

Ocular Hypertension Treatment Study

Manual of Procedures

Version 4.2

4/1/2017

Ocular Hypertension Treatment Study
 Manual of Procedures
 Version 4.2 – 4/1/2017

Summary of Changes

Section	Revision
2.3 2.5.1 2.6 5.1 5.2 5.13	Clarified that the OCT Reading Center will accept electronic OCT scans from OHTS and non-OHTS clinics
2.3	Added information pertaining to collecting data on deceased participants Added information pertaining to collecting data since the participant's last OHTS visit (interim data)
Appendix 2-K	Added Sample E-Mail to HIPAA Privacy Officer for approval to collecting data on deceased participants
Chapter11 Appendix	Added "Protocol for Submission Uploads" to clarify procedures for submitting all visual field data, including fields obtained at participant visit and those considered interim fields

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Version 3.0 – 4/1/2016

Summary of Changes

Section	Revision
2.3	<p>Corrected the reimbursement for travel to \$50 per visit</p> <p>Clarified stipulations for airfare & hotel for participants who live at least 100 miles from clinical center</p> <p>Corrected information collected from participants who are unwilling or unable to return to the OHTS clinic</p> <ul style="list-style-type: none"> -Interim OCT scans from OHTS clinics -Interim visual fields from OHTS & non-OHTS clinics -Telephone Medical History summary
2.4	<p>Added information for release of interim data and telephone medical history summary</p> <p>Added table to outline which forms are required by each participant scenario</p>
2.5	<p>Renamed Visit 1 to Core Schedule of Tests and Measures (Level 1 Data)</p> <p>Created separate tables for Core Measures (Level 1 data) and Level 2 & 3 measures</p> <p>Removed paragraph regarding participants who developed optic disc POAG and obtaining 2 sets of photographs at 2nd visit. Both sets of photographs are taken during the Core Measures (Level 1) visit.</p>
2.6	<p>Interim OCT scans and Visual Fields</p> <ul style="list-style-type: none"> -Interim OCT scans collected from OHTS clinics -Interim visual fields collected from OHTS and non-OHTS clinics <p>Clarification for methods to de-identify and transmit interim OCT scans and visual fields</p>
2.8	<p>Explain the order in which the Optic Disc Reading Center will review photographs</p>
2.10	<p>Changed word “current” to “OHTS 3”</p>
2.12	<p>Added route of transmission of OCT scans to reading center</p>
2.13	<p>Explained Endpoint Committee review of OCT scans</p>
2.14	<p>Explained Endpoint Committee review of OCT scans</p>
5.2	<p>Added tables for Level 1, Level 2 & Level 3 data collection</p>

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 Version 2.0 – 12/17/2015

Summary of Changes

Section 2.2 Section 2.3 Section 2.4	Added sentence regarding use of a legally acceptable representative “The LAR may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys, if approved by the local IRB.”
Section 2.4	Added Table to clarify consent process Removed instructions for obtaining Medicare Release form – OHTS will not obtain these releases from participants.
Section 2.5	Removed instructions for obtaining Medicare Release form – OHTS will not obtain these releases from participants. Removed statement that the Optic Disc Reading Center will notify the clinic within 7 days to obtain a 2 nd set of photographs. All photographs will be taken at the first visit.
Section 2.10	Removed statement that the Optic Disc Reading Center will notify the clinic within 7 days to obtain a 2 nd set of photographs. All photographs will be taken at the first visit.
Appendix 2-E	Updated sample informed consent with currently approved consent
Appendix 2-J	Replaced Medicare Release form with Sample Note to File for documenting LAR assistance with quality of life forms.

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1.0 Introduction

The goal of OHTS Phase 3 is to provide evidence-based, 20-year guidelines for the management of patients with ocular hypertension.

1.1 Specific Aims of OHTS Phase 3

Three key goals must be accomplished to develop evidence-based, 20-year guidelines for the management of patients with ocular hypertension:

1) Determine the 20-year incidence and severity of POAG in the OHTS cohort.

- 1a) Re-examine participants to determine the incidence of POAG using the same visual field and optic disc criteria and adjudication protocol as in OHTS Phase 1 and 2. To reflect current clinical practice, OCT measurement of peripapillary nerve fiber layer thickness and macular ganglion cell complex will be used in the secondary determination of POAG incidence. Incidence and severity of POAG will be determined for the overall sample as well as in the sub-group of self-reported African American participants (approximately 25% of the cohort).
- 1b) Determine the frequency and rate of POAG progression in the OHTS cohort. We will document the proportion of participants who progressed from POAG diagnosed by optic disc deterioration to perimetric POAG, from unilateral to bilateral POAG and from unilateral to bilateral perimetric POAG. Severity of visual field loss will be quantified by mean deviation (MD) of the better eye.

2) Develop a 20-year prediction model for stratifying OHT patients by their risk for developing POAG and, among those who developed POAG, a prediction model for the rate of visual field loss.

- 2a) Develop a 20-year prediction model for the risk of developing POAG. In addition to the published predictive factors, other potential predictive factors will be assessed including systolic and diastolic perfusion pressure, sleep apnea, body mass index, history of diabetes, myopia, axial length, optic disc hemorrhage, level of IOP (treated/untreated), variability of IOP, systemic medication usage (statins, beta blockers, ACE inhibitors) and genetic factors. Previously, we reported that the higher incidence of POAG among African American participants was largely due to larger baseline cup/disc ratio and thinner central corneal thickness. We will determine if this association still holds at 20 years.
- 2b) Develop a prediction model for the rate of glaucomatous visual field loss as measured by the change in mean deviation over time (slope of the curve). A prediction model will be developed for the rate of glaucomatous visual field loss that will evaluate baseline and intercurrent factors (listed above for developing POAG).

3) Determine the frequency and severity of self-reported functional limitations associated with POAG.

The frequency and severity of self-reported functional limitations (SF-36, NEI VFQ, Nelson glaucoma survey, self-reported falls and vehicle accidents, Owsley Driving Habits Survey) in participants who did/did not develop POAG will be compared to differentiate functional limitations associated with POAG from normal aging and other co-morbidities. Self-reported functional limitations will be correlated with socio-demographic factors and clinical measures (ETDRS visual acuity, Pelli Robson Contrast Sensitivity and mean deviation of the better eye). We will examine the association of the rate and duration of visual field loss on self-reported functional limitations.

1.2 Results of OHTS Phase 1

Prior to the Ocular Hypertension Treatment Study there was conflicting evidence as to whether early medical treatment to lower IOP was safe and effective in delaying or preventing the onset of glaucomatous damage in individuals with elevated intraocular pressure (a condition referred to as ocular hypertension). In 2002, OHTS reported that early medical treatment does indeed delay or prevent the onset of primary open-angle glaucoma (POAG) in ocular hypertensive individuals¹. The OHTS enrolled and randomized 1,636 participants with intraocular pressures (IOP) of ≥ 24 mmHg and ≤ 32 mm Hg in one eye, and ≥ 21 mm Hg and ≤ 32 mm Hg in the fellow eye to either treatment with commercially-available topical ocular hypotensive medication or to observation. At 60 months, there were 125 participants who developed POAG (89 randomized to observation, 36 randomized to medication) confirmed by November 8, 2001. The cumulative frequency of developing POAG was 4.4% in the medication group and 9.5% in the observation group². A follow-up paper in 2004 reported that early medical treatment also delays or prevents the onset of POAG in African Americans. At that time there were 148 participants who developed POAG (104 randomized to observation, 44 randomized to medication) in which the first suspicious date was on or before June 1, 2002, with final confirmation no later than September 11, 2003³.

Utilizing data from OHTS Phase 1, we created a prediction model to assess the risk that patients with ocular hypertension would develop POAG over the next 5 years. The model included baseline age, IOP, cup/disc ratio, central corneal thickness (CCT) and pattern standard deviation⁴. The model has good predictive accuracy (c statistic=0.75) and has been validated in the European Glaucoma Prevention Study⁵. The model has been widely utilized and has altered clinical practice in the U.S. and many other countries⁶⁻⁸. The model has allowed patients and clinicians to make evidence-based decisions about the frequency of examinations and tests and the potential benefit of early treatment.

The finding that CCT is a powerful predictor of the onset of POAG was an unexpected finding. One might assume that CCT has an effect on prognosis because it influences the measurement of IOP. However, the effect of CCT appears to be too influential to be explained by a 1 or 2mmHg misreading of IOP⁹. It is likely that CCT is a biomarker for other properties of the eye effecting prognosis (e.g. corneal hysteresis, ocular rigidity, lamina cribrosa structure and deformability).

1.3 Results of OHTS Phase 2

The OHTS Phase 1 definitively demonstrated that topical ocular hypotensive medication is effective in delaying or preventing the onset of POAG in participants with ocular hypertension, but did not answer one important question, “When should treatment be initiated?” In large part the answer depends on whether there is a penalty for delaying treatment. To answer this question, participants in the observation group who had completed 7 years of follow-up without ocular hypotensive medication started ocular hypotensive medication while the participants in the medication group continued medication. Eighty-eight percent (1,366 of the 1,558) of surviving participants signed a new consent form to participate in OHTS Phase 2 in 2002.

The treatment and follow-up were the same as in Phase 1. The same schedule of tests and measures as well as the same process for the ascertainment of the primary outcome were used in Phase 2. Data collection in OHTS Phase 2 concluded in March 2009.

After the initiation of treatment, the incidence of POAG in the observation group became equivalent to that in the medication group. The hazard ratio for randomization to medication in OHTS Phase 2 was 1.06 (95% CI 0.74-1.50; P=.77). The cumulative proportion of participants who developed POAG from the time of randomization to 13.0 years of follow-up was 0.22 (95% CI, 0.19-0.25) in the original observation group and 0.16 (95% CI, 0.13-0.19) in the original medication group (complementary log chi square p-value tested at 13.0 years, p=0.0089). The protective effect of treatment was observed for both glaucomatous visual field abnormality (p=0.016) and glaucomatous optic disc deterioration (p=0.0015). Treatment reduced the cumulative proportion of participants who developed POAG by 30%-40% at all levels of risk for developing the disease. The absolute number of POAG cases prevented was highest among participants at highest risk of developing POAG¹⁰. The incidence of POAG was higher in African American participants than other participants in OHTS 1 and 2. The cumulative proportion of African Americans developing POAG over 13 years was .28 vs .16 in the other participants. The increased incidence was associated with the larger baseline cup/disc ratio and thinner central corneal thickness in African Americans¹⁰.

Hispanic participants also had higher incidence of POAG than the overall group. The number of Hispanic participants was small which limits interpretation of the data, but the incidence of POAG in Hispanic participants was similar to the incidence in African American participants.

1.4 Impact of OHTS Phase 1 and 2

The results from OHTS had an immediate and profound effect on clinical practice world-wide. OHTS data were considered to be Level A1 evidence for the safety and efficacy of early medical treatment in patients with ocular hypertension. A list of OHTS publications is in Appendix A. The effect of treatment was greater in high risk patients and the OHTS prediction model performed well in separating patients at high and low risk for developing POAG. Delaying treatment had relatively little effect on the prognosis of patients at low risk. OHTS found that the prognosis was worse for African American participants with ocular hypertension. The higher

risk for African Americans was associated with larger baseline cup/disc ratio and thinner central corneal thickness.

Corneal thickness measurements were assigned a CPT Category 1 code by Medicare citing the Gordon et. al. 2002 publication...“procedure’s clinical efficacy is proven and documented”. A 95% random sample of the Medicare database 2003-2006 confirmed that pachymetry for patients with ICD-9 codes for open angle glaucoma or glaucoma suspect increased from 11.1% to 24.5% after the 2002 publication of the prediction model¹¹.

The major OHTS publications were among the most commonly cited manuscripts in Ophthalmology over the past decade. According to **Essential Science Indicators Citations**, 2 OHTS articles published in 2002 (Kass, et. al., 2002¹ and Gordon, et. al., 2002⁴) ranked in the top 10% of all papers published in clinical medicine, not just ophthalmology, as of 2007. Over the 15 year period from 1999 to 2014 the Kass 2002¹ manuscript was the most cited paper in ophthalmology (Cathy Sarli, Washington University Medical Library, personal communication). These publications have been incorporated into the Preferred Practice Guidelines of the American Academy of Ophthalmology, the American Optometric Association and many other national and regional organizations. ARVO abstracts with the key word “corneal thickness” more than doubled from 54 abstracts in 2002 the year of the OHTS publications to more than 100 abstracts thereafter.

