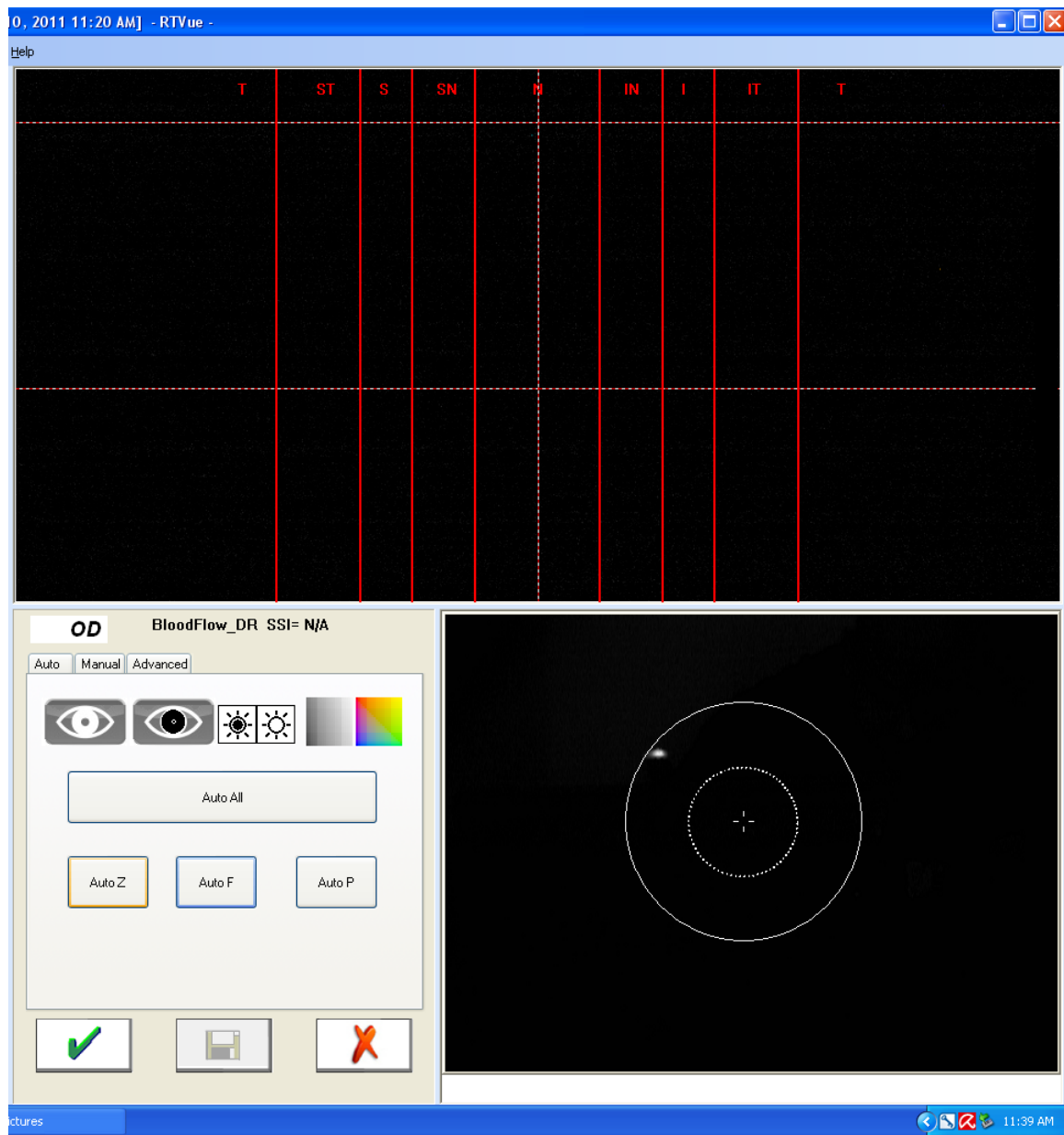
Figure 8. New guide lines added to RTVue screen

The guide lines are used to line up the OCT retinal image features and to confirm that the OCT beam is in the recommended position within the pupil. When the optimized beam path is reached, the retina should follow a sinusoidal curve with large amplitude. The amplitude of the sinusoidal variation H is defined as the distance between highest inner limiter membrane (ILM) and lowest retinal pigment epithelial (RPE) positions. The amplitude H should be close to the distance between the two horizontal lines, marked as D in Figure 9. For an OCT beam passing through the SN portion of the pupil, the peak (highest point) of the RPE sinusoid should be between the two red vertical lines that outline the SN portion, as shown in Figure 9. For an OCT beam passing through the IN portion of the pupil, the peak of the RPE sinusoid should be between the two red vertical

lines that outline the IN portion, as shown in Figure 10. A recommended process for lining up the image for SN and IN positions is shown in section 19.2.2.3
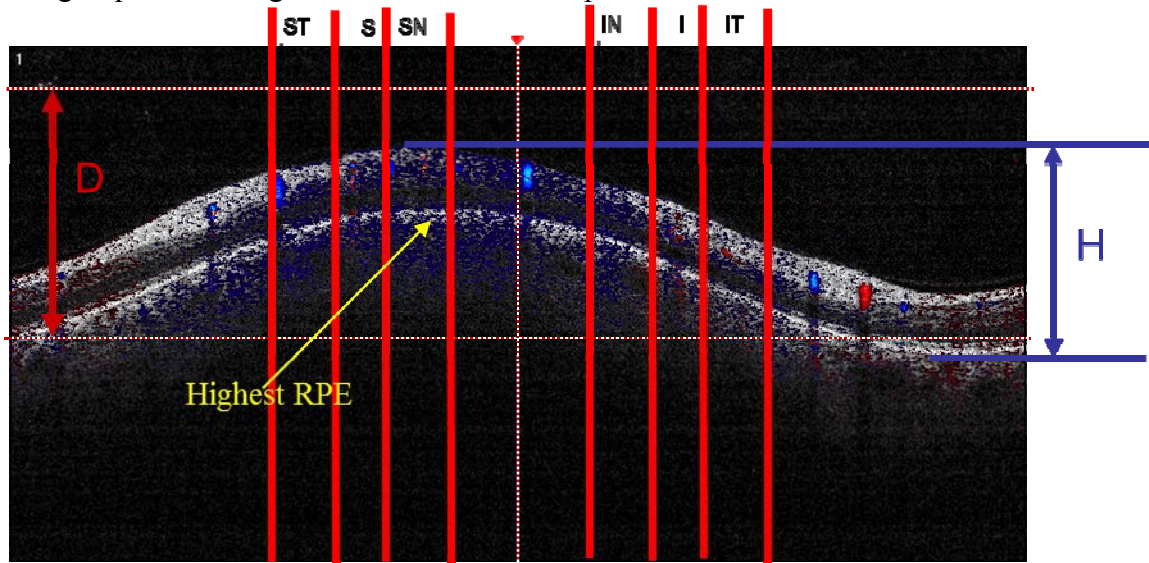
Figure 9.   Image of the OCT beam passing through the SN portion of the pupil. The highest RPE position will be between the two red vertical lines that outline the SN portion. The distance H between the top of the retina to the bottom of the RPE should be approximately equal to distance D between two horizontal red lines.
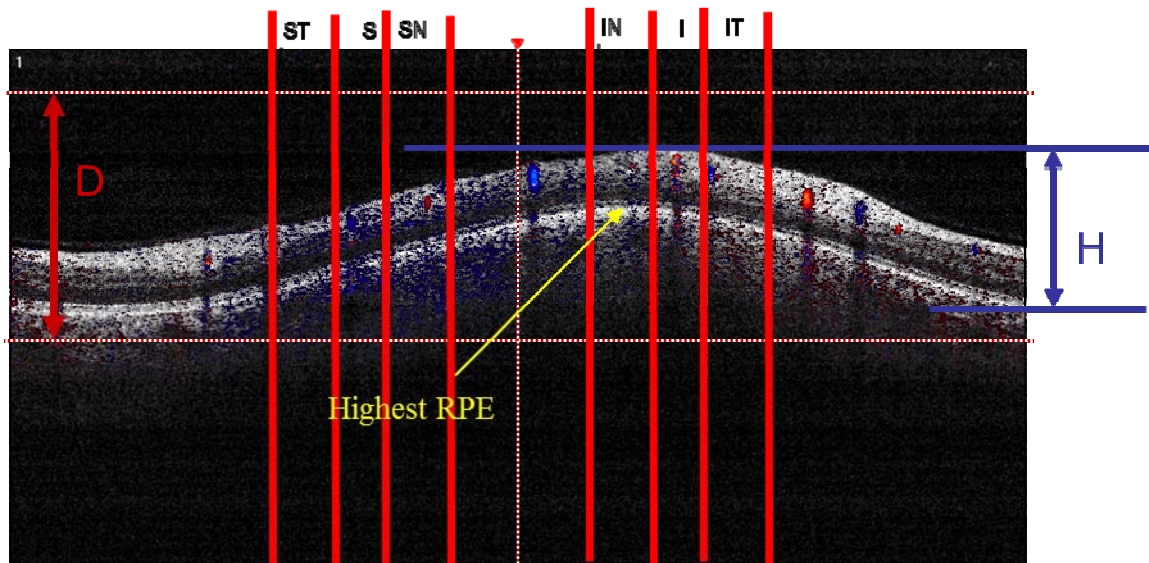

Figure 10.   Image of the OCT beam passing through the IN portion of the pupil. The highest RPE position will be between the two red vertical lines that outline the IN portion.

19.2.2.3   Adjustments for Supranasal and Infranasal Positions

1. With the OCT beam through the center of the pupil, the retinal contour on the image should follow a shallow sinusoidal curve. Look at the RPE layer to find the peak (highest point) of the sinusoid. When the beam is centered on the pupil, the horizontal location of the RPE peak should be equal to one half of the image width (Figure 11).
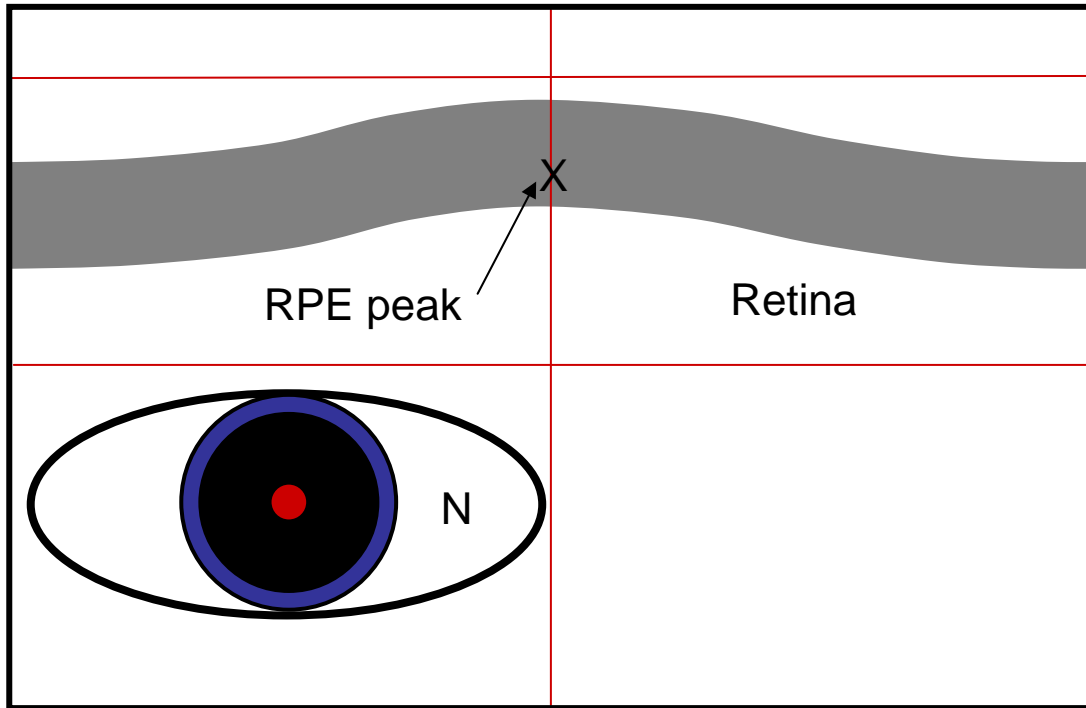

Figure 11. Retina contour with OCT beam passing through the pupil center.

2. Slowly move the OCT scanning module in the nasal direction; the sinusoidal variation of the retina contour will increase during the process. Stop when the top of the retina (peak position of the ILM) is approximately at the level of the top red horizontal guideline and the lowest RPE position is at the level of the bottom red horizontal guideline (Figure 12). However, if the signal strength becomes too low (likely due to the iris blocking the beam), move the OCT scanning module slightly back towards the center to restore signal strength.
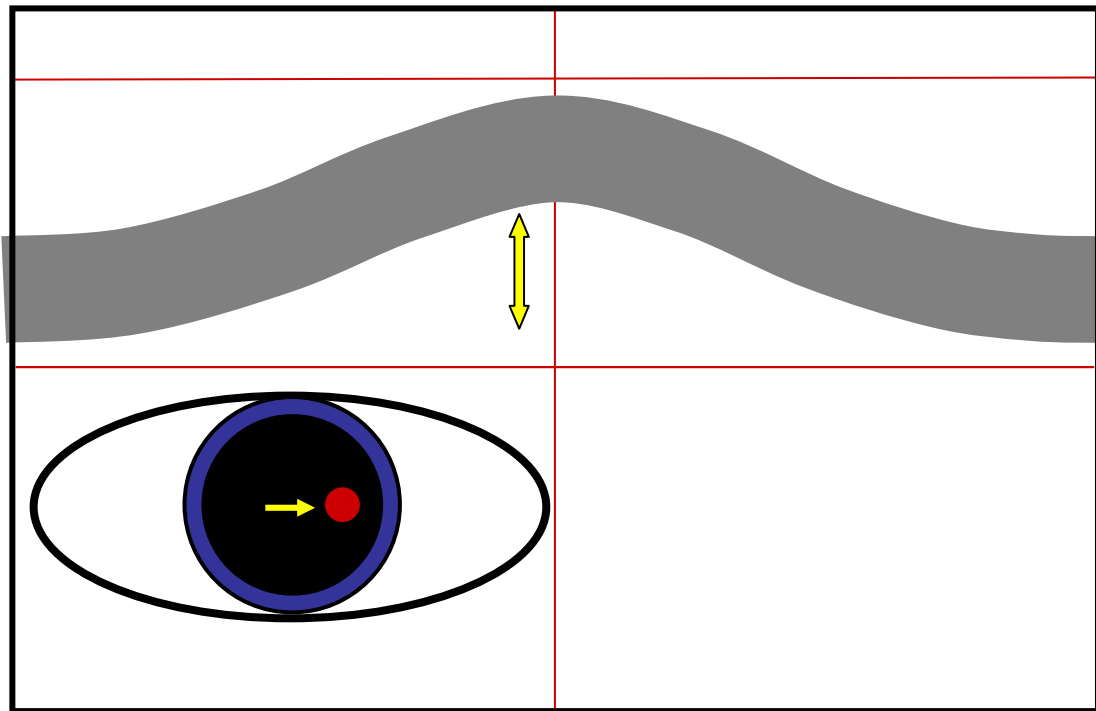
Figure 12. The amplitude of the sinusoidal variation in retinal contour is increased by moving the scan module nasally (N).

3. Move the OCT scanning module higher (for a beam position in the SN portion of pupil) by twisting the joystick counter clockwise. The peak of the retinal sinusoid will move left (Figure 13). Place the peak of the RPE sinusoid between the two red vertical guidelines that mark the SN portion, as shown in Figure 9. The top of the retina (peak position of the ILM) should be approximately at the level of the top red horizontal guideline and the lowest RPE position is approximately at the level of the bottom red horizontal guideline (Figure 13). The absolute vertical position of the retina is not critical. It is more important that the distance between the top of the retina to the bottom of the RPE is approximately equal to the distance between two horizontal red lines. However, if the signal strength becomes too low (likely due to the iris blocking the beam), move the OCT scanning module slightly back towards the center to restore signal strength. Capture three Doppler scans at this position.
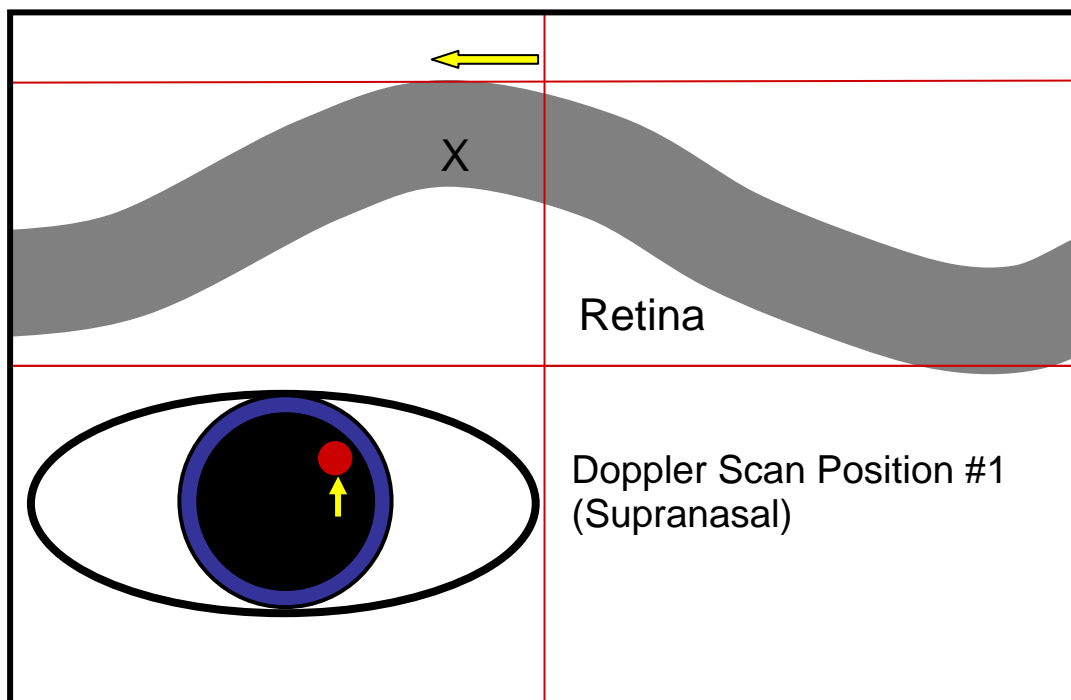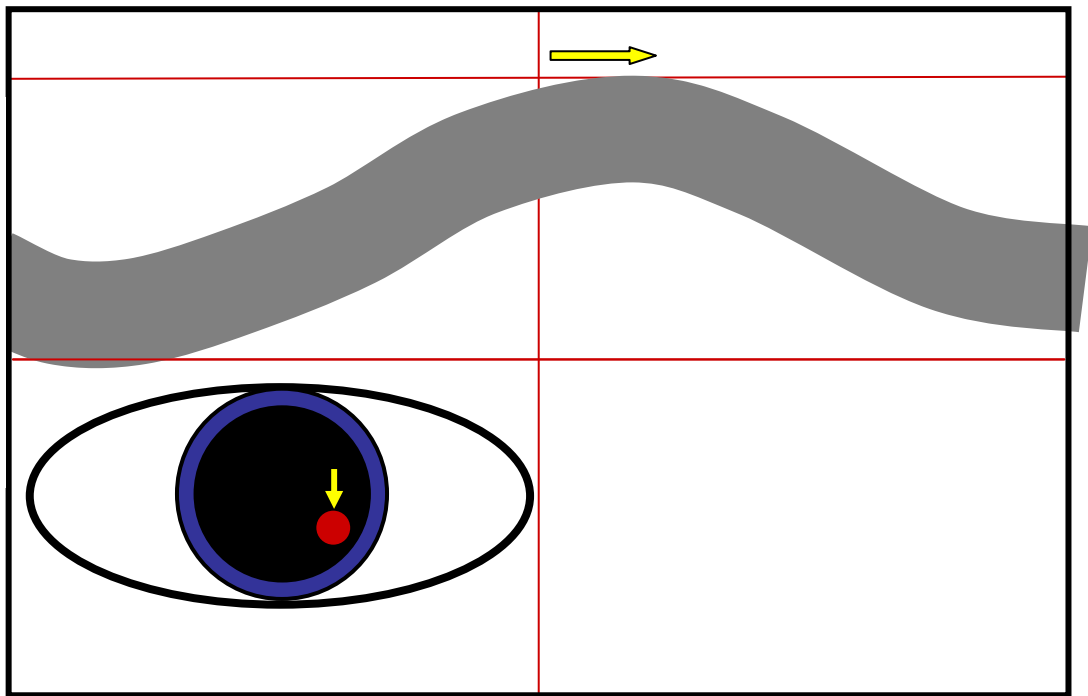