Evidence from surveys suggests that OHTS has influenced the management of patients with ocular hypertension. Among 206 members of the American Glaucoma Society who responded to their survey, 96% in academic practice and 93% in private practice agreed to the statement, “My clinical practice has been significantly impact by (OHTS)”. Ninety-nine percent agreed or strongly agreed that they “routinely check central corneal thickness when evaluating patients with ocular hypertension⁸.” In separate survey studies of ophthalmologists, Boland et. al.⁷ and Mansberger⁶ concluded that the OHTS prediction model for the development of POAG enabled the ophthalmologists to make evidence-based treatment decisions which also reduced the variability between ophthalmologists in patient management.

The interactive web-site for estimating the risk of developing POAG has been used heavily world-wide. From 2006 to date, there have been 170,356 page views world-wide according to STATCOUNTER. In 2013, there were 23,907 page views – 2,915 were returning visitors. Six percent of the visitors spent 5-20 minutes on the site, 2.5% spent 20 minutes to an hour and 19% spent more than an hour per visit. The web-site attracted visitors world-wide – 574 visitors from Spain, 331 from India, 161 from Thailand and 158 from the Russian Federation. Pfizer Pharmaceuticals distributed hand held calculators with the OHTS Prediction Model to ophthalmologists and optometrists world-wide.

1.5 OHTS Phase 3

1.5.1 Public Health Significance

In all surveys, glaucoma is among the leading causes of blindness in the U.S. and worldwide¹²⁻¹⁶. It is estimated that more than 2.5 million people in the U.S. have glaucoma and that more than 130,000 persons are legally blind from the disease¹⁵. Population surveys indicate that fewer than 50% of those with glaucomatous visual field loss have received appropriate diagnosis and treatment¹⁷⁻¹⁹.

Glaucoma is the leading cause of blindness in African Americans²⁰⁻²⁴. In the Baltimore Eye Survey²⁵, the age-adjusted prevalence rates of POAG were four to five times higher in African Americans than in whites. The prevalence ranged from 1.2% in African Americans aged 40 through 49 years to 11.3% in those 80 years and older²³. These findings were confirmed in the Barbados Eye Study which reported a high prevalence and incidence of POAG among blacks in an Afro-Caribbean population^{18,24}. The prevalence of POAG in some Hispanic groups is similar to that of African Americans²⁶.

Ocular hypertension occurs in 4-7% of the people in the U.S. above age 40. Using data from the 2010 U.S. Census we estimate that 2.5-4.7 million people in the U.S. have ocular hypertension. Ocular hypertension is an important risk factor for the development of POAG and the only modifiable risk factor at present. The prevalence of ocular hypertension will rise in the coming decades with the aging of the baby boomer generation. The question is how to manage this large group of people in an effective and cost effective manner. There is a high cost to the individual and to society for examinations, tests and medications for ocular hypertension.

The current Preferred Practice Guidelines from the American Academy of Ophthalmology and the American Optometric Association recommend a frank discussion between clinicians and patients with OHT about the relative benefits and risks of the alternative management strategies so patients can participate in developing an appropriate plan of action. Frank discussions of alternatives and risks are universally accepted as part of good medical care. However, frank discussions are more productive if the patients and clinicians have high quality, long-term data to inform discussion.

1.5.2 Patient-Centered Care

Across medicine there is an attempt to increase the value and appropriateness of care and to diminish wasteful care. This approach has been given different names including personalized medicine, patient centered care, parsimonious medicine and evidence based medicine. While these terms are not strictly synonymous, they share several key features: 1) Risk stratification of patients. 2) Estimation of potential treatment benefit. 3) Estimation of the frequency and severity of potential adverse events. 4) Inclusion of shared patient-clinician decision making and 5) Inclusion of patient-reported outcomes as a key measure of treatment success. The study we propose, OHTS Phase 3, will provide 20-year data so that patient-centered care will be possible for patients with OHT.

Applying principles of patient-centered care to the management of patients with ocular hypertension will require additional long term follow-up of patients to determine the incidence and severity of POAG, a better prediction model for determining who is at high or low risk of developing POAG, a model for predicting the rate of visual field loss and a better understanding of the correlation of visual loss from POAG with participant reported functional limitations.

1.5.3 Long-term Follow-up

We are proposing to extend the OHTS follow-up to 20 years or more. The only previous 20-year studies of ocular hypertension were published more than 25 years ago, were conducted on racially and ethnically homogeneous cohorts in Scandinavia, utilized examination methods and tests no longer in use and were limited by small sample sizes^{27,28}. A 20-year follow-up has relevance to patients. For OHT patients in their sixties and seventies, 20 years approaches median life expectancy. For patients in their forties and fifties, 20 years is approximately 50% of median life expectancy. In 2008/2009, approximately 83% of the OHTS cohort had not developed POAG over a mean 13 years follow-up. On this basis, we recommended that the majority of OHT patients could be followed without early preventative medical treatment. This recommendation requires the test of long-term follow-up.

1.5.4 Risk Stratification

Risk stratification is a key to practicing patient-centered medicine. An accurate model to stratify risk is necessary for patients and clinicians to make evidence-based decisions about the appropriate frequency of examinations and tests and the value of early treatment. These studies determined incidence only and did not report on progression or visual limitations. Evidence-based models allow for risk adjusted allocation of resources which will reduce patient and clinician burden while reducing healthcare expenses. OHTS developed a predictive model (based on baseline age, intraocular pressure, cup to disc ratio, central corneal thickness and pattern standard deviation) that performs reasonably well in separating ocular hypertensive patients at high risk and low risk of developing POAG. This model was independently validated in the European Glaucoma Prevention Study⁵ and has been useful to clinicians and patients in making decisions about the frequency of examinations and tests and the potential benefit of early treatment⁶⁻⁸. However, the OHTS prediction model in widest use estimates the 5 year risk of developing POAG. We know that most patients with ocular hypertension will live with this condition for far longer than 5 years. We believe the model can be improved by extending the follow-up time and including other baseline and intercurrent risk factors such as optic disc hemorrhage, level of intraocular pressure (treated/untreated), long-term variability of intraocular pressure, diabetes mellitus, systolic and diastolic perfusion pressure, body mass index, sleep apnea, myopia, axial length, systemic medication usage (beta blockers, statins, ACE inhibitors) and genetic factors. In similar fashion, we will develop a model for the rate of glaucomatous visual field loss. The better the prediction model, the more information patients and clinicians will have to make informed decisions and practice patient-centered medicine.

1.5.5 POAG and Functional Limitations

While developing POAG is an important clinical landmark, the true goal of managing patients with ocular hypertension is to prevent the development of functional limitations from POAG. In 2013, the U.S. Preventative Services Task Force (USPSTF) concluded that “there was inadequate evidence that treatment of increased IOP or early asymptomatic POAG reduces the number of persons who will develop impaired vision and quality of life....Treatments that are effective in reducing intraocular pressure have potential harms and their effectiveness in reducing patient perceived impairments in vision related functions is uncertain.” Additionally the task force concluded that “more evidence is needed on the link between the intermediate glaucoma outcome of optic nerve damage and visual field loss and the health outcomes of visual disability and patient reported outcome”. The study we propose will address many of the gaps in knowledge identified by the USPSTF.

In re-examinations in 2015/16, we will have a median follow-up of 10 years (range 1-20 years) for the participants who developed POAG in OHTS. We will determine the proportion of participants who report functional limitations associated with POAG 20 years after study enrollment and 10 years (median) after the diagnosis of POAG. We will also have concurrent controls who did not develop POAG over 20 years. This will enable us to determine the excess burden of participant-reported functional limitations associated with POAG.

1.5.6 Race/Ethnicity

Glaucoma is the leading cause of irreversible blindness in African Americans^{13,18,21-24,29-32}. In the Baltimore Eye Study, the prevalence of POAG was 4 to 5 times higher among participants of African ancestry than European ancestry. We need more information about the rate of progression of glaucoma in African Americans especially long term. The OHTS enrolled 408 participants of African ancestry, 22% (91 of 408) of whom developed POAG by 2009. As of 2008/2009, these participants had completed visual field testing every 6 months for a median of 7 years prior to developing POAG and a median of 5 years after developing POAG. The median follow-up after diagnosis of POAG will be 10-11 years in 2015/16.

The OHTS prediction model stated that some African Americans are at low risk for developing POAG and could be followed without treatment. Given the high incidence and prevalence of POAG in African Americans we must determine the true risk profile out to 20 years. We must ensure that the practice guidelines derived from OHTS are correct for this minority population which suffers such a heavy burden from POAG. OHTS can make a unique and important contribution to the understanding of the risk of developing POAG, the rate of progression of glaucomatous visual loss and its impact on functional limitations and quality of life in African Americans. To our knowledge, the only other current prospective study on glaucomatous progression in African Americans is the ADAGES Study which has followed 686 African Americans for approximately 4-5 years.

1.5.7 Statistical Power

One might be concerned that OHTS does not have the statistical power to answer the research questions posed. One might think that these questions are better answered in a large population-based study. However, the large sample sizes of population-based studies do not necessarily give them greater statistical power. While the total sample size of the OHTS is small compared to population-based studies, OHTS has a larger number of incident POAG cases than any population-based study. Using the harmonic mean ($n' = 2n_{ANB} / (n_A + n_B)$), it is possible to estimate the statistical power of studies with normal equally varying samples of cases and controls of different sample size³³. We computed the harmonic mean for OHTS and for population-based studies that reported incident open-angle glaucoma. At the last data freeze in 2009, OHTS had 279 participants who developed definite POAG in one or both eyes and 1,357 controls. Using the harmonic mean, the effective sample size of the OHTS is equivalent to 462 cases and 462 controls and, if we assume 121 additional incident POAG cases by 2015/16, this would increase to 604 cases and 604 controls. In Table 1, the effective sample size of OHTS is compared to population-based studies reporting incident open-angle glaucoma. These comparisons assume that all other factors affecting statistical power are constant across studies.

Study	N Sample	Percent African Ancestry	N Incident Probable or Definite OAG	Years after Baseline	N' Equivalence to 2 groups of cases and controls of equal size
OHTS 2008	1,636	25%	279	13	462
OHTS 2015-2016	1,636	25%	400	20	604
Blue Mountain Eye Study Kawasaki, 2013 ³⁴	2,417	<1%	82	10	158
Los Angeles Latino Eye Study, 2012 ³⁵	3,772	Not included	87	4-5	170
Ponza Eye Study Cedrone, 2012 ³⁶	411	Not reported	15	12	29
Beijing Eye Study Wang 2012 ³⁷	3,251	0%	23	5	46
Rotterdam Study Ramdas, 2011 ³⁸	3882	0%	108	9.7	200
Barbados Eye Studies Nemesure, 2007 ³⁹	3,222	93%	125	9	240
Visual Impairment Project Mukesh, 2002 ⁴⁰	2,594	0%	62 39 possible, 13 probable 10 definite	4.5	121

The large number of incident POAG cases gives OHTS more statistical power than larger population-based incidence studies to identify risk factors associated with the development of

POAG and glaucomatous functional limitations. (See MOP Chapter 8 “Statistical Issues and Analyses”).

1.6 Potential Impact of OHTS Phase 3

OHTS Phase 1 and 2 have changed the management of patients with OHT in the U.S. and most other developed nations. We anticipate OHTS Phase 3 will have similar impact. We have an outstanding team of Investigators, Coordinators, Photographers and Technicians, most of whom have been with the study since its inception (Chapter 2 Appendix). The three Reading Centers have the same Directors as in OHTS Phase 1 and 2 and utilize the same process to assess outcome data. This team has produced high quality data and publications which have been widely cited and have had major impact. We have a large cohort of well-studied, participants who are available for additional examinations and tests. We have the largest inception cohort of participants with POAG (n=279) as of 2009 ever reported. We also have a large concurrent control group (n=1357) of participants who underwent the same battery of examinations and tests and who did not develop POAG.

OHTS Phase 3 will produce 20-year evidence-based guidelines for the management of patients with OHT. This will include the incidence and severity of POAG over a 20-year follow-up in a cohort including 25% self-identified African Americans. We will develop a 20-year risk model for developing POAG and a model for the rate of progression of POAG. These data will be of great relevance to patients and clinicians in establishing evidence-based, patient-centered care. Patients and clinicians will have information to inform choices about the optimal frequency of examinations and tests and the potential benefit of early medical treatment. This should reduce patient and clinician burden and conserve medical resources. Direct costs of glaucoma treatment were estimated to be \$5.8 billion in 2013 (<http://costofvision.prevblindness.org/cost/direct-costs/medical-costs-by-disorder>). The risk model for progression of visual field loss developed from an inception cohort of patients who developed POAG should aid patients and clinicians in deciding about the appropriate intensity of treatment based on individualized risk for slow vs. rapid progression.