Figure 13. The position of the peak of the curve pattern can be adjusted by twisting the joystick. Twisting the joystick up (superior) moves the curve's peak to the left.

4. Move the OCT scanning module lower (for a beam position in the IN portion of the pupil) by twisting the joystick clockwise. The peak of the RPE sinusoid will move right (Figure 14). Place the peak of the RPE sinusoid between the two red vertical guidelines that mark the IN portion, as shown in Figure 10. The top of the retina (peak position of the ILM) should be approximately at the level of the top red horizontal guideline and the lowest RPE position should be approximately at the level of the bottom red horizontal guideline (Figure 14). The absolute vertical position of the retina is not critical. It is more important that the distance between the top of the retina and the bottom of the RPE be approximately equal to the distance between the two horizontal red lines. However, if the signal strength becomes too low (likely due to the iris blocking the beam), move the OCT scanning module slightly back towards the center to restore signal strength. Capture three Doppler scans at this position.

Figure 14. The position of the peak of the curve pattern can be adjusted to the right by twisting the joystick down

19.2.2.4　　　Adjustments for Other Pupil Positions

Other pupil position adjustments can be made. They are similar to the adjustments described in the section 19.2.2.3 for SN and IN positions.
  1. For S and I positions, follow Step 1 in 19.2.2.3. However, instead of moving the scanner to left and right, move the scanner up and down. If the signal strength becomes too low (as in section 19.2.2.3), move the OCT scanning module slightly

towards the center to restore signal strength. Ensure the RPE curve has a large amplitude and the peak of the pattern is located close to the S or I region.

2. For ST and IT positions, follow step 1 in 19.2.2.3. Then move the scanner up and down to S and I locations, and finally in the T direction. Make sure the RPE curve has large amplitude and the peak of the pattern is located close to the ST or IT region.

19.2.3 Image Quality Check and Related Adjustment

After the user pushes **Stop**, an image quality check report is generated in a pop-up window (Figure 15). It provides three different sets of information, the Overall Doppler Score, Image Quality and Dual Angle Protocol. The Overall Doppler Score is used to compare different beam positions for the same eye. Then second set, Image Quality, tells the user if the quality check has passed and lists the three parameters that were checked:
1. Intensity Signal Strength
2. Eye movement
3. Doppler signal

If the reason the quality check fails is due to #1, first check the image to see if it is due to a blink. If not due to a blink, it is likely due to the iris that maybe blocking the beam. Therefore the OCT scanning module should be moved slightly back towards the center to restore signal strength.

If the reason the quality check fails is due to #2, try the scan again and tell the patient to blink and hold. Push the **Stop** button as once the data is stable.

If the reason the quality check fails is due to #3, it is probably because the beam is too close to pupil center. Move the OCT scanning module slightly from the center to increase the sinusoidal curve's amplitude (H in Figure 9).

The last set of information is at the bottom of the message box. It lists how well the scan followed the dual angle protocol. If the "Beam through pupil center" check is "Yes," it means that the beam is close to center. Note that if "Beam through pupil center" equals "Yes," then the beam location indicated below this parameter is not reliable and should NOT be used as for the scan beam position check. Beam location tells the operator in which section of the pupil the beam may be located. This result is more reliable than the judgment made by the location of the peak of the RPE curve in the guide lines, especially when the beam is somewhere between pupil center and pupil edge.
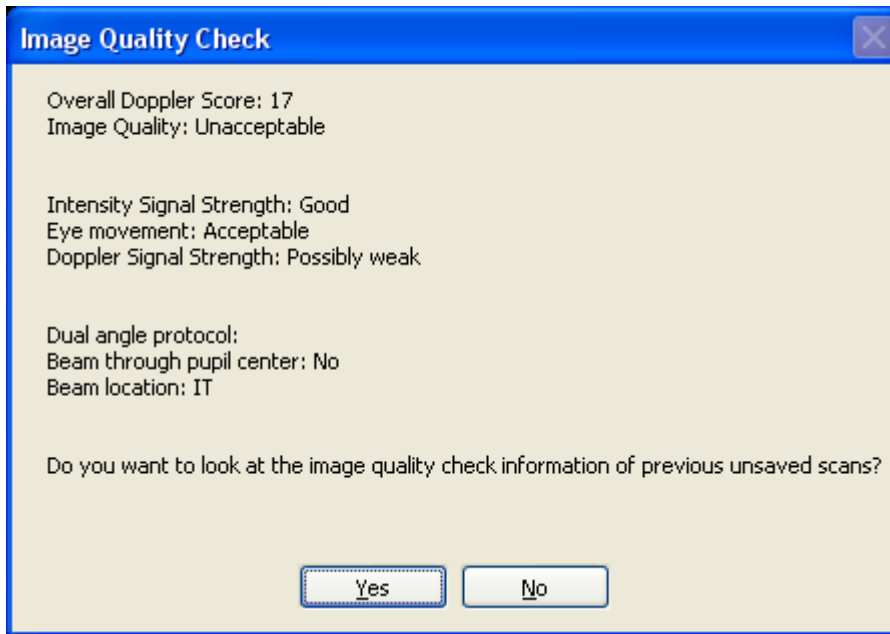
Figure 15 Image Quality Check. This check shows that the scan may have a weak Doppler scan. The operator should move the beam to the edge of pupil.

At the bottom of the Image Quality Check dialog box there are two buttons designed to compare unsaved scans. Click **No** if the image passes the quality check. The **Yes** button is only useful if the quality check consistently fails for all S or I beam positions. Push the **Yes** button to trigger another pop-up dialog window which allows the user to check all previous unsaved scan's image quality (up to 4 scans). If this occurs, the operator needs to compare the overall Doppler score of the unsaved scans in order to choose the best position (Figure 16). The higher the overall Doppler score, the better the image quality. Additionally, if the Intensity Signal Strength is weak for a scan, then the Overall Doppler Score of this particular scan should not be used in comparing the beam position.
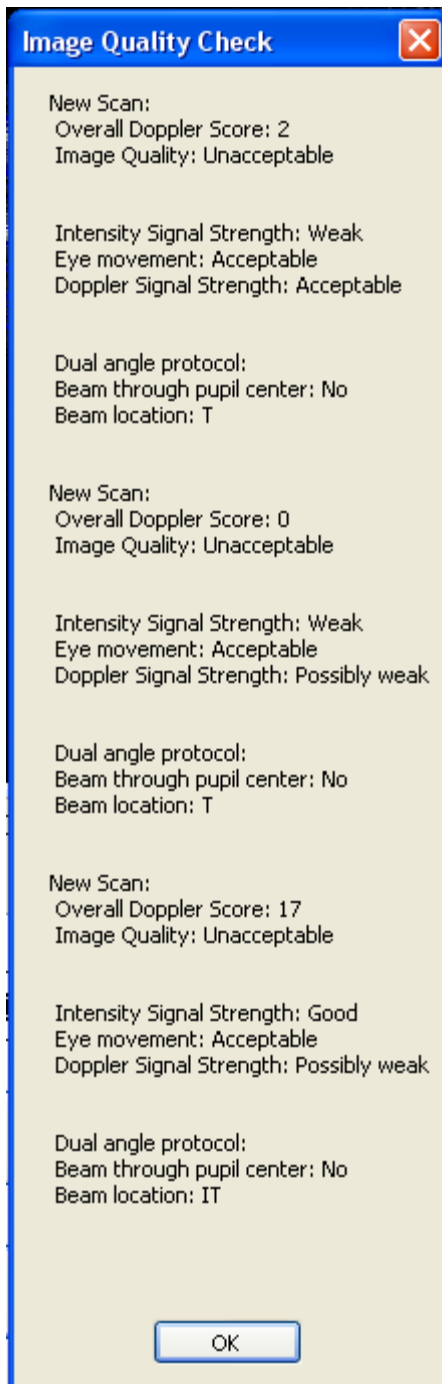
Figure 16 Checking previous unsaved scans' image quality. This one shows IT is the best beam location in the three previous unsaved scans.

After all scans are completed, the user can check the image quality on the analysis page of the RTVue software for each Doppler scan (Figure 17). The user can push the **Quality Check** button at top of the screen to review the image quality of current Doppler scan.
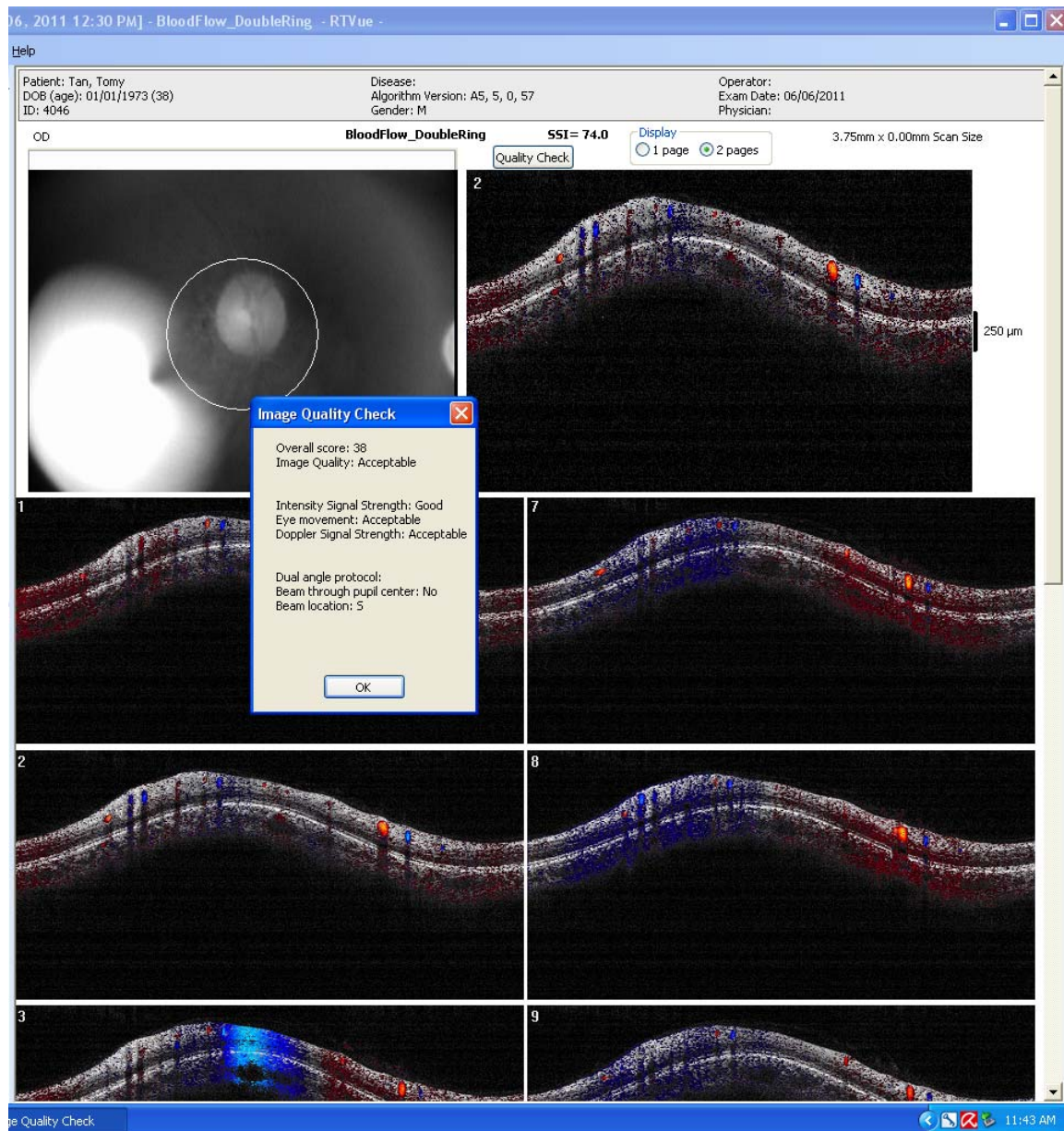
Figure 17 Reviewing the image quality on the analysis page

19.2.4 Systemic Conditions and Medications

Systemic conditions and medications that affect ocular blood flow must be recorded because they may affect retinal blood flow.

Antihypertensive and pressure medications must also be recorded because they can affect blood pressure. Anticoagulation and antiplatelet medications are to be recorded because they may affect blood viscosity and therefore blood flow. Diabetes-related medications

are to be recorded as an indication of the severity of diabetes mellitus, which affects the microcirculation.

For a list of these medications, please refer to Appendix 1. The classes of medications taken by the subject are recorded in the visit form (Appendix 4) and will need to be entered into the central database.

The patient's blood pressure (systolic and diastolic), height (in centimeters) and weight (in kilograms) are needed in order to analyze the Doppler OCT data. These should be recorded on the Doppler-OCT Retinal Blood Flow Data Collection Form (Appendix 2) and in the central database. If the scans are done on more than one eye under more than one condition, multiple sheets should be completed.

It is preferred to take the blood pressure (Appendix 5) using the right arm for every visit. If use of the right arm is contraindicated medically, use the left arm and record this on the data collection form. Record the arm, the time and condition of the patient.

19.3   Quality Control and Data Analysis

19.3.1 Common Scan Quality Criteria

Ideally, the operator should review the quality of each Doppler scan on the analysis page and check how many OCT images pass the quality check (section 19.2.3). Three superior (SN preferred) and three inferior (IN preferred) scans should be selected from the saved scans at one visit. If there are not enough valid scans, the Center will need to decide if a rescan of the patient is necessary or if the data can be sent "as is."

19.3.2 Data Transfer to Coordinating Center

The Doppler scan, the 3D Disk scans and disc photograph will be sent to the USC/DEI OCT reading center for blood flow measurement using the Doppler Optical Coherence Tomography Of Retinal Circulation (DOCTORC) Software, a semi-automatic computer program for blood vessel detection and blood flow calculation. The results will then be forwarded to the DOCTORC central database. The data transfer to the reading center is scheduled every 3 months or more frequently if needed for data analysis and manuscript preparation.

An external USB hard disk is used to transfer the data. Because Doppler data exceeds 150MB per scan, the hard disk capacity should be typically be 1GB*eyes*visits per eye.

Step 1. Data Transfer Output
Connect the external hard disk to the USB port of the RTVue. Build a folder for transferring the data under the root directory of the external hard disk. The folder name can be formatted as "DOCTORC+study name+site name+export date" (for example: d:\DOCTORC_AIGS_USC_20090719).

Step 2. Subject Naming Convention

To protect the confidential information of patients, Protected Health Information, the patient's name must be changed to an ID number if this has not been previously done. For example, AIGS patients can be identified using the following rules:

1. **Last Name** should be anonymized. Use AIGS site ID+patient ID. For example, 4031 for USC site (4)+patient ID (031).
2. **First Name** should be anonymized. Use AIGS site ID+patient ID.

For other studies, the data should use study ID + patient ID to replace the last name and first name. The study ID should a unique ID used to separate different study in DOCTORC group. Contact Michelle Montalto for a study ID if the ID is not assigned before or coordinator did not know the study ID. (montalto@ohsu.edu, 503-494-1616)

An alternative method to anonymize the patient name is to input the study ID + patient ID in the subject ID field of the patient setup page in the RTVue and choose "Anonymous" when output database.

When the grading center imports the data, the patient's name will become the ID using either one of above two methods.

Each study of each center is assigned a specific study ID. If the coordinator does not know the study ID of the center, please contact Sharon Bi <bis@ccf.org> or Michelle Montalto <montalto@ohsu.edu>.