OHTS Phase 3 will give us a much better understanding of the frequency and severity of functional limitations due to POAG and how they relate to changes in clinical measures of vision (visual acuity, visual field and contrast sensitivity) over time.

Some experts have opined that patients with OHT who are destined to develop POAG do so in the first few years after diagnosis. A 20-year follow-up should determine whether this hypothesis is correct or not.

OHTS Phase 3 will be very helpful in determining the effect of POAG on the utilization of medical resources. We will obtain permission to query the Medicare database to compare resource utilization in patients with/without POAG.

1.7 Innovation

- Provide evidence-based, 20-year recommendations for the management of ocular hypertensive patients using current clinical assessment tools. For patients in their sixties and seventies, a 20-year time span approaches mean life expectancy. For patients in their forties and fifties, a 20-year time span is approximately 50% of the mean life expectancy.
- Determine the incidence and severity of POAG in a racially mixed inception cohort of ocular hypertensive patient over a 20-year period of time. The OHTS inception cohort has included approximately 25% African Americans from study onset.
- Develop a prediction model for the rate of visual field loss (mean deviation) from the onset of POAG diagnosed using a standardized protocol.
- Provide longitudinal data on incidence and severity of patient-reported functional limitations using an inception cohort with a median of 10 years after POAG diagnosis. While developing POAG is an important clinical landmark, the true goal of management is to prevent ocular hypertensive patients from developing functional limitations that impede activities of daily living, reduce independence and increase the incidence of falls and accidents.
- Acquire consent to search Medicare records to compare health care utilization in OHTS participants who did/did not develop POAG. This approach is innovative because the validity of the diagnosis is protected by using the OHTS definition of POAG rather than the ICD-9 or ICD-10 code which may or may not be correct.

1.8 Data Sharing

OHTS has already shared data to support 16 other studies. We continue to receive 3-5 requests per year to share data with outside investigators. A 20-year follow-up with additional endpoints will greatly aid investigations into a variety of subjects including: 1) the incidence and rate of structural and functional changes in POAG, 2) structure-function relationships at different stages of POAG, 3) genetic influences on the development and progression of POAG, 4) the utilization of health care resources related to POAG, 5) the optimal timing and frequency of examinations for patients with ocular hypertension, and 6) the prognosis and response to medical treatment of African American patients with ocular hypertension and POAG.

One of the primary methods for dissemination and translation of OHTS results into clinical practice is through the OHTS web-based prediction model for the development of POAG. We will assess new clinical factors that might improve the prediction model and modify the software to allow re-calculation of risk to reflect changes in baseline and intercurrent factors. This will allow the clinicians to refresh the patient's risk status dynamically.

OHTS investigators have been and remain committed to widespread sharing of resources to facilitate research. We will continue to commit substantial resources to facilitate data sharing including customized datasets and personnel support in addition to a public website documenting the protocol, case-report forms annotated with variable names, and SAS formats and output of summary data for the purpose of replication. All articles from the Coordinating Center are

annotated to facilitate replication and transparency such that numeric values can be tracked to a directory with SAS program code and specific dataset freeze.

Who will have access to OHTS data? The Executive/Steering Committee reviews data requests primarily to minimize overlap in study hypotheses and to insure scientific integrity. The initial request is a concept letter stating the study hypotheses and data requested. If approved, a data use agreement is signed which states the hypotheses, data requested, specifies funding sources and acknowledgments and requests a draft copy of the manuscript prior to submission. The data use agreement is signed by the requester, the Study Chair and the Coordinating Center Director.

To date, OHTS data have supported 16 projects, ten of which were NIH funded. Seven of the investigators were early stage investigators. We continue to receive 3-5 requests annually for OHTS data. Details of OHTS data sharing are given below. The value of the OHTS dataset will be enriched by 20 year data on POAG incidence and longitudinal structural and functional measures collected concurrently with patient-reported limitations in visual function and quality of life.

Table A.1 OHTS Resource Sharing

	Study	Primary Investigator **Early stage investigator	Status
1.	R01 EY02037 Effect of Topical Ocular Hypotensive Agents on the Corneal Endothelium in Eyes with Ocular Hypertension	Bourne, W **Herman, D Mayo Clinic	Completed
2.	1 R03 EY015498-01 EGPS/OHTS validation of prediction model for the development of primary open angle glaucoma ^{5,41}	Miglior, S University of Milano-Bicocca	Completed
3.	Longitudinal and cross –sectional analyses of visual field progression in participants of the Ocular Hypertension treatment study ⁴²	Artes, P Chauhan, B Dalhousie University	Completed
4.	R01 EY019117 Confocal Scanning Laser Ophthalmoscopy ⁴³⁻⁴⁶	**Zangwill, L UC-San Diego	Completed
5.	R03 EY017862-01 Development of a Vision Specific Utilities Elicitation Method ^{47,48}	**Kymes, S Washington University School of Medicine	Completed
6.	COA Change in Mean Deviation Project: Value of IOP Model ⁴⁹	**Kymes, S Washington University School of Medicine	Completed
7.	5R21EY019117-02 OHTS and EGPS: Glaucoma Detection using Confocal Scanning Laser Ophthalmoscopy	**Zangwill, L UC-San Diego	Completed
8.	R01 EY018825-01A1 Genetics of Quantitative Traits Associated with Glaucoma	**Fingert, J et. al. University of Iowa	Active

9.	R21 EY019521-01 Evaluation of the Frequency of Visual Field Testing in Ocular Hypertensives	**Kymes, S Washington University School of Medicine	Completed
10.	R01 EY017299 Computer Analysis of Optic Disc Images in Glaucoma	Stone, R University of Pennsylvania	Active
11.	Pharmacogenomics study in OHTS 1 and 2 participants treated initially with beta blocker or prostaglandins	***Moroi, S University of Michigan	Active
12.	Analyses of visual field progression ⁵⁰⁻⁵⁴	Demirel, S Devers Eye Institute	Active
13.	R21 EY019954-02 Peripapillary Atrophy Progression During the Ocular Hypertension Treatment Study	**Budenz, D University of Miami	Active
14.	1R01 EY023187-01 Genetic Determinants of Optic Nerve Head Structure	**Scheetz, T Fingert, J Abramoff, M University of Iowa	Active
15.	Refinement of point-wise linear regression criteria for determining glaucoma progression	Kummett, C University of Iowa	Active
16.	Does improved contrast sensitivity with IOP lowering necessarily indicate reversible glaucoma-induced dysfunction?	Anderson, A The University of Melbourne	Completed
17.	Compare the effectiveness of two or more types of topical ocular hypertension medication on lowering intraocular pressure (IOP) and reducing the incidence of primary open-angle glaucoma (POAG).	Kempen, J Joffe, M University of Pennsylvania	Active
18.	Validating the dynamic structure-function model in the Ocular Hypertension Treatment Study (OHTS) cohort	Racette, L Indiana University	Active

What data will be shared? All data collected in OHTS from the time of study enrollment will be shared – clinical tests and measurements, clinical and medical history, visual fields, optic disc images and genomic data. At the conclusion of OHTS Phase 3, de-identified 20-year follow-up data will be merged into de-identified OHTS Phase 1 and 2 datasets currently available. De-identification includes assigning a random participant ID, a random clinic ID, setting all date values relative to the day of randomization (day 0) and reporting age as an integer value at randomization.

When will the data be shared?

Some data can be shared before the study closes so long as the request does not conflict with the study goals and compete for resources. Other data will become available following publication of the specific aims.

Where will the data to be shared be located?

The clinical and image data are stored on secure servers at Washington University School of Medicine, St. Louis, MO while the study is funded. Genetic data and selected clinical data are stored at dbGaP. Instructions for requesting data will be placed on the OHTS public website.

Appendix 1-A OHTS Publications

Current to July 31, 2015

1. Gordon MO, Kass MA and the Ocular Hypertension Treatment Study (OHTS) Group: [The Ocular Hypertension Treatment Study: Design and Baseline Description of the Participants](#). Arch Ophthalmol 1999; 117:573-83. [PMID: 10326953](#).
2. Keltner JL, Johnson CA, Quigg JM, Cello KE, Kass MA, Gordon MO for the Ocular Hypertension Study Group. [Confirmation of Visual Field Abnormalities in the Ocular Hypertension Treatment Study](#). Arch Ophthalmol 2000; 118:1187-94. [PMID: 10980763](#).
3. Piltz J, Gross R, Shin DH, Beiser JA, Dorr DA, Kass MA, Gordon MO and the Ocular Hypertension Treatment Study Group. [Contralateral Effect of Topical \$\beta\$ -Adrenergic Antagonists in Initial One-eyed Trials in the Ocular Hypertension Treatment Study](#). Am J Ophthalmol 2000; 130:441-53. [PMID: 11024416](#).
4. Brandt JD, Beiser JA, Gordon MO, Kass MA and the Ocular Hypertension Treatment Study (OHTS) Group. [Central Corneal Thickness in the Ocular Hypertension Treatment Study \(OHTS\)](#). Ophthalmology 2001; 108:1779-88. [PMID: 11581049](#).
5. Feuer WJ, Parrish RK, II, Schiffman JC, Anderson DR, Budenz DL, Wells MC, Hess DJ, Kass MA, Gordon MO, and the Ocular Hypertension Treatment Study Group. [The Ocular Hypertension Treatment Study: Reproducibility of Cup/Disk Ratio Measurements Over Time at an Optic Disc Reading Center](#). Am J Ophthalmol 2002; 133:19-28. [PMID: 11755836](#).
6. Johnson CA, Keltner JL, Cello KE, Kass MA, Gordon MO, Budenz DL, Gaasterland DE, Werner E, and the Ocular Hypertension Study Group. [Baseline Visual Field Characteristics in the Ocular Hypertension Treatment Study](#). Ophthalmology 2002; 109:432-7. [PMID: 11874743](#).
7. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JK, Miller JP, Parrish, RK, Wilson MR, Gordon MO for the Ocular Hypertension Treatment Study Group. [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. [PMID: 12049574](#). [Editorial].
8. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JK, Miller JP, Parrish RK, Wilson MR, Kass MA for the Ocular Hypertension Treatment Study Group. [The Ocular Hypertension Treatment Study: Baseline Factors That Predict the Onset of Primary Open-Angle Glaucoma](#). Arch Ophthalmol 2002; 120:714-20. [PMID: 12049575](#).
9. Keltner JL, Johnson CA, Cello KE, Edwards MA, Bandermann SE, Kass MA, Gordon MO for the Ocular Hypertension Study Group. [Classification of Visual Field Abnormalities in the Ocular Hypertension Treatment Study](#). Arch Ophthalmol 2003;121:643-50. [PMID: 12742841](#).

10. Zangwill LM, Weinreb RN, Berry CC, Smith AR, Dirkes KA, Coleman AL, Piltz-Seymour JR, Liebmann JM, Cioffi GA, Trick G, Brandt JD, Gordon MO, Kass MA, for the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. [Racial Differences in Optic Disc Topography: Baseline Results From the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study](#). Arch Ophthalmol 2004; 122:22-8. [PMID: 14718290](#).
11. Zangwill LM, Weinreb RN, Berry CC, Smith AR, Dirkes KA, Liebmann JM, Brandt JD, Trick G, Cioffi GA, Coleman AL, Piltz-Seymour JR, Gordon MO, Kass MA and the OHTS CSLO Ancillary Study Group. [The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study: Study Design and Baseline Factors](#). Am J Ophthalmol 2004; 137:219-27. [PMID: 14962409](#).
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2.0 Introduction OHTS 20-Year Follow-up Study (Phase 3) Protocol

The true goal of managing patients with ocular hypertension is not just to prevent the onset of POAG but to prevent functional limitations associated with the disease. Given the large number of patients with ocular hypertension, reaching this goal requires risk stratification to use medical resources in a cost-effective manner.