Step 3. Output Database

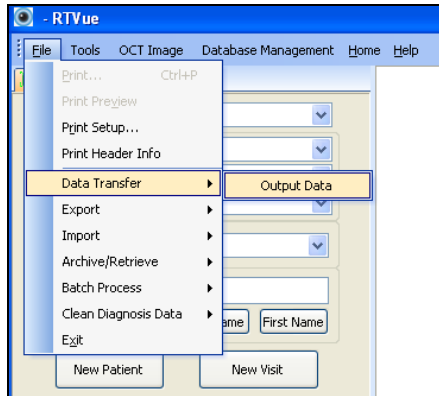Go to menu "File->Data Transfer->Output Data" as is shown in the following image:

Figure 15. Output database

Choose the folder that was created in Step 1 on the external hard disk. If you have not created the folder in Step 1, you can do so now.
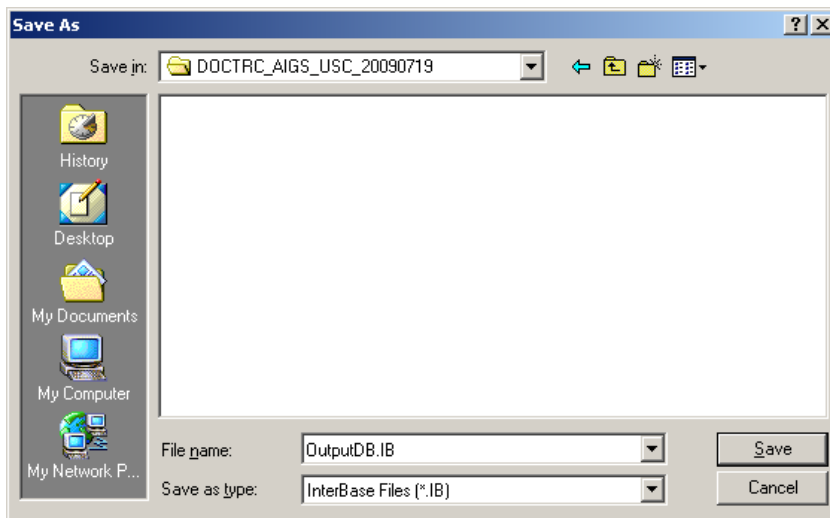

Figure 16. Select the export folder

Step 4. Choose the scans of the blood flow subjects

1. Find all of the subjects in the AIG study. You can search by patient name or by EMR ID. For example, if you renamed the patient's last name to "site ID+patient ID" you can input the site ID to find all AIGS patients.
2. Choose the required visits below each subject. Choose only visits that occurred after the last data transfer. Note if the patient name is not changed to ID and the subject ID

is filled following the rules in step 2, "Anonomous" box must be checked (left-bottom of figure 17) before starting output.

3. Click the **Start Output** button at the bottom left. This will take about 6 minutes per visit.

4. After the output process is done, click the **Save and Exit** button at the right bottom. This step must be performed; otherwise the data is not saved completely.

Figure 17. Select visits and output

Step 5. Find the Disc photograph for the same eye

For each eye, a disc photograph is also needed from that same visit. If a disc photograph from that visit is not available, choose a disc photograph from the visit with the closest

date. A stereoscopic picture is not required but acceptable. The disc photograph should be in TIF or JPG format and the image should be high resolution (1200X600 pixels or higher). Collect all of the patient's disc photographs in to a single folder on the external hard disc being used to transfer the data to the grading center.
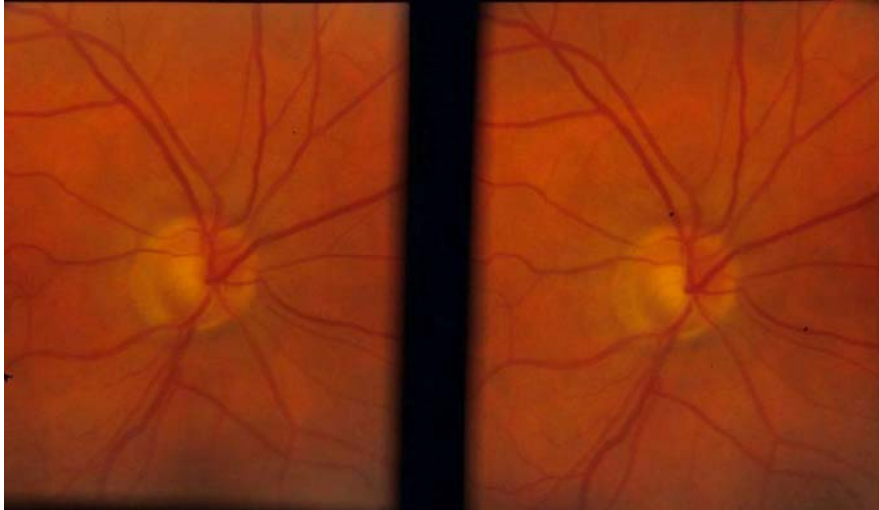

Figure 18 Example of disc photograph

Step 5. Send the data to the USC/DEI DOCTORC reading center

Send the USB external hard disk through Fedex/UPS to USC. Send the disk to:

Elnaz Rakhshan
Suite 3607, DEI
1450 San Pablo street,
Los Angeles, CA- 90033.
Phone : 323-442-6535.

Label the package as DOCTORC+Study ID+center ID+collection date

Step 6. Input the patient information into DOCTORC central database

The clinical coordinator also needs to input the patient and visit information into the DOCTORC central database. Please see Appendix 5 for the introduction to the central database. The Doppler blood flow grading center will input the blood flow result. The PI or researchers can review the data for their own study and export results into Excel files as needed.

19.3.3 Data Review and Interpretation

Step 1. The transferred data will be verified and backed-up to a central raw data database maintained by Elnaz Rakhshan at Doheny Doppler OCT grading center at USC. The data will then be transformed into a format where each visit is saved in an individual folder. For example: DOCTORC_AIGS_USC STUDY ID_VISIT ID_EYE_DATE OF SCAN (4032_2178_OD_2008-09-12).

Step 2. The data will be graded at the Doheny Doppler OCT reading center using DOCTORC semi-automatic grading software. The semi-automatic software will be used to review and interpret the results. The OCT reading center will input the blood flow measurement results into the DOCTORC central database and the grading details will be recorded in an Excel file on an external disk.

Step 3. The data with the grading results will be sent to Ou Tan at Oregon Health & Science University for backup and to aid in the development of the fully automatic software. Lastly, the external hard disk will be sent back to the clinical center without the customized blood flow measurement.

Ou Tan, PhD
Casey Eye Institute, Oregon Health & Science University
3375 S.W. Terwilliger Blvd.
Portland, OR 97239-4197
tano@ohsu.edu
503 494 9436 (o)

19.4 Management of Doppler-OCT Data Files

19.4.1 Logbook
All images will be obtained using the subject name and study ID number. The technician or photographer performing the imaging, referred to as the "operator," should keep a bound logbook containing the subject's study ID, date of exam, the operator's name and type of visit. The entries should be made in chronological order with the newest exams on top.

19.4.2 Information for Participants

The height, weight, and blood pressure measurements can be provided to the study participants. People with hypertension (systolic pressure ≥140 or diastolic pressure ≥90) should be told that they have hypertension and advised to see a medical doctor if they have not already done so. People with severe hypertension (systolic pressure ≥180 or diastolic pressure ≥110) should be told that they have severe hypertension and advised to seek urgent medical attention (i.e., the patient should be advised to go to the emergency room rather than completing the Doppler scans).

The American Heart Association defines high blood pressure, or hypertension, in an adult as a systolic pressure of 140 mm Hg or higher and/or a diastolic pressure of 90 mm Hg or higher. Blood pressure is measured in millimeters of mercury (mm Hg).

Blood pressure (mm Hg)	Normal	Prehypertension	Hypertension
Systolic (top number)	less than 120	120-139	140 or higher
Diastolic	less than 80	80-89	90 or higher

mm Hg = millimeters of mercury

19.4.3 Paper Files
The operator will fill out the AIGS Doppler OCT Data Collection Form (Doppler-OCT DCF). The Doppler-OCT DCF will be given to the clinical coordinator for review and filing. This form should be collected at all Doppler visits.

19.4.4 Central Database
The central database records whether a participant has consented to the Doppler OCT ancillary study. Systemic medications will be recorded in the central database. Systolic and diastolic blood pressure readings will be recorded in the central database. Height and weight will be recorded. The Doppler OCT scan SSI values are recorded. Eye length may also affect blood flow measurement (this is measured at the AIG baseline visit as part of the standard protocol). The flow measurements are not recorded at this time because the algorithm is still being actively developed and is subject to change.

19.4.5 Data Archiving
Archiving is not currently required.

19.4.6 Handling of Missing Data
If a participant consents to the Doppler OCT study, Doppler OCT should be performed at all follow-up visits. For these participants, if Doppler is not performed on a visit specified in the study protocol, this is considered missing data and the scanning must be performed within 2 months of the scheduled visit. Subjects participating in the ancillary study should comply with all scheduled visits.

19.5 Personnel
The clinical coordinator at the clinical center is responsible for maintaining the Doppler OCT DCFs.

The clinical investigator(s) at the clinical centers are responsible for quality control and for certifying that the person taking the blood pressure measurement is qualified to do so.

All personnel involved in this ancillary study should read this chapter and be familiar with the overall AIGS design and goals.

19.5.1 Basic Qualifications
All personnel must be qualified ophthalmic technicians (COA, COT or COMT), ophthalmic photographers or medical doctors.

19.5.2 Demonstration of Practical Competency
The principal investigator of the clinical center should verify that the operator has demonstrated competency in the following:

- Adjusting the comfort features for the patient, such as the chin rest and chair
- Entering patient data
- Operating the FD-OCT Doppler system and proper acquisition
- Identifying image quality problems (e.g., **framing, blinks, poor fixation, OCT image intensity, frame repeatability).**
- Saving the image data, archiving images, and making back-ups of the database

Appendix to Chapter 19

Medications that affect blood circulation should be recorded by category in the central database. The following categories of medications are recognized:

1 Antihypertensive Medications

To aid in identifying these medications under categories, they are listed below.