OHTS Phase 3 will re-examine study participants 20 plus years after enrollment to document clinical status and the incidence and severity of self-reported functional limitations. The 279 participants who developed POAG in OHTS Phase 1 or 2 will have more than 10 years of post-POAG follow-up by Phase 3. The timing of re-examination at 20 years is meaningful because 20 years approaches the median life expectancy of OHT patients in their 60's and 70's and half the median life expectancy of patients in their 40's and 50's. For the first time, patients with ocular hypertension and clinicians will have high quality data about the long-term risk of developing POAG and functional limitations associated with the disease. These data will facilitate patient-centered care so that patients and clinicians can decide on the appropriate frequency of tests and examinations and the potential benefit of preventative treatment.

2.1 Specific Aims of OHTS Phase 3

Three key goals must be accomplished to develop evidence-based, 20-year guidelines for the management of patients with ocular hypertension:

- 1) Determine the 20-year incidence and severity of POAG in the OHTS cohort.**
 - 1a) Re-examine participants to determine the incidence of POAG using the same visual field and optic disc criteria and adjudication protocol as in OHTS Phase 1 and 2. To reflect current clinical practice, OCT measurement of peripapillary nerve fiber layer thickness and macular ganglion cell complex will be used in the secondary determination of POAG. Incidence and severity of POAG will be determined for the overall sample as well as in the sub-group of self-reported African American participants (approximately 25% of the cohort).
 - 1b) Determine the frequency and time frame of POAG progression in the OHTS cohort. We will document the proportion of participants who progressed from POAG diagnosed by optic disc deterioration to perimetric POAG, from unilateral to bilateral POAG and from unilateral to bilateral perimetric POAG. Severity of visual field loss will be quantified by mean deviation (MD).
- 2) Develop a 20-year prediction model for stratifying OHT patients by their risk for developing POAG and, among those who developed POAG, a prediction model for the rate of visual field loss.**
 - 2a) Develop a 20-year prediction model for the risk of developing POAG. In addition to previously published predictive factors, other potential predictive factors will be assessed including systolic and diastolic perfusion pressure, sleep apnea, body mass index, history of diabetes, myopia, axial length, optic disc hemorrhage, level of IOP

(treated/ untreated), variability of IOP, systemic medication usage (statins, beta blockers, ACE inhibitors) and genetic markers. Previously, we reported that the higher risk of developing POAG among African American participants was largely due to larger baseline cup/disc ratio and thinner central corneal thickness. We will determine if this association still holds at 20 years.

- 2b) Develop a prediction model for the rate of glaucomatous visual field loss as measured by the change in mean deviation over time (slope of the curve). A prediction model will be developed for the rate of glaucomatous visual field loss that will evaluate baseline and intercurrent factors (listed above for developing POAG).

3) Determine the frequency and severity of self-reported functional limitations associated with POAG.

The frequency and severity of self-reported functional limitations (SF-36, NEI VFQ, Nelson glaucoma survey, self-reported falls and vehicle accidents, Owsley Driving Habits Survey) in participants who did/did not develop POAG will be compared to differentiate functional limitations associated with POAG from normal aging and other co-morbidities. Self-reported functional limitations will be correlated with socio-demographic factors and clinical measures (ETDRS visual acuity, Pelli Robson contrast sensitivity, mean deviation) of the eye with the better mean deviation. We will examine the association of the rate and duration of visual field loss on self-reported functional limitations.

2.2 Participant Eligibility

The goal in the 20-year follow-up study is to examine all surviving participants randomized to OHTS. This includes participants who did not enroll in OHTS Phase 2 and participants who are unable to perform some study tests and measures. Almost all participants should be able to complete quality of life surveys which are an important outcome in OHTS Phase 3. Every effort will be made to complete all clinical tests on all participants. Quality of life surveys will be completed at follow-up visits or by telephone for participants unable/unwilling to return for follow-up visits. A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

2.3 Contacting Participants, Visit Completion and Retention

The Clinical Center Coordinator will contact participants, schedule study visits and help arrange transportation. The Clinical Center Coordinator should first try to contact participants who are not currently active at the OHTS Clinical Center. Several attempts should be made by e-mail, postal mail and by telephone to contact participants at various times of day, days of the week and months of the year. If these attempts are unsuccessful, contact family and friends for updated contact information. If these attempts fail, the Clinical Center Coordinator should notify the Coordinating Center to request assistance from a professional tracing service. The professional service will query several databases, including Lorton Data, Intelius, and TransUnion Credit

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Bureau among others, for current address/telephone number as well as attempt to establish the participant's vital status.

Patients who are currently being followed in the Clinical Center should be contacted to explain OHTS Phase 3, to schedule study visits, to arrange transportation and to make sure the participant has adequate time to complete the OHTS examination. Participants will be provided \$25 total for lunch for themselves and their drivers/visit if applicable, the costs of transportation up to \$50/visit and a \$50 stipend/visit (if permitted by the local IRB).

Every effort should be made to attain 100% visit completion rate. Because transportation to the Clinical Center can be a serious impediment to participants whose median age will be 75 by the time of OHTS Phase 3, the study will provide up to \$50 for transportation for each visit. If the participant lives more than 100 miles from the Clinical Center, the Clinical Center should contact the Coordinating Center to consider the possibility of providing the cost of airfare and/or of completing examinations at an OHTS Clinical Center closer to the participant.

Participants who are unable/unwilling to return to the clinical center can give verbal consent to complete telephone QOL surveys and written consent by postal mail to release interim electronic OCT scans, VF tests from OHTS and non-OHTS clinics and a medical history summary either completed by a clinician or via telephone interview. The LAR may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys and Medical History Summary if approved by the local IRB.

The Clinical Center Coordinator should attempt to collect VF tests, OCT scans and medical history for participants who are deceased since March 2009. The Clinical Center Coordinator will need to alert the local IRB and HIPAA Privacy Officer that they intend to collect these data. A sample e-mail to the HIPAA Privacy Officer appears as Appendix 2-K. The deceased participant's next of kin or power of attorney will need to sign a Medical Release form. We do not need to collect consent for deceased participants; the consent use is limited to participants who are alive.

The Clinical Center Coordinator should attempt to collect interim data for participants who had a visual field conversion in OHTS 1 and 2, visual field conversion in OHTS 3, are unable or unwilling to come to complete an OHTS 3 visit or for participants who died after March 2009 (end of OHTS 2). Interim data consists of visual fields, electronic OCT scans and medical history completed by a clinician or via telephone interview by the Clinical Center Coordinator. The participant or their LAR will need to sign an informed consent form and a Medical Release form.

2.4 Education and Informed Consent

The Clinical Center Investigator and/or the Clinical Center Coordinator must educate the participant about the study in detail, answer all questions and secure written consent for participation (Appendix 2-E – Consent Form). The flyer describing OHTS Phase 3 and study web page URL should be given to the participant along with a copy of the consent form that is dated and signed by the participant or LAR and person who obtained consent at the Clinical

Center. Participants and family members are encouraged to contact the Clinical Center Investigator or the Clinical Center Coordinator with any questions that arise at any time. The consent form must be stored in HIPAA compliant secure files separate from research data.

Participants can agree to participate in the following components of OHTS:

1. All OHTS Phase 3 examinations, tests and measures including release of OCT scans.
Request the participant to sign Consent to Participate in Phase 3 Examination (Appendix 2-E).
2. If the participant developed visual field POAG in OHTS Phase 1 or 2 or is found to have developed visual field POAG in OHTS Phase 3, request the participant to sign the release of visual field tests from OHTS and non-OHTS clinics and OCT scans taken at an OHTS clinic since their last OHTS visit to document interim changes (Appendix 2-I).
3. If the participant is unable/unwilling to return to the Clinical Center for examination, the participant can give: verbal consent to complete telephone QOL Survey (Appendix 2-G); written consent by postal mail for release of visual fields, OCT scans (Appendix 2-I), medical history summary.
4. A LAR may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys and Telephone Medical History Summary if approved by the local IRB. A Note to File should be placed in the participant’s chart to document the assistance from the LAR with completion of the Quality of Life surveys and Telephone Medical History Summary (Appendix 2-J).

1. Patient Comes to Clinical Center

(Ophthalmic care since last OHTS visit has been provided at OHTS clinic)

Informed Consent	Core Tests & Measures	QOL forms	Short Form Consent	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
X	X	X						

2. Patient Comes to Clinical Center

(Ophthalmic care since last OHTS visit has been provided at non-OHTS clinic)

Informed Consent	Core Tests & Measures	QOL forms	Short Form Consent	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
X	X	X		X				

3. **Cognitively Impaired** Patient Comes to Clinical Center & LAR signs consent

(Ophthalmic care since last OHTS visit has been provided at OHTS clinic)

Informed Consent Signed by LAR	Core Tests & Measures	QOL forms (Completed by patient - assisted by LAR)	Short Form Consent	Medical Release for interim data*	Medical History Summary Form **	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
X	X	X						

4. **Cognitively Impaired** Patient Comes to Clinical Center & LAR signs consent

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(Ophthalmic care since last OHTS visit has been provided at non-OHTS clinic)

Informed Consent Signed by LAR	Core Tests & Measures	QOL forms (LAR assists patient)	Short Form Consent	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
X	X	X		X				

5. Patient is **unwilling or unable** to come to clinic and agrees to Quality of Life surveys, Medical History via telephone, and agrees to release all interim visual fields done at OHTS and non-OHTS clinics or OCT images done at OHTS clinics

Informed Consent	Core Tests & Measures	QOL forms	Short Form Consent	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
			X	X		X	X	X

6. Patient is **unwilling or unable** to come to clinic and agrees to Quality of Life surveys and Medical History via telephone (does not agree to release interim visual fields or OCT images)

Informed Consent	Core Tests & Measures	QOL forms	Short Form Consent	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent	Telephone QOL Forms	Telephone Medical History
						X	X	X

7. **Cognitively Impaired** Patient is unwilling or unable to come to clinic and agrees to Quality of Life surveys and Medical History via telephone (does not agree to release interim visual fields or OCT images)

Must have local IRB approval to collect QOL and Medical History from LAR

Informed Consent Signed by LAR	Core Tests & Measures	QOL forms	Short Form Consent signed by LAR	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent – assisted by LAR	Telephone QOL Forms - assisted by LAR	Telephone Medical History – assisted by LAR
						X	X	X

8. **Cognitively Impaired** Patient is unwilling or unable to come to clinic and agrees to Quality of Life surveys, Medical History via telephone, and agrees to release all interim visual fields done at OHTS and non-OHTS clinics or OCT images done at OHTS clinics

Must have local IRB approval to collect QOL and Medical History from LAR

Informed Consent Signed by LAR	Core Tests & Measures	QOL forms	Short Form Consent – signed by LAR	Medical Release for interim data*	Medical History Summary Form**	Telephone QOL Consent – assisted by LAR	Telephone QOL Forms - assisted by LAR	Telephone Medical History – assisted by LAR
			X	X		X	X	X

* Medical Release to obtain all interim visual fields done if participant was POAG in OHTS 1/2 or possible conversion/progression in OHTS 3 at OHTS and non-OHTS clinics or OCT images for all participants done at OHTS clinics

** Medical History Summary (MH) form sent to non-OHTS clinician for completion

2.5 Visits, Examination and Measures

2.5.1 Core Schedule of Tests and Measures (Level 1 Data)

<p>Assessments should be completed within 6 mos.</p> <p>More than one visit may be needed to complete all <u>core tests and measures</u></p>	<p>Neither eye is POAG</p>
<p>Consent Forms</p>	
<p>Consent for OHTS Phase 3 Examination</p> <ul style="list-style-type: none"> All pts. consent to release electronic OCT scans taken since their last OHTS visit For pts. diagnosed with visual field POAG in OHTS Phase 1 or 2 or newly diagnosed in Phase 3, consent to release <u>both</u> electronic OCT scans and VF's since their last OHTS visit 	X
<p>*For pts. unable/unwilling to come into clinic</p> <p>Verbal consent for telephone QOL survey & written release of electronic OCT scans, VF tests, and medical history summary since their last OHTS visit</p>	(X)*
<p>Quality of Life Surveys (QOL)</p>	
Ocular Symptom Checklist	X
NEI-VFQ, SF-36, Functional Measures	X
<p>Clinical Tests and Measures (FV Form)</p>	
Updated ocular/systemic medical history, height and weight, history, medications and smoking	X
Blood pressure	X
Refraction	X
Snellen VA at each visit	X
ETDRS Best corrected visual acuity	X
Pelli-Robson Contrast Sensitivity	X
<p>Humphrey program 30-2</p> <p>SITA Standard visual fields (VF)</p> <p>*Retest for abnormality or unreliability required per protocol or VFRC</p>	(X)*
Optical Coherence Tomography (OCT) RNFL & Macula	X
External eye examination at each visit	X
Slit-lamp examination at each visit	X
Corneal Hysteresis	X
Applanation tonometry at each visit	X
Dilated ophthalmoscopic exam/indirect ophthalmoscopy	X
2 sets of the "best quality possible" stereoscopic optic disc photographs for each eye	2 stereo pairs per eye
Gonioscopy	X

OHTS Phase 3 tests and measures should be completed within a 6-month window. Some participants will be able to complete core tests and measures in one visit. Other participants may need more than one visit to complete core tests and measures. Technicians should test a participant even if he/she may appear “unable” to perform reliably due to e.g. dementia, muscular skeletal problems, poor vision and/or poor fixation. Results should be submitted to the Reading Center with an explanation on the case report form from the Clinical Center Investigator explaining why retesting is unlikely to improve test quality.

The following participants may be required by protocol and/or by a Reading Center to complete more than one visit for additional tests and measures:

1. **Participants whose visual fields (VF) or optic disc photos** are poor quality may benefit from retesting as determined by the Clinical Center Investigator and/or required by the respective reading center. If the Clinical Center Investigator believes that repeating the test is very unlikely to yield better data, the reason should be recorded on the form and the test need not be repeated.
2. **Participants whose visual fields are suspicious for conversion:**
 - a. Visual Field Reading Center will notify the clinic within 7 days of receipt of visual fields if a 2nd or 3rd visual field is required to confirm suspected conversion defined as $p < 5\%$ for the PSD or GHT is outside normal limits on Humphrey 30-2 SITA Standard visual field. If the visual field obviously meets OHTS criteria for abnormality, the Clinical Center is permitted to retest VF(s) prior to notification of abnormality by the VFRC.
3. **Participants who developed visual field POAG** previously in OHTS Phase 1 or 2 are required by protocol to complete 3 visual fields in the affected eye(s) to assess visual field progression.

2.5.2 Level 2 and/or 3 Data, Examination and Measures

Assessments should be completed within 6 months of Core Tests and Measures	
Level 2 or 3 Data as Required by a Reading Center or for Assessment of POAG Status	
Repeat Clinical Tests and Measures (RV Form)	
Snellen VA at each visit	X
Humphrey program 30-2 SITA Standard visual fields (VF) *Retest for abnormality or unreliability required per protocol or VFRC	(X)*
*External eye examination at each visit	X
*Slit-lamp examination at each visit	X
*Direct ophthalmoscopic examination	X

Applanation tonometry at each visit	X
2 sets of the “best quality possible” stereoscopic optic disc photographs for each eye (if required by Reading Center) *Retest for poor quality photographs if required by the ODRC	2 stereo pairs per eye

*Only dilate if repeat photographs are required

2.6 Retrieval of OCT Scans and Visual Fields Since the Last OHTS Visit

We will retrieve electronic OCT scans taken from all OHTS participants since their last OHTS visit to date. The OCT scans retrieved must be electronic and not PDF copies.

The Clinical Center Investigator or Clinical Center Coordinator will obtain written release for electronic OCT scans at the time of examination or written release by postal mail. The electronic OCT scans are retrieved, de-identified and transmitted via secure internet or flash drive to the OCT Reading Center via the WUSTL Box at the Coordinating Center.

For participants who developed visual field POAG in OHTS Phase 1 or 2 or were found to have newly developed visual field POAG in Phase 3, we will retrieve both electronic OCT scans and visual fields. The Clinical Center Investigator or Clinical Center Coordinator will obtain written release for electronic OCT scans visual field tests since their last OHTS visit to date from OHTS and non-OHTS Clinical Centers.

The electronic OCT scans are de-identified and transmitted via secure internet to the WUSTL Box at the Coordinating Center. If needed, the Clinical Centers can make arrangement to send the electronic OCT scans by flash drive to the Coordinating Center for upload to the WUSTL Box. The Visual Fields are de-identified and transmitted via secure internet to the VFRC website. The OCT Reading Center (OCTRC) and the Visual Field Reading Center (VFRC) determine if the data are useable for analyses and review by the Endpoint Committee for outcome determination.

For participants who are unable or unwilling to return for a visit, we will retrieve electronic OCT scans, VF tests and medical history summary as a surrogate for an OHTS examination. The Clinical Center Investigator or Clinical Center Coordinator will obtain written consent by postal mail for release of electronic OCT scans, VF tests and medical history from OHTS Clinical Centers and non-OHTS clinicians since the last OHTS visit to date. Electronic OCT scans and VF tests are de-identified and transmitted via secure internet or flash drive as stated above.

2.7 Treatment and Follow-up of Participants

There is no treatment protocol in OHTS Phase 3. OHTS Phase 3 is strictly observational. Treatment is at the discretion of the participant’s eye care clinician.

If a participant has been receiving eye care from a non-OHTS facility, the OHTS Clinical Center Investigator will provide a full report of OHTS Phase 3 study tests and measures to the participant and his/her eye care clinician with the permission of the participant.

Participants who have not been seeing an eye care clinician after OHTS Phase 1 or Phase 2 will be advised that they need to have ongoing eye care after OHTS Phase 3. They may choose to be seen at the OHTS Clinical Center or be referred to other eye care clinicians. OHTS Phase 3 does not include follow-up visits beyond those visits needed to complete OHTS Phase 3 examinations.

2.8 Determination of Conversion to POAG

Aim 1a of OHTS Phase 3 is to determine the 20-year incidence of POAG conversion. The operational definition of POAG conversion is the same as in OHTS Phase 1 and 2 to insure consistency. POAG conversion is defined as reproducible VF abnormality and/or reproducible optic disc deterioration from baseline that is attributed to POAG by a masked Endpoint Committee.

The steps for determination of conversion to POAG are outlined below:

1. Confirmation of deterioration in the optic disc from baseline requires 2 independent sets of stereoscopic optic disc photographs that are graded independently by certified, masked readers at the Optic Disc Reading Center to show deterioration from baseline stereoscopic photographs. If the first of the two sets shows progression from baseline, the second set is read. If the first set does not show progression from baseline, the second set is not read. If optic disc deterioration is confirmed by the second set, the endpoint review process is initiated.

Progression of peripapillary thinning cannot be determined because OCT imaging was not performed in OHTS Phase 1 or 2. Each Reading Center has trained and certified graders, masked to all participant data, who determine occurrence of confirmed progression after POAG conversion.

2. Confirmation of visual field abnormality requires 3 consecutive VF tests to demonstrate the abnormality in the same location and on the same index/indices (Glaucoma Hemifield Test outside normal limits or pattern standard deviation below the lower 5% probability level) as determined independently by certified, masked graders at the Visual Field Reading Center. If VF abnormality is confirmed by 3 VF tests, the endpoint review process is initiated.
3. To initiate the Endpoint Committee review process, the Reading Center prepares a narrative description of the confirmed change and forwards baseline data and OHTS Phase 3 data for both eyes to the Coordinating Center for Endpoint Committee review. The Coordinating Center will request the OHTS clinician prepare a report for the Endpoint Committee of ocular or systemic factors other than POAG that could account for the change.

4. Masked Endpoint Committee will determine whether the confirmed optic disc deterioration and/or confirmed VF abnormality is due to POAG i.e., disc POAG or VF POAG conversion. The Endpoint Committee protocol for conversion is described in detail in 2.13.

The Coordinating Center notifies the appropriate Reading Center and the Clinical Center of the Endpoint Committee's decision.

2.9 Determination of Progression due to POAG

Aim 1b of OHTS Phase 3 is to determine POAG progression in eyes/participants that developed either VF POAG or optic disc POAG or both in OHTS Phase 1 or 2. OHTS Phase 1 and 2 did not assess disease progression. Progression due to POAG is defined as reproducible visual field progression from the time of VF POAG conversion and/or reproducible optic disc deterioration from the time of optic disc POAG conversion.

The steps for confirmation of glaucomatous VF and/or optic disc progression are outlined below:

In OHTS Phase 3, glaucomatous VF progression will be determined in the following steps:

1. 3 visual fields will be completed in eyes that developed VF POAG in OHTS Phase 1 or 2.
2. Each VF will be read independently by masked graders at the VFRC in the order that the VF tests were completed by the participant in OHTS Phase 3. The VFRC will determine the occurrence of VF progression using trend analysis among other things.
3. If the VFRC determines the occurrence of VF progression, Endpoint Committee review is initiated. VFRC prepares a narrative description of VF progression and sends baseline VF's, VF's from the time of conversion and OHTS Phase 3 VF's for both eyes for Endpoint Committee review. OHTS clinical investigator prepares a report of ocular or systemic factors other than POAG that could account for VF progression.
4. Endpoint Committee determines whether confirmed VF progression is due to POAG i.e., POAG VF progression. Endpoint Committee protocol for progression is described in detail in 2.14.

In OHTS Phase 3, progressive glaucomatous optic disc deterioration will be determined in the following steps:

1. 2 "best possible quality" stereophotographs will be taken in eyes that developed optic disc POAG in OHTS Phase 1 or 2.
2. The first of the 2 sets of stereo photographs will be read independently by masked graders at the ODRC. If the first set shows progression from the first set of conversion photographs, the second set is read to confirm progression. If the first of 2 sets of stereo photographs does not show progression, the second set is not read. In this manner, the

index of suspicion for detection of change is the same in OHTS Phases 1, 2 and 3 for both disc conversion and progression.

3. If both the 1st and 2nd sets of stereophotographs show progression from the conversion set, the eye is confirmed to have optic disc progression and Endpoint Review is initiated. The ODRC prepares a narrative description of the optic disc progression and sends stereophotographs of both eyes from baseline, time of disc POAG conversion and OHTS Phase 3. OHTS clinical investigator prepares a report of ocular or systemic factors other than POAG that could account for VF progression.
4. Masked Endpoint Committee review determines whether the confirmed optic disc deterioration in the optic disc due to POAG i.e., disc POAG progression. Endpoint Committee protocol for progression is described in detail in 2.14.

The Coordinating Center notifies the appropriate Reading Center and the Clinical Center of the Endpoint Committee decision.

2.10 Stereoscopic Optic Disc Photography Protocol

In OHTS Phase 1 and 2, film was used for optic disc photography in most Clinical Centers. OHTS Phase 3 will use digitized optic disc images (see Appendix 12-A for Study of Agreement between Gratings of Film and Digitized Stereophotographs). All previous stereoscopic optic disc images have been digitized.

OHTS Phase 3 requires two digital stereo photographs of each eye of the “best quality possible” in all participants. Digital stereoscopic optic disc photographs are taken by OHTS certified photographers (optic disc photography protocol is described in detail in [Chapter 12](#)).

Within 14 days of receipt of the stereoscopic optic disc photographs, the ODRC will provide a quality report on each set of stereophotographs (stereo, focus, magnification, clarity) and notify the Clinical Center if a participant requires retesting because of poor photographic quality. Repeat testing should be done within 3 months. Photographers are encouraged to photograph participants even if a good quality photograph may be improbable e.g. cognitive impairment, poor fixation, lens opacification. If repeat photography is unlikely to improve quality, the Clinical Investigator should record an explanation on the photography form. These photographs should be transmitted to the ODRC via the WUSTL Box at the Coordinating Center via flash drive or secure internet.

The ODRC generates reports on the photographic quality of each set of stereophotographs, quarterly performance reports to the Clinical Centers and the Coordinating Center and semi-annual reports to the Executive/Steering Committee.

2.10.1 Determination of Optic Disc Conversion

Within 14 days of receipt, certified masked readers review stereoscopic optic disc photographs for presence of deterioration from baseline. They estimate vertical and horizontal cup-to-disc

ratio for quantitative assessment of change over time. For eyes that have not previously developed optic disc POAG, OHTS 3 photographs are compared to baseline photographs. Readers determine whether baseline photographs vs. the OHTS 3 photographs differ in masked side-by-side comparisons. If the two sets of photographs differ, readers must determine their correct order – i.e., that the OHTS 3 set shows deterioration from the baseline photographs.

Deterioration (change from baseline) is defined as a generalized or localized thinning of the optic disc rim as judged by one or more of the following:

- A change in the position of the vessels greater than would be expected from a shift in the position of the eye
- Development of a notch
- Development of an acquired pit
- Overall thinning of the rim

Disc hemorrhages, nerve fiber layer dropout on disc images, or changes in the depth of the cup are not considered evidence of optic disc change in OHTS.