Antihypertensive – Beta Blockers

Generic	**Brand**
acebutolol	Sectral, Rhotral, Monitan
atenolol	Tenormin
bextaxolol	Kerlone
bisoprolol	Zebeta, Monocor
carvedilol	Coreg
esmolol	Brevibloc
labetalol	Trandate
metoprolol	Lopressor, Toprol-XL, Betaloc
nadolol	Corgard
oxprenolol	Trasicor, Slow-Trasicor
penbutolol	Levatol
pindolol	Visken
propranolol	Inderal, Inderal LA, InnoPran XL
timolol	Biocadren

Antihypertensive – Calcium Channel Blockers (CCBs)

Generic	**Brand**
amlodipine	Norvasc
felodipine	Plendil, Renedil
isradipine	DynaCirc, DynaCirc CR
nicardipine	Cardene, Cardene SR
nifedipine	Procardia, Adalat, Procardia XL, Adalat CC, Adalat XL, Adalat PA
nisoldipine	Sular
diltiazem	Cardizem, Cardizem Sr, Cardizem LA, Cardizem CD, Cartia XT, Dilacor XR, Diltiazem CD, Diltia XT, Tiazac, Taztia XT
verapamil	Isoptin, Calan, Covera-HS, Verelen, Verelan PM, Chronovera, Veramil

Antihypertensive – Diuretics

Generic	Brand
acetazolamide	Diamox
bumetanide	Bumex, Burinex
ethacrynic Acid	Edecrin
furosemide	Lasix
torsemide	Demadex
amiloride	Midamor
triamterene	Dyrenium
bendroflumethiazide	Naturetin-5
chlorothiazide	Diuril
chlorthalidone	Thalitone
hydrochlorothiazide	HCTZ, Esidrix, Oretic, Microzide
indapamide	Lozol, Lozide
methyclothiazide	Enduron, Aquatensen
metolazone	Zaroxolyn
polythiazide	Renese

Antihypertensive – Nitrates

Generic	Brand
amyl nitrite	
isosorbide dinitrate	Isordil, Dilatrate-SR, Cedocard Sr, Coronex
nitroglycerin intravenous infusion	Tridil
nitroglycerin ointment	Nitrol, Nitro-BID
nitroglycerin spray	Nitrolingual
nitroglycerin sublingual	Nitrostat, Nitro-Quick
nitroglycerin sustained release	
nitroglycerin transdermal	Minitran, Nitro-Dur, Trinipatch
nitroglycerin transmucosal	Nitroguard

2 Pressor Medications

Generic	Brand
dobutamine	Dobutrex
dopamine	Intropin
ephedrine	
epinephrine	EpiPen, EpiPen Jr, Twinject, adrenalin
inamrinone	Amrinone
mephentermine	Wyamine
metaraminol	Aramine
midodrine	Orvaten, ProAmatine, Amatine
milrinone	Primacor
phenylephrine	Neo-Synephrine

3 Anticoagulant Medications

Generic	Brand
dalteparin	Fragmin
enoxaparin	Lovenox
fondaparinux	Arixtra
heparin	Hepalean
tinzaparin	Innohep
argatroban	
bivalirudin	Angiomax
lepirudin	Refludan
warfarin	Coumadin, Jantoven

4 Antiplatelet Medications

Generic	Brand
abciximab	ReoPro
aspirin/Dipyridamole	Aggrenox
aspirin	Ecotrin, Empirin, Halfprin, Bayer, ASA, Entrophen, Asaphen, Novasen
clopidogrel	Plavix
dipyridamole	Persantine
Eptifibatide	Integrilin
Ticlopidine	Ticlid
Tirofiban	Aggrastat

5 Diabetes-Related Medications

To aid in identifying these medications under categories, they are listed below:

Diabetes – Insulins

Generic	Brand
insulin	Apidra, Novolin, NovoLog, Humulin, Humalong, Lantus, Levemir, Novo-Rapid

Diabetes –Non-Insulin

Generic	Brand
acabose	Precose, Prandase
exenatide	Byetta
miglitol	Glyset
	ACTOPLUS Met

	Avandamet
	Glucovance
	Metaglip
metformin	Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet
pioglitazone	Actos
rosiglitazone	Avandia
nateglinide	Starlix
repaglinide	Prandin, Gluconorm
chlorpropamide	Diabinese
tolbutamide	Orinase, Tol-Tab
gliclazide	Diamicron, Diamicron MR
glimepride	Amaryl
glipizide	Glucotrol, Glucotrol XL
glyburide	Micronase, DiaBeta, Glynase, PresTab, Euglucon

AIGS Doppler-OCT Blood Flow Data Collection Form

Subject Study ID:		Investigator:	
Visit Code:		Coordinator:	
Photographer:		Eye (circle one)	Right Left
Date:		Time:	A.M. / P.M.

Dilating Eye Drops

Tropicamide	( ) Yes ( ) No
Phenylephrine	( ) Yes ( ) No

Systemic Medications
(See Chapter 19 Appendix 1 for classifications)

Antihypertensive - Beta Blocker	( ) Yes ( ) No
Antihypertensive - Calcium Channel Blocker	( ) Yes ( ) No
Antihypertensive - Diuretic	( ) Yes ( ) No
Antihypertensive - Nitrate	( ) Yes ( ) No
Pressor	( ) Yes ( ) No
Anticoagulant	( ) Yes ( ) No
Antiplatelet	( ) Yes ( ) No
Diabetes- Insulin	( ) Yes ( ) No
Diabetes- Non-Insulin	( ) Yes ( ) No

Biometric Measurements

Height (cm)	
Weight (kg)	
Blood Pressure	Systolic Diastolic
Arm blood pressure taken (circle one)	Right Left

Doppler OCT Scans

Pattern	Scan #	Quality
Blood Flow (Double Ring)	1	
	2	
	3	
	4	
	5	
	6	
3D Disk (6mm)	1	

Notes:

Clinical Site:_____

Date:_____

Participant ID:_____

Blood Flow Study Medical History Questionnaire
(to be filled out at the first Doppler OCT visit)

Has a doctor ever told you that you have any of the following conditions?	Yes	No
1. Diabetes Mellitus If yes, for how many years: _____	[ ]	[ ]
2. High blood pressure	[ ]	[ ]
3. Heart attack, coronary artery disease, or other heart disease	[ ]	[ ]
4. Stroke or transient ischemic heart attack	[ ]	[ ]
5. Carotid artery blockage	[ ]	[ ]
6. Peripheral vascular disease (poor circulation in arms or legs)	[ ]	[ ]
7. Migraine	[ ]	[ ]
8. Cold hands ("Raynaud's phenomenon")	[ ]	[ ]
9. Diabetic retinopathy	[ ]	[ ]
10. Have you smoked cigarette or used other tobacco products in the past 12 months?	[ ]	[ ]

List other medical conditions and eye conditions:

Blood Flow Study Medication Questionnaire
(to be filled out at every Doppler OCT visit)

	Yes	No
1. Do you take any medication for high blood pressure?	[ ]	[ ]

List medication:

2. Do you take any medication for a heart condition?	[ ]	[ ]

List medication:

3. Do you take any medication to thin your blood (examples: warfarin, asparin)?	[ ]	[ ]

List medication:

4. Do you take any medication for diabetes (examples: insulin, Glucotrol)?	[ ]	[ ]

List medication:

5: List other medications:

Interview conducted by: _____

DOCTORC Data Input Instructions

Introduction

The DOCTORC central database is designed to host both the patient information and blood flow result for multiple studies, including the AIGS study. To start the DOCTORC central database, visit the following link: https://clinicalresearch.ccf.org/forms/frmservlet?config=doctrf. Input your user name and password. If you do not have a user name, check with Sharon Bi at bis@ccf.org. After logging in, you will see an interface as shown in figure 1. Each Clinical Site is responsible for entering their patient information and visit information. The Doppler reading center is responsible for the input of the blood flow information. After the information is added, the data can be reviewed online or exported as an excel file.
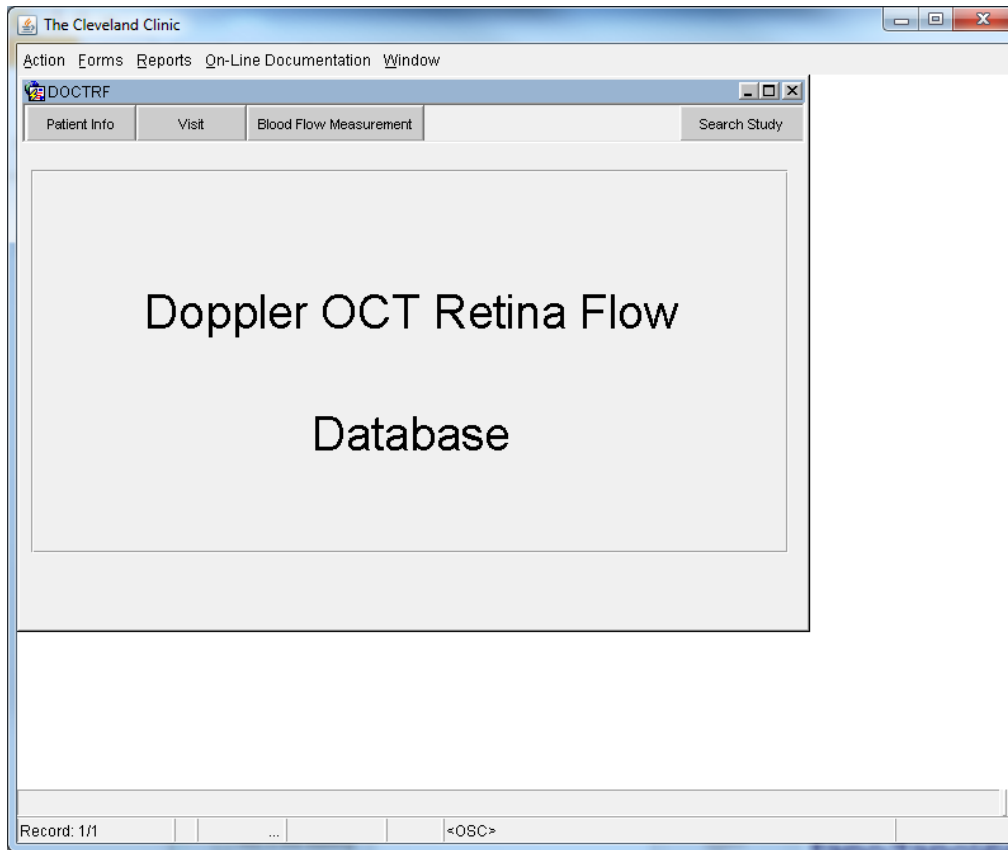
Figure 1. Main window of DOCTORC central database