If the first set of stereo photographs for an eye shows deterioration from baseline, the ODRC independently grades the second set of stereo photographs in the same manner. If the first set of stereo photographs does not show deterioration from baseline, the ODRC will not grade the second set of stereo photographs. If the second set of photographs confirms the presence of deterioration, the ODRC prepares a narrative description of confirmed deterioration and forwards baseline data and OHTS 3 stereo photographs for both eyes to the Coordinating Center.

Upon notification of confirmed optic disc deterioration from baseline, the Coordinating Center prepares an electronic file for Endpoint Committee review. The Coordinating Center will also request the OHTS clinician to prepare a report for the Endpoint Committee of ocular or systemic factors other than POAG that could account for the optic disc deterioration. The Endpoint Committee will determine whether the optic disc deterioration from baseline is due to POAG i.e., conversion due to POAG and whether the deterioration is clinically significant. Endpoint Committee protocol is described in detail in 2.13.

The Coordinating Center notifies the ODRC and the Clinical Center of the Endpoint Committee decision.

2.10.2 Determination of Optic Disc Progression

For participants who developed optic disc POAG in OHTS Phase 1 or 2, two sets of photographs in the affected eye(s) are required to assess optic disc progression. Within 14 days of receipt, certified masked readers review OHTS 3 stereoscopic optic disc photographs for presence of progression from first set that confirmed conversion to optic disc POAG. They estimate the vertical and horizontal cup-to-disc ratio of the first of two OHTS 3 photographs for quantitative assessment of change to the conversion set. Readers determine whether the OHTS 3 set differs from the conversion set in masked side-by-side comparisons. If the two sets of photographs

differ, readers must ascertain their correct order i.e., - that OHTS 3 set shows progression from the conversion set.

If the OHTS 3 set shows deterioration from the conversion set, the ODRC independently grades the second set of OHTS 3 photographs for the eye in the same manner. If the first set of OHTS 3 stereo photographs does not show deterioration from conversion baseline, the ODRC will not grade the second set of OHTS 3 photographs. If the second set of photographs confirms the occurrence of progression since conversion, the eye is classified as showing confirmed optic disc “progression” after optic disc conversion. ODRC prepares a narrative description of confirmed progression and forwards baseline photographs, conversion photographs and OHTS 3 photographs for both eyes to the Coordinating Center.

Upon notification of confirmed progression, the Coordinating Center prepares an electronic file for Endpoint Committee determination of whether the confirmed progression was due to POAG i.e., optic disc progression due to POAG (details of Endpoint Committee review are in section 2.20). The Coordinating Center also requests the OHTS clinician to prepare a report for the Endpoint Committee of ocular or systemic factors other than POAG that could account for the progression. The Endpoint Committee will determine whether the confirmed progression is due to POAG i.e., progression due to POAG and whether the progression is clinically significant. Endpoint Committee protocol is described in detail in 2.14. The Coordinating Center notifies the ODRC and the Clinical Center of the Endpoint Committee decision.

2.11 Visual Field Testing Protocol

All ocular hypertensive eyes need at least one Humphrey 30-2 SITA Standard visual field test. Visual field testing is performed by OHTS certified visual field technicians (visual field protocol is detail in MOP Chapter 11.9). Visual fields are transmitted within 14 days to the Visual Field Reading Center (VFRC) via secure internet, thumb drive or floppy disk.

Repeat testing may be required due to poor quality or suspected abnormality. If the visual field meets criteria for abnormality (if $p < 5\%$ for the PSD or if the GHT is outside normal limits), the VFRC may require a 2nd or 3rd visual field test. Three visual field tests are required to confirm visual field abnormality because an initial abnormal visual field test is often not reproduced upon retesting¹. If the visual field obviously meets criteria for abnormality (if $p < 5\%$ for the PSD or if the GHT is outside normal limits), the VF test may be repeated prior to notification by the VFRC confirming abnormality.

Visual field technicians should test participants even if they may not be able to perform a reliable visual field test e.g. cognitive impairment, poor fixation, lens opacification. The visual field technician should transmit the visual fields to the VFRC with an explanation from the Clinical Center Investigator recorded on the visual field form for poor test quality. If the Clinical Center Investigator believes that repeating the test is very unlikely to yield better data, the test is not repeated.

Within 14 days of receipt of the visual field tests, the VFRC will provide a quality report on each visual field test (correct program, reliability indices, labeling) and notify the Clinical Center if a

participant needs to be retested because of poor quality of the visual fields. Repeat testing should be done within 3 months.

Within 14 days of receipt of the visual field tests, the VFRC will notify the Clinical Center if the participant needs to be retested because of suspected visual field abnormality (if $p < 5\%$ for the PSD or if the GHT is outside normal limits). Retesting should be done within 3 months. If the VFRC determines that the repeat (second) visual field demonstrates abnormality on the same index and in the same location, a third visual field within 3 months will be required. If the third visual field test read in a masked fashion without knowledge of previous results confirms abnormality of the same index and in the same location, the suspected abnormality is confirmed.

The VFRC generates reports on the quality of each visual field received, quarterly reports to Clinical Centers, semi-annual reports to the Executive/Steering Committee and Coordinating Center.

2.11.1 Determination of Visual Field Conversion

The visual fields are considered abnormal if $p < 5\%$ for the PSD or if the GHT is outside normal limits as determined by the VFRC. The VFRC notifies the Clinical Center to schedule a 2nd visual field within 3 months to confirm suspected visual field conversion. If the visual field obviously meets these criteria for abnormality, the VF test may be repeated prior to notification by the VFRC of the abnormality. If the VFRC considers the 2nd visual field reliable and abnormal, the VFRC notifies the Clinical Center to schedule a 3rd confirmation visual field within 3 months.

If the third visual field is also reliable and abnormal, the VFRC prepares a narrative description of the confirmed abnormality. The abnormalities on all three visual fields **must be of the same character and location for the abnormality to be “confirmed”**. The VFRC transmits reliable baseline visual fields and the OHTS 3 visual fields of the affected and fellow eyes to the Coordinating Center.

Upon notification of confirmed visual field abnormality, the Coordinating Center prepares an electronic file for Endpoint Committee review. The Coordinating Center also requests the OHTS clinician to prepare a report for the Endpoint Committee of ocular or systemic factors other than POAG that could account for VF abnormality. The Endpoint Committee will determine whether the confirmed VF abnormality is due to POAG i.e., conversion due to POAG. Endpoint Committee protocol is described in detail in 2.13.

The Coordinating Center notifies the VFRC and the Clinical Center of this decision.

2.11.2 Determination of Visual Field Progression After Perimetric POAG Conversion

Participants who developed VF POAG in OHTS Phase 1 or 2 will complete 3 visual field tests in the affected eye(s) in OHTS Phase 3 to determine the presence of visual field progression. All 3

visual field tests in the affected eye(s) should be performed within 3 months of each other. If the three VF's in OHTS Phase 3 indicate progression, the VFRC will prepare a narrative description of the confirmed VF progression and forward visual fields from baseline, visual fields at the time of VF POAG conversion and OHTS Phase 3 VF's of both eyes for Endpoint Committee review. The Coordinating Center will also request the OHTS clinician to prepare a report for the Endpoint Committee of ocular or systemic factors other than POAG that could account for the VF progression. The Endpoint Committee will determine whether the confirmed VF progression is due to POAG i.e., progression due to POAG. Endpoint Committee protocol is described in detail in 2.14.

The Coordinating Center notifies the VFRC and the Clinical Center of this decision.

Most OHTS participants have performed a sufficient number of visual field examinations to satisfy the requirements for trend analysis (linear regression). Trend analysis will provide a determination of progression at values below the lower 5% probability level, a rate of progression, the confidence limits and residuals for the linear regression. Because the rate of progression has been reported to become steeper when a participant has reached greater amounts of glaucomatous visual field loss, the VFRC will utilize a bilinear regression procedure. This will provide a rate of progression prior to and after VF POAG is diagnosed.

2.12 Optical Coherence Tomography (OCT) Protocol

Spectralis and Cirrus spectral domain OCT image acquisition are performed by OHTS certified technicians (OCT protocol is described in detail in section 13.0). All available images for each eye of participants are to be transmitted to the OCT Reading Center (OCTRC) via the WUSTL Box at the Coordinating Center via secure internet on a monthly basis.

2.13 Endpoint Committee Determination of Conversion to POAG

The Endpoint Committee determines whether confirmed visual field change or optic disc deterioration as documented by the Reading Center(s) is due to POAG or not. Many systemic and ocular conditions other than POAG can cause reproducible visual field loss, optic disc change and/or peripapillary nerve fiber layer thinning².

Endpoint Committee members for OHTS Phase 3 are the same as for OHTS Phase 1 and 2.

- 1) Dale K. Heuer, M.D., Medical College of Wisconsin, Milwaukee, WI
- 2) Eve J. Higginbotham, M.D., Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
- 3) Richard K. Parrish, II, M.D., University of Miami School of Medicine, Miami, FL

The Reading Center transmits a narrative description of confirmed change, the date of the finding and baseline data for both eyes to the Coordinating Center. The Coordinating Center prepares a secure web page for review by the Endpoint Committee that includes the following information:

- 1) Summary of medical/ocular histories that is masked as to randomization, IOP, previous glaucoma surgery and treatment.
- 2) Optic disc photographs: Baseline sets of disc photographs and OHTS Phase 3 for both eyes.
- 3) Visual field tests: Baseline normal and reliable visual fields and all visual fields in OHTS Phase 3 for both eyes.
- 4) Narrative description from the appropriate Reading Center.
- 5) Clinical Center Investigator report of ocular and systemic factors, other than POAG, that could cause the confirmed change.

Endpoint Committee members independently check one of the following options on the data entry system: “Probably due to... 1) POAG or 2) Not POAG.” In addition, the Endpoint Committee determines whether changes in the optic disc from baseline are/are not “clinically significant”. The OHTS Data and Safety Monitoring Committee in OHTS Phase 1 & 2 recommended that disc conversion had to be clinically significant to be classified a primary outcome. If data are of poor quality or incomplete, members use the same aforementioned options but check an option for incomplete or poor quality data. In this manner, a decision is made using the same scale but weighted for quality and completeness of the data. After each member casts his/her vote, they can view other members’ votes and can change their vote to reach consensus. If consensus is not reached, the case is discussed on the monthly consensus call. Adjudication is complete when the three members achieve consensus.

After consensus is achieved, the Endpoint Committee members can access the link to OCT data for both eyes. Each member independently checks whether the change is “Probably due to... 1) POAG or 2) Not POAG.” Consensus is not required for POAG determination after OCT review. Each member completes one additional question: Did OCT affect your level of confidence in your decision: a. More confident with initial decision, b. Less confident with initial decision, c. No influence on initial decision, 4. Changed initial decision.

The Coordinating Center notifies the appropriate Reading Center and the Clinical Center of the Endpoint Committee decision. The Clinical Center informs the participant and, with the participant’s consent, his/her clinician.

2.14 Endpoint Committee Determination of Progression of POAG

Adjudication of reproducible visual field or optic disc progression is similar to the consensus process for incident POAG conversion.

The Reading Center transmits a narrative description of confirmed progression after conversion to POAG, the date(s) of the conversion and data for both eyes from baseline. The Coordinating Center prepares a secure web page for review by the Endpoint Committee that includes the following information:

- 1) Summary of pertinent medical/ocular histories. Summary is masked to randomization, IOP, previous glaucoma surgery and treatment.
- 2) For optic disc progression since optic disc POAG conversion in OHTS Phase 1 or 2:
 - Optic disc photographs: Baseline sets of disc photographs, available photographs at the time of disc POAG conversion and OHTS Phase 3 sets for both eyes.
 - Visual field tests: Baseline normal and reliable VF's, available VF's at the time of disc POAG conversion and all OHTS Phase 3 VF's for both eyes.
- 3) For visual field progression since visual field POAG conversion in OHTS Phase 1 or 2:
 - Optic disc photographs: Baseline sets of optic disc photographs, available sets at the time of VF POAG conversion and OHTS Phase 3 sets for both eyes.
 - Visual field tests: Normal and reliable baseline VF's, VF's at the time of VF POAG conversion and all OHTS Phase 3 VF's for both eyes.
- 4) Narrative description from the appropriate Reading Center.
- 5) Clinician's report of ocular and systemic factors, other than POAG, that could cause confirmed progression.