Clinical Center:

Patient Information

Enter new patient information (figure 2) by clicking the **Patient Info** tab in figure 1. The following fields are required:

1. Site
2. Patient ID
3. Name Code
4. Study

5. Date of Birth
6. Gender
7. Native American, Asian, Pacific Islander, Black, White, Others and Ethnic
8. Weight (kg)
9. Height (cm)

Save the entered information by clicking **Action -> Save** or by clicking the **Save** icon.

Figure 2. Paitent Information

Visit Information

Note, if the patient has previously been entered in the database, the Patient Information step can be skipped.

Enter the visit information (figure 3) by clicking the **Visit** tab in figure 1.

a. Fill in the appropriate **Site**, and **Patient ID**. The **Study** field will automatically fill from the information input when the patient info was added to the database.

b. Fill in the **Visit Type** by either clicking the **Choose a Value from the List** button or typing the number in by hand.
c. Fill in the **Visit Date**
d. Select the appropriate answer in the drop-down menus for **Medications**.
e. Fill in the **IOP Determination** information and **Visual Acuity** information as in the Central Database.
f. Save the entered information by clicking **Action -> Save** or by clicking the **Save** icon.

Fgiure 3. Visit information page

Reading Center:

Enter the blood flow information (figure 4) by clicking the **Blood Flow Measurement** tab in figure 1.

a. Fill in the appropriate **Study** (i.e. 1000 for AIGS). If the study number is not known, hold down the **Ctrl** key and **L** to bring up a list of possible studies.
b. Select the appropriate **Site** from the drop down menu and fill in the 3-digit **Patient ID**.

c. Fill in the **Visit Type**, **Scan Date** and **Time**. The **Test Sequence** field will fill automatically. If the visit has not been added by the clinic, blood flow information cannot be entered until the visit is entered.

d. Fill in the following fields: **Valid**, **Average Signal Strength Index**, **Average Eye Movement**, **Valid Vessel Area**, **Number of Valid Scans**, **Total Retinal Blood Flow**, **Superior Hemisphere Blood Flow**, **Inferior Hemisphere Blood Flow**, **Venous Area**, **Venous Velocity**, **Arterial Area** and **Arterial Velocity** (See table below).

e. Save the entered information by clicking **Action -> Save** or by clicking the **Save** icon

Figure 4. Blood flow information input and review page

For entering the fields in step **d** using the data exported from the DOCTORC software, refer to the following table:

Field in DOCTORC Software Data Export	Field in the DOCTORC central database Blood Flow Measurement tab	Data Example in DOCTORC Software Data Export	Example Data in Central Database	Comment
Visit Info	Study ID	N/A	AIGS	Dataset name
Visit Info	Site ID	4100_1921_os_2011-06-14	USC	Determined by study
Visit Info	patient ID	4100_1921_os_2011-06-14	100	Determined by study
Visit Info	Eye	4100_1921_os_2011-06-14	OS column	OD/OS is input on same page for central database
Visit Info	Date	4100_1921_os_2011-06-14	6/14/2011	
Visit Info	Visit	4100_1921_os_2011-06-14		Determined by study
Grader	N/A	Tomy	N/A	
DOCTORC version	N/A	2.1.1.2	N/A	
Validated	Valid	Yes	yes	
Original Scan #	Number of scans read	6	6	Scans in this visit
Valid Scan#	Valid Scan	6	6	# of scans that passed the quality check
Valid Vein Area Ratio	Valid vessel area (%)	0.659216523	0.66	0-1
AVG SSI	Average Signal strength index	55.24199295	55.24	0-100
AVG Eye Movement	Average Eye Movement	32.34574127	32.35	0-1000
Angle-Doppler Correlation	N/A	0.303441375	N/A	
Equivlent Scan #	N/A	1.769230723	N/A	
Blood Flow(ul/min)	Total Retinal Blood Flow	43.48863983	43.5	
Superior Hemisphere Blood Flow(ul/min)	Superior Hemisphere Vein Blood Flow	24.36440849	24.4	
Inferior hemisphere Blood Flow(ul/min)	Inferior Hemisphere Vein Blood Flow	19.12423134	19.1	
Venous Area(mm^2)	Venous Area	0.048995044	0.049	
Venous Velocity(mm/s)	Venous Velocity	14.79355049	14.8	
Arterial Area(mm^2)	Arterial Area	0.040210348	0.040	
Arterial Velocity(mm/s)	Arterial Velocity	18.02547646	18.0	
Superior Hemisphere Vein Area(mm^2)	N/A	0.023800788	N/A	
Inferior Hemisphere Vein Area (mm^2)	N/A	0.025194256	N/A	

Review and Export

Researchers, coordinators and graders of the AIGS study can review the AIGS data or export the data to an excel file.

Click on one of the three tabs in figure 1 to review the corresponding page. Once in the desired page, click the query button in the menu toolbar bar (figure 5), input the site and study ID and then click the "execute query" button (to the right of the query button) to review the information of selected patients.
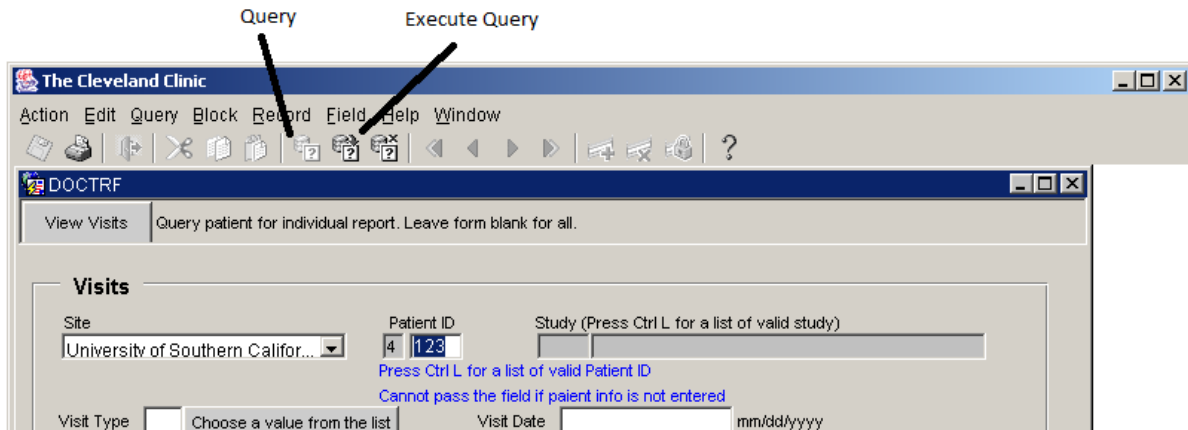
Figure 5. Review patient/visit/blood flow information

To export data into an excel file, click the "Search Study" button in figure 1. Select the AIGS study and click the button below to export the information (patient info, visit info, blood flow data, etc.) into an excel file. After selecting one of the "get ???" buttons, select "Save File" and choose a local path to save the file.

Figure 6. Exporting data

AIGS Clinical Check List	**Baseline Visit For <u>Normal</u> subjects**

Consent Patient
   ↓
Obtain History →   →   →   No refractive surgery, no corticosteroid use.
   ↓
Refraction →   →   →   →   Must be ≤+3.00 or ≥-7.00 spherical equivalent.
   ↓

Vision using EDTRS → →   VA of 20/40 or better in each eye
   ↓
Visual Field (HVF) → → →   2 VF's must be Within Normal Limits
 24-2 SITA Standard
   ↓
IOP Check →   →   →   →   IOP must be < 21mmHg in each eye.
   ↓
Gonioscopy →   →   →   Record in Schaffer Grade – If okay then dilate
   ↓   for stereo disk photography and dilated fundus
                                               exam, if not done at qualifying.

Central corneal Thickness measurement   Must be ≥ 0.500 mm to qualify.
   ↓
Axial length measurement →   Can be done using "IOL Master"
   ↓
Imaging to be performed:
(Can be done in any order)

HRTII →   →   →   →   2 scan sets
   ↓
GDX → →   →   →   3 ECC
   ↓
Stratus OCT →   →   →   2 sets of:
   ↓   Fast RNFL
                                               Fast Macular Thickness
                                               Fast Optic Disc

                                               3 sets of
RTVue OCT→   →   →   RNFL 3.45
   ↓   GCC (renamed) EMM5 (renamed) ONH
                                               (renamed)
                                               1 set of
                                               Disc 3D
                                               3 sets of
                                               Doppler 3D Disc 6x6mm - center
                                               Doppler Double ring blood flow – supranasal
                                               Doppler Double ring blood flow - infranasal

                                               4 Stereo pairs

Stereo Disk Photography or Nidek 3Dx →
   ↓

                                               Final determination of group subject is placed in.