Endpoint Committee members independently check one of the following options on the in the data entry system: "Probably due to... 1) POAG or 2) Not POAG." In addition, the Endpoint Committee determines whether disc progression is clinically significant.

If data is of poor quality or incomplete, members use the same aforementioned options but check an option for incomplete or poor quality data. In this manner, a decision is made using the same scale but weighted for quality and completeness of the data. After each member casts his vote, he/she can view other members' votes and change their vote to reach consensus. If consensus is not reached, the case is discussed on the monthly consensus call. Adjudication is complete when the three members achieve consensus.

After consensus is achieved, Endpoint Committee members can access the link to OCT data for both eyes. Each member independently checks whether the change is "Probably due to... 1) POAG or 2) Not POAG." Consensus is not required for POAG determination after OCT review. Each member completes one additional question: Did OCT affect your level of confidence in your decision: a. More confident with initial decision, b. Less confident with initial decision, c. No influence on initial decision, 4. Changed initial decision.

The Coordinating Center notifies the appropriate Reading Center and the Clinical Center of the Endpoint Committee's decision. The Clinical Center informs the participant and, with the participant's consent, his/her clinician.

2.15 Protecting Masking at Reading Centers

The Visual Field Reading Center and the Optic Disc Reading Center are responsible for determining the occurrence of conversion or progression in a masked fashion without knowledge of the participant's clinical or medical history, original randomization assignment, treatment status or previous OHTS POAG diagnosis.

Clinical Center personnel must be careful to guard against inadvertent disclosure of information to Reading Center personnel i.e., the participant's original randomization status, ocular or systemic conditions, or POAG endpoint status. Clinical Centers should direct queries to the Coordinating Center if these questions could unmask readers.

Personnel at the Visual Field Reading Center and Optic Disc Reading Center must be vigilant and deter cross-talk between Reading Centers and deter inadvertent disclosure by Clinical Center personnel of the participant's clinical or POAG endpoint status.

2.16 Clinical Centers

The Clinical Centers in OHTS were originally selected by virtue of their recruitment, data quality and retention of study participants. These Clinical Centers have produced high quality data and achieved excellent participant retention in OHTS Phase 1 and 2.

OHTS Phase 3 includes all original 26 Clinical Centers and their satellites, many with the same personnel (Appendix 2-D for listing of Phase 3 Clinical Centers and personnel). Clinical Center personnel consist of an OHTS certified Clinical Center Investigator, Clinical Center Coordinator, visual field technician, photographer, and imaging technician. Each of these positions requires a backup person who is study certified. An individual can be certified for more than one role and can back up more than one position, i.e., a technician could back up the Coordinator or the photographer or both (see Chapter 14, Clinical Center, for more information).

2.17 Human Participants

2.17.1 Entry Criteria

In OHTS Phase 3, the goal is to consent and examine all surviving participants randomized to OHTS. This includes participants who did not enroll in Phase 2 as well as participants who might be unable to perform some study tests and measures.

2.17.2 Exclusion Criteria for OHTS

Participants cannot be enrolled in OHTS Phase 3 if they cannot provide informed consent or refuse to give informed consent for participation.

2.17.3 Confidentiality and Protection of Subjects

All reasonable measures are taken to protect the confidentiality of study records and participant identity. The protocol requires that study information on hard copy is kept in locked file cabinets in secure offices and is available only to the OHTS Clinical Center Investigators and Clinical Center Coordinators at the various Clinical Centers. Study information is coded by ID number only, with no personal identifiers or locator information. The confidentiality of all study related records will be maintained in accordance with State and Federal laws. OHTS is committed to being in compliance with Health Insurance Portability and Accountability Act guidelines and requirements.

Participants are advised in the consent form that there is a possibility that their medical research record, including identifying information at the Clinical Center, may be inspected and photocopied by officials of Federal or State government agencies and the University Human Studies Committees.

At each participating OHTS Clinical Center and the Resource Center, all personnel must complete certification for human studies research that is approved by their local IRB. The local IRB approves renewal of the OHTS protocol annually and approves protocol modifications as needed. No protocol changes can be implemented at a Clinical Center prior to approval by its local IRB.

2.17.4 Risks

The risk of participation in OHTS 20-year follow-up examinations is minimal. No action is taken to initiate, terminate or change the participant's current treatment. Results of diagnostic tests and measures will be explained to the participant with a written report to both the participant and the participant's clinician with the participant's permission.

Participants in OHTS have elevated IOP and are at risk for developing POAG whether they participate in the study or not. Risks to participants include developing conditions that could

occur with at least equal frequency whether the participant is in OHTS Phase 3 or not. The participants in OHTS receive their care from highly skilled glaucoma specialists. Visual fields, optic disc photographs and OCT images are reviewed in standardized fashion by trained, certified technicians and ophthalmologists. Thus, the standard of care in OHTS at least meets standard of care in the community.

Participants in OHTS could develop a corneal abrasion or a subconjunctival hemorrhage from clinical examination. OHTS includes routine clinical tests performed by highly skilled certified clinicians and certified study technicians and interpreted by experienced specialists. Thus, the rate of adverse events should be lower than would occur with standard care.

2.17.5 Benefits

Participants in this study will receive eye examination(s) that meet or exceed the standard quality of care. Examination results and recommendations about care will be provided to the participant and his/her clinician with the participant's permission. The benefits of this study to society are great. Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. Given the large and growing number of individuals with ocular hypertension and glaucoma, information about the benefits and risks of early treatment, who is at risk of developing glaucoma which causes functional limitations and who should receive treatment have great public health importance.

Thus, the potential benefits are high and the study introduces few, if any, additional risks. The risk/benefit ratio is very favorable.

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Appendix 2-A Synopsis of OHTS Randomized Trial (Phase 1)

Phase 1 of OHTS was a randomized trial to determine if ocular hypotensive medication was safe and effective in preventing the development of POAG. Up to that time, most studies had found that early treatment of ocular hypertension was not effective in preventing the onset of POAG. Between 1994-1996, 1,636 participants including 408 self-identified African Americans were randomized to treatment with commercially available topical ocular hypotensive medication (n=819) or to observation (n=817). Recruitment for OHTS started February 1994 and ended October 1996.

The inclusion and exclusion criteria for OHTS are summarized in Appendix Table 1 below.

Table 1: Inclusion Criteria
<ul style="list-style-type: none"> • IOP of ≥ 24 mm Hg and ≤ 32 mm Hg in at least one eye. • IOP of ≥ 21 mm Hg and ≤ 32 mm Hg in fellow eye. • Age 40 to 80 years, inclusive. • Normal and reliable Humphrey 30-2 SITA Standard visual fields for both eyes as determined by the Visual Field Reading Center. • Normal optic discs in both eyes on clinical examination and on review of stereoscopic photographs as determined by the Optic Disc Reading Center. • Written informed consent.
Exclusion Criteria
<ul style="list-style-type: none"> • Best-corrected visual acuity worse than 20/40 in either eye. • Previous intraocular surgery excepting uncomplicated extracapsular cataract extraction with posterior chamber-intraocular lens implant and no escape of vitreous to the anterior chamber, strabismus, cosmetic lid surgery, and radial keratotomy. • A life-threatening or debilitating disease. • Secondary causes of elevated IOP including ocular and systemic corticosteroid use. • Angle-closure glaucoma or anatomically narrow angles — 75% of the circumference of the angle must be grade II or more by Shaffer criteria. • Other diseases that cause visual field loss or optic disc abnormalities. • Difference in cup-to-disc ratios (horizontal by contour) of the two eyes > 0.2. • Background diabetic retinopathy, defined as at least one microaneurysm seen on direct ophthalmoscopy with a dilated pupil. • Inability to visualize or photograph the optic discs. • Pregnant or nursing women as determined by participant self-report and testing.

Appendix 2-B Demographic Characteristics of Participants in OHTS Phase 1

		African American		Other		Overall	
		n	%	n	%	n	%
Gender	Male	140	34%	565	46%	705	43%
	Female	269	66%	663	54%	931	57%
Mean Age \pm S.D. (years)		54.5 \pm 9.0		55.7 \pm 9.7		55.4 \pm 9.6	
Age (years)	40 \leq age < 50	137	34%	385	31%	521	32%
	50 \leq age < 60	143	35%	400	33%	543	33%
	60 \leq age < 70	107	26%	318	26%	425	26%
	70 \leq age \leq 80	22	5%	125	10%	145	9%
Marital Status	Single	65	16%	146	12%	211	13%
	Married	198	48%	857	70%	1054	64%
	Divorced/Separated	102	25%	158	13%	260	16%
	Widowed	44	11%	67	6%	111	7%
Education	\leq 6th grade	4	1%	12	1%	16	1%
	Grade 7-11	53	13%	44	4%	97	6%
	Grade 12/GED	141	35%	287	23%	428	26%
	1+ years of college	171	42%	584	48%	754	46%
	1+ years of graduate school	40	10%	300	24%	340	21%

Baseline Clinical Characteristics of Self-Identified African American Participants and Other Participants

	African American		Other		Overall ¹
	OD	OS	OD	OS	
Intraocular Pressure ¹ Mean \pm S.D. (mm Hg)	25.2 \pm 3.0	25.0 \pm 3.1	25.0 \pm 3.0	24.7 \pm 2.9	24.9 \pm 2.7
Refractive Error ¹ Spherical Equivalent (D) \pm S.D.	-0.35 \pm 2.01	-0.32 \pm 1.99	-0.72 \pm 2.46	-0.74 \pm 2.49	-0.63 \pm 2.33
C/D Ratio (Mean \pm S.D.) ¹	0.42 \pm 0.18	0.42 \pm 0.17	0.34 \pm 0.19	0.35 \pm 0.19	0.36 \pm 0.18
Visual Field Mean Deviation (dB) ¹ \pm S.D.	0.06 \pm 1.11	0.06 \pm 1.14	0.29 \pm 1.07	0.31 \pm 1.13	0.24 \pm 1.05
Visual Field Pattern Standard Deviation (dB) ¹ \pm S.D.	1.93 \pm 0.25	1.91 \pm 0.24	1.92 \pm 0.24	1.90 \pm 0.26	1.91 \pm 0.21
Visual Field Corrected Pattern Standard Deviation (dB) ¹ \pm S.D.	1.06 \pm 0.46	1.10 \pm 0.45	1.14 \pm 0.45	1.12 \pm 0.46	1.12 \pm 0.35
Previous Topical Ocular Hypotensive Medication	38%		37%		37%
Family History of Glaucoma	43%		44%		44%
High Blood Pressure	56%		32%		38%
Heart Disease	9%		5%		6%
Diabetes	19%		10%		12%

¹ For eye specific variables the overall represents the average of the mean for the right and left eye.

Treatment and Follow-up The IOP treatment goal was (1) an IOP \leq 24 mm Hg and (2) a minimum 20% reduction in IOP from baseline but not $<$ 18mmHg. Neither the participant nor the clinician was masked to the randomization assignment. Follow-up visits were every 6 months and included an eye examination, Humphrey 30-2 SITA Standard visual field test and IOP measurements. Stereoscopic optic disc photography was performed at 12 month intervals.

Endpoint was the development of POAG defined as a reproducible visual field abnormality and/or reproducible optic disc deterioration determined by masked graders at reading centers and attributed to POAG by the masked Endpoint Committee. Participants who developed POAG continued to be followed with regularly scheduled visits and tests.

Results OHTS randomized trial (Phase 1) provided definitive evidence of the safety and efficacy of topical ocular hypotensive medication in reducing the incidence of POAG in ocular hypertensive individuals. The cumulative 5-year probability of developing POAG was significantly lower in the medication group (4.4 %) than in the observation group (9.5 %), (hazard ratio, 0.40; 95% confidence interval, 0.27 to 0.59; Mantel log rank $P < 0.0001$) (Kass, 2002). Treatment was also significantly protective among self-identified African American participants (Higginbotham, 2004).

OHTS developed a multivariate prediction model for the development of POAG that includes baseline central corneal thickness, age, IOP, cup/disc ratio and visual field pattern standard deviation. The prediction model was independently validated in the European Glaucoma Prevention Study and has demonstrated good predictive accuracy (C-statistic 0.75).

Appendix 2-C Synopsis of OHTS Phase 2

The OHTS randomized trial definitively demonstrated that topical ocular hypotensive medication was effective in preventing POAG, but did not answer one important question, “When should treatment be initiated?” In large part the answer depends on whether there is a penalty for delaying treatment. To answer this question, participants in the observation group who had completed 7 years of follow-up without ocular hypotensive medication started ocular hypotensive medication while the participants in the medication group continued medication. Eight-eight percent (1,366 of the 1,558 surviving participants) signed a new consent form to participate in OHTS Phase 2 in 2002.

Treatment and Follow-up was the same as in Phase 1. Participants in the medication group continued on their medication regimen and participants in the observation group started their medication regimen. The same schedule of tests and measures as well as the ascertainment of the primary outcome was used in Phase 2.

Results After the initiation of treatment, the incidence of POAG in the observation group became equivalent to that in the medication group (hazard ratio for randomization to medication was 1.06 (95% CI 0.74-1.50, P=77). The cumulative proportion of participants who developed POAG from the time of randomization to 13.0 years of follow-up was 0.22 (95% CI, 0.19-0.25) in the original observation group and 0.16 (95% CI, 0.13-0.19) in the original medication group (complementary log log chi square p-value tested at 13.0 yrs, p=0.0089). The protective effect of treatment was observed for both glaucomatous visual field abnormality (p =0.016) and glaucomatous optic disc deterioration (p=0.0015). Treatment reduced the cumulative proportion of participants who developed POAG by 30%-40% at all levels of risk for developing POAG. The absolute number of POAG cases prevented was highest among participants at highest risk of developing POAG.

Appendix 2-D Participating Clinical Centers in OHTS Phase 3

OHTS Clinical Centers and Clinical Investigators as of 09/30/2015.

Current listing of personnel in OHTS Phase 3 Clinical Centers and Resource Centers is available at <http://ohts.wustl.edu/investigators.html>.

Site Number	Main clinic PIs/sites are in bold. * Certified in OHTS Phase 1 or Phase 2	Clinic Center Investigator
A1	Bascom Palmer Eye Institute	* Steven Gedde, MD
B1/B2	Eye Consultants of Atlanta	* Thomas Harbin, MD
B3	Eye Physicians and Surgeons	*Paul McManus, MD
C1	Alkek Eye Center (Formally: Baylor Cullen Eye Institute)	Peter Chang, MD *Silvia Orengo-Nania, MD
D1	Devers Eye Institute	* Steve Mansberger, MD Robert Kinast, MD
E1	Emory University Eye Center	* Allen Beck, MD *Anastasios Costarides, MD
F1	Henry Ford Medical Center – Detroit	* Nauman Imami, MD
F2	Henry Ford Satellite – Troy Henry Ford Optimeyes Supervision	*Aldo Fantin, MD *David Crandall, MD
F3	Henry Ford Satellite – Dearborn	*Deborah Darnley-Fisch, MD
F4	Henry Ford Satellite – Livonia	Same as F1/2/3
G1	John Hopkins Hospital	* Henry Jampel, MD
G2	Krieger Eye Institute	* Donald Abrams, MD
G5	University of Maryland, Baltimore	Osamah Saeedi, MD
H1/H2	Jules Stein	* Anne Coleman, MD Salwa Abdel-Aziz, MD Daniel Choi, MD JoAnn Giaconi, MD Simon Law, MD
J1	Kellogg Eye Center	* Sayoko Moroi, MD, PhD Sarah Wood, OD
J2	Kresge Eye	* Bret Hughes, MD *Mark Juzych, MD Anju Goyal, MD Aman Shukairy, MD Justin Tannir, MD
J3	Great Lakes Ophthalmology	* John O’Grady, MD
K1	University of Louisville	* Joern Soltau, MD Judit Mohay Ambus, MD
L1	Mayo	Cheryl Khanna, MD Jeffrey Bennett, OD Arthur Sit, MD
L1	Mayo Scottsdale AZ Satellite	*Steven Cobb, MD Dharmendra Patel, MD

M1	Columbia University	*Jeffrey Liebmann, MD Lama Al-Aswad, MD Dana Blumberg, MD, MPH *George Cioffi, MD Carlos Gustavo DeMoraes, MD, MPH
N1	Ohio State University	*Paul Weber, MD Andrea Sawchyn, MD
P1	Salus University	*Richard Bennett, OD
P2	Mayfair Eye Associates Optometrist	*Richard Bennett, OD
Q1	Scheie Eye Institute	*Eydie Miller, MD *Prithvi Sankar, MD
Q2	Glaucoma Care Center	*Jody Piltz, MD
Q2	Glaucoma Care Center Satellite	*Jody Piltz, MD
R1	UC- Davis	*James Brandt, MD *Michelle Lim, MD Annie Baik, MD
S1	UC- San Diego	*Robert Weinreb, MD *Rigby Slight, MD
T1	UC- San Francisco	*Shan Lin, MD
U1	University Suburban Health Center	*Kathleen Lamping, MD
V2	Eye Associates of Washington DC	*Frank Ashburn, MD
V3	Washington Eye Physicians & Surgeons	*Arthur Schwartz, MD *Howard Weiss, MD
W1	Washington University	Anjali Bhorade, MD John Lind, MD

Appendix 2-E Consent Form to Participate in 20-Year Follow-up Study

Clinical Centers will adapt template as needed and replace highlighted sections accordingly.

INFORMED CONSENT DOCUMENT

Project Title: Ocular Hypertension Treatment Study: 20 Year Follow-up

Principal Investigator: Anjali Bhorade, MD

Research Team Contact: Sarah Brown, Coordinator, 314-747-5832

If you are the legally authorized representative of a person who is being invited to participate in this study, the word “you” in this document refers to the person you represent. As the legally authorized representative, you will be asked to read and sign this document to give permission for the person you represent to participate in this research study.

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study and about your rights and responsibilities as a research participant.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have any questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions, you understand the study and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you were a participant in the Ocular Hypertension Treatment Study (OHTS).

The purpose of the OHTS 20-year follow-up study is to determine how many people have developed glaucoma, how many have mild versus severe glaucoma and how many people have functional limitations because of glaucoma. We will also develop a 20-year prediction model of who is at high or low risk for developing glaucoma or for progressing rapidly.

WHAT WILL HAPPEN DURING THIS STUDY?

If you are returning to Washington University for study visits, you will be asked to complete one to three study visits. During these visits you will receive a complete eye examination. All tests and measures are standard for individuals with ocular hypertension or glaucoma. No procedures or tests are experimental. The OHTS eye examination includes visual acuity, contrast

sensitivity, visual fields and optic disc photography and optical coherence tomography (OCT scans). Measures of general health to be performed include blood pressure, height and weight.

All participants, regardless of whether you return to **Washington University** for an examination, will complete a survey about your general quality of life, vision and ability to function. You are free to skip any questions that you would prefer not to answer.

Your visual fields, optic disc photographs, optical coherence tomography and will be reviewed by a team of nationally recognized experts in the field who are masked as to your identity.

We will ask you to release data related to your diagnosis of ocular hypertension or glaucoma from your last OHTS visit to date, specifically visual fields and OCT scans. This data will help us to understand if and when glaucoma damage might have occurred.

WILL YOU SAVE MY RESEARCH DATA TO USE IN FUTURE RESEARCH STUDIES?

As part of this study, we are obtaining survey and medical record data from you, and exam data from some participants. We would like to use this data for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding ocular hypertension and glaucoma, or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data you give up any property rights you may have in the data.

We will share your data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at **Washington University**, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Your data will be stored without your name or any other kind of link that would enable us to identify which data are yours. Therefore, it will be available for use in future research studies indefinitely and cannot be removed.

Please place your initials in the blank next to Yes or No for each of the questions

below: My data may be stored and used for future research as described above.

 Yes **No**
Initials **Initials**

My data may be shared with other researchers and used by these researchers for the future research as described above.

 Yes No
Initials Initials

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 31 people will take part in this study conducted by investigators at Washington University. Approximately 1,327 participants in the Ocular Hypertension Treatment Study nation-wide will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, and you are coming to Washington University for an exam, you will be asked to complete one to three visits over an approximately six month period at dates and times convenient for you. The first visit will take approximately four to six hours. You are welcome to take breaks during the examination to avoid getting tired. The study will cover the cost of lunch for you and a companion at each visit. If a second or third visit is needed, it should take approximately two hours. If you are not returning to Washington University for an exam, completing the surveys will take 30-60 minutes.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

The risk of participation in OHTS 20-year follow-up examinations is minimal. All tests and measures are standard for individuals with ocular hypertension or glaucoma. No procedures or tests are experimental. No action is taken to initiate, terminate or change your current treatment.

There is a small chance you could develop a corneal abrasion or a subconjunctival hemorrhage from clinical examination. OHTS includes routine clinical tests performed by highly skilled certified clinicians and certified study technicians and interpreted by experienced specialists. Thus, the rate of adverse events should be lower than would occur with standard care.

The eye drop placed in your eyes may sting or burn for a few seconds or minutes. Your vision may be blurry after your eyes are dilated and you may be sensitive to bright lights. We will provide you with sunglasses if you need them.

Some questions about your health and vision may bother or embarrass you. You may skip any question that you prefer not to answer.

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you

secure, and we think the risk of accidental disclosure is very small. Please see the section in this consent form titled “*How will you keep my information confidential?*” for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You will not benefit from being in this study. It is possible that our examination will provide information about your eyes that is important for you to know. However, we hope that, in the future, other people might benefit from this study because we will learn about how many people develop open angle glaucoma over a 20-year period, the functional limitations associated with the disease, and the progression of the disease.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

As part of this study you will receive tests and procedures that are similar to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor. If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

If you do not have insurance, the study will cover the cost of your examination.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) and address in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you, which will take approximately 2 weeks. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

You will receive a \$50 check for each of up to 3 completed visits. The study will cover the cost of transportation for each visit if needed and a \$25 voucher for lunch each for you and a companion at each visit. The study will also pay airfare and hotel costs for participants who are visiting **St. Louis** from out of town.

Participants completing phone surveys will receive a \$50 check for their time.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health is funding this research study. This means that Washington University is receiving payments from the National Institutes of Health to do this study. No one on the research team will receive a direct payment or increase in salary from the National Institutes of Health for doing this study.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- National Institutes of Health
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- **Washington University's Institutional Review Board** (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, all research data are identified only by study code. Research data are stored in locked cabinets in locked offices with restricted access at **Washington University**. Electronic files containing research data are encrypted and transmitted to secure databases behind firewalls accessible only by password. The confidentiality of all study related records will be maintained in accordance with State and Federal Laws and Health Insurance Portability Act regulations. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the **University's Privacy Officer at 866-747-4975**.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
 - your insurance payment or enrollment in any health plans.
 - any benefits to which you are entitled.
- However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research.
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
- To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at <http://hrpo.wustl.edu/participants>.
- The research team may only use and share information already collected for the study.
- Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
- You will not be allowed to continue to participate in the study.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. You may also choose to only complete a portion of the study visit tests and measures. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Anjali Bhorade, MD, OHTS Clinical Center Investigator at 314-362-3973 Ms. Sarah Brown, Coordinator at 314-747-5832. If you experience a research-related injury, please contact: Anjali Bhorade, MD, OHTS Clinical Center Investigator at 314-362-3973 or name, Ms. Sarah Brown, Coordinator at 314-747-5832.

If you have questions, concerns or complaints about your rights as a research participant please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445 or email hrpo@wusm.wustl.edu.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Do not sign this form if today's date is after \$STAMP_EXP_DT.

(Signature of Participant)

(Date)

(Participant's name – printed)

Legally Authorized Representative's Name and Relationship to Participant:

Do not sign this form if today's date is after \$STAMP_EXP_DT.

(Participant's name – printed)

(Signature of Legally Authorized Representative)

(Date)

<hr/> (Name of Legally Authorized Representative - printed)(Relationship to Participant – printed)
--

Who should sign as the Legally Authorized Representative (LAR)?

If the participant has a legal guardian or attorney-in-fact this individual must sign as the LAR.

If there is no legal guardian or attorney-in-fact the individuals listed below may sign in order of priority.

- (1) Spouse unless the participant has no spouse, or is separated, or the spouse is physically or mentally incapable of giving consent or the spouse's whereabouts is unknown or the spouse is overseas;
- (2) Adult child;
- (3) Parent;
- (4) Brother or sister;
- (5) Relative by blood or marriage.

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

(Signature of Person who Obtained Consent)

(Date)

(Name of Person who Obtained Consent - printed)

Appendix 2-F Telephone Recruitment Script