Final Examination by Investigator →   →
(Dilated fundus exam, if not done at baseline)

Xgtukqp": 08

AIGS Clinical Check List

**12 month – 60 month follow-up visits
For <u>Normal</u> subjects**

Obtain History → → →

No refractive surgery, no corticosteroid use.

↓

Refraction → → → →

Must be ≤+3.00 or ≥-7.00 spherical equivalent.

↓

Vision using EDTRS → →

VA of 20/40 or better in each eye

↓

Visual Field (HVF) → →
24-2 SITA Standard

Is not required until 48 month visit, or if subject has undergone cataract surgery since baseline.

↓

IOP Check → → → →

IOP must be <21mmHg in each eye.

↓

Gonioscopy → → →

Not done

↓

Corneal Thickness measurement →

Not done

↓

Axial length measurement →

Not done

↓

Imaging to be performed:
(Can be done in any order)

HRTII → → → →

2 scan sets

↓

GDX → → → →

3 ECC

↓

Stratus OCT → → →

2 Sets of:
Fast RNFL
Fast Macular Thickness
Fast Optic Disc

↓

3 sets of
RNFL 3.45
GCC (MM7) (renamed) EMM5 (renamed) ONH (renamed)

RTVue OCT→ → →

3 sets of
Doppler 3D disc 6x6mm – centerDoppler
Double ring blood flow – supranasal
Doppler Double ring blood flow - infranasal

Only needs to be done at 48 month visit.

Stereo Disc Photography or Nidek 3Dx →

Re-evaluate if subject still qualifies for study.

↓

Final Examination by Investigator → →
(Dilated fundus exam, if not done at baseline)

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AIGS Clinical Flow Sheet   **Baseline Visit For <u>PG</u> and <u>GSPPG</u> subjects**

Consent Patient
  ↓
Obtain History →   →   →   Cataract surgery or refractive surgery okay.
  ↓

Refraction →   →   →   →   Must be ≤+3.00 or ≥-7.00 spherical equivalent.
  ↓

Vision using EDTRS →   →   VA of 20/40 or better in each eye
  ↓
Visual Field (HVF)   →   →   GSPPG = 2 VF's Borderline or Within Normal
 24-2 SITA Standard   Limits
  ↓
                                                 PG = 2 VF's Outside Normal Limits

IOP Check →   →   →   →   GSPPG OHT defined as IOP≥24mmHg in one
  ↓   eye and IOP ≥ 22mmHg in the fellow eye, on or
                                                 off glaucoma meds. May use previously
                                                 recorded pre-medication IOP.

Gonioscopy →   →   →   Record in Schaffer Grade – If okay then dilate
  ↓   for stereo disk photography and dilated fundus
                                                 exam, if not done at qualifying.

Corneal Thickness measurement
  ↓
Axial length measurement →   Can be done using "IOL Master"
  ↓
Imaging to be performed:
(Can be done in any order)

HRTII →   →   →   →   2 Sets
  ↓
GDX → →   →   →   3 ECC
  ↓
Stratus OCT →   →   →   2 sets of:
  ↓   Fast RNFL
                                                 Fast Macular Thickness
                                                 Fast Optic Disc

                                                 3 sets of
RTVue OCT → →   →   RNFL 3.45
                                                 GCC (renamed)
                                                 ONH (renamed) 1 set of
                                                 Doppler 3D disc 6x6mm – center
                                                 Doppler Double ring blood flow – supranasal
                                                 Dopper Double ring blood flow - infranasal

                                                 4 Stereo Pairs

Stereo Disc Photography or Nidek 3Dx →
  ↓
Final Examination by Investigator →   →   Final determination of group subject will be
(Dilated fundus exam, if not done at baseline)   placed in.

Xgtukqp": 0ß

AIGS Clinical Check List

Obtain History → → →

↓

Refraction → → → →

↓

Vision using EDTRS → →

↓

Visual Field (HVF) → →
24-2 SITA Standard

↓

IOP Check → → → →

↓

Gonioscopy → → →

↓

Corneal Thickness measurement

↓

Axial length measurement →

↓

Imaging to be performed:
(Can be done in any order)

HRTII → → → →

↓

GDX → → → →

↓

Stratus OCT → → →

↓

RTVue OCT → → →

↓

Stereo Disc Photography or Nidek 3Dx →

↓

Final Examination by Investigator → →
(Dilated fundus exam, if not done at baseline)

---

6 month – 60 month follow-up visits
For <u>PG</u> and <u>GSPPG</u> subjects
Check for any changes in medication or history.

Must be ≤+3.00 or ≥-7.00 spherical equivalent.

VA of 20/40 or better in each eye

GSPPG: If there is possible conversion (ie. OD Borderline at Baseline, OD Outside Normal Limits at 6 month) , VF must be done 2 more times to confirm.

PG: run glaucoma progression analysis program, if there is progression, get 2 more VF to confirm.

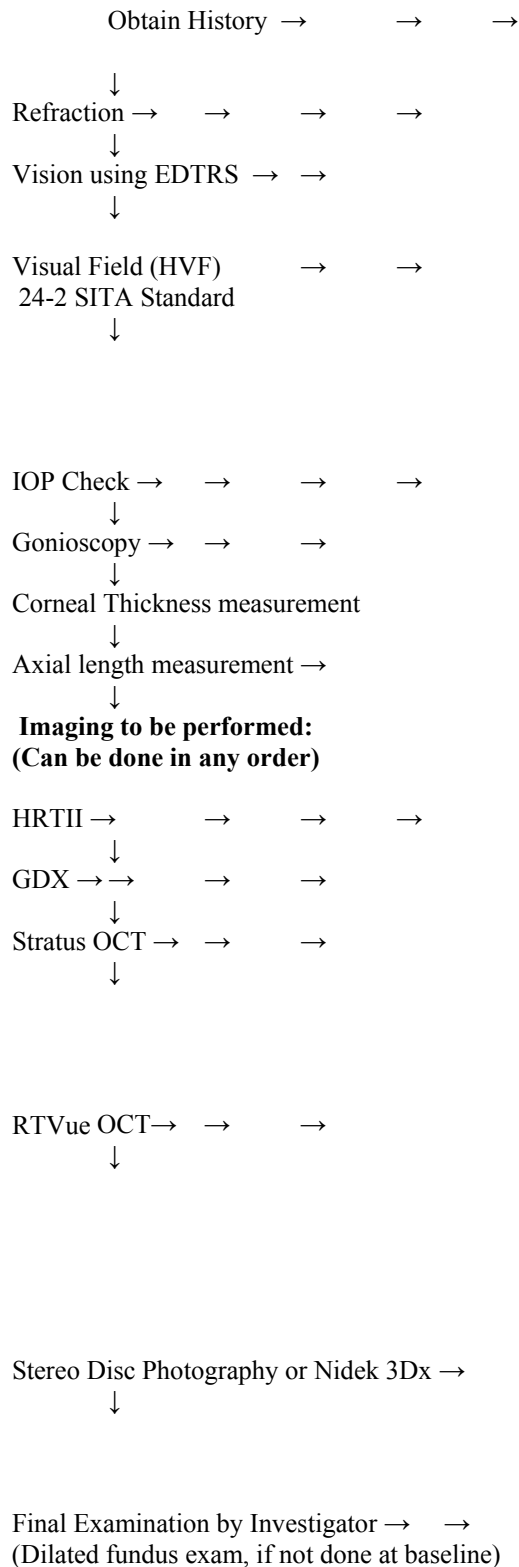Goldmann applanation protocol.

Not done

Not done

Not done

2 scan sets

3 ECC

2 sets of:
Fast RNFL
Fast Macular Thickness
Fast Optic Disc

3 sets of
RNFL 3.45
GCC (renamed)OHN (renamed)
Doppler 3D Disc 6x6mm – center
Doppler Double ring blood flow – supransal
Doppler Double ring blood flow - infranasal
Done at 12, 24, 36, 48, and 60 month follow-up visits.Done at 6, 18, 30, 42, and 54 month follow-up visits only if investigator notes a change in optic disc on clinical examination.

Re-evaluate if subject still qualifies for study.

Changes to AIGS MOP (Version 8.1)

This version of the AIGS Manual of Procedures was completed on March 30, 2012. AIGS MOP Version 8.1 supersedes Version 8.0. Changes specific to each chapter are listed below.

Chapter 13 – HRT II or III Procedures
13.4.2 Paper Files

…identify them.   In order to complete the HRT DCF either of the below printouts may be used:

- HRT follow up report: The parameter to be used is called *Topography Std. Dev.* and it is available in the table, the third line from the bottom;
- The OU report: The parameter is available on top left of each eye's image and is called *Quality: (SD);*

After reviewing one or both of the reports mentioned above, the HRT DCF field *Topography Standard Deviation < 40* should be completed by circling either "Yes" or "No" for the appropriate scan (1 or 2).

The HRT-DCF and scan printouts are then given to the clinical coordinator for review and filing. The coordinator should record the interpretation of the HRT test (abnormality, progression and topographic change analysis) on the patient tracking form.

Chapter 13 – HRT DCF

The HRD DCF was modified changing the last question on the DCF from

TCA < 40 to *Topography Standard Deviation < 40.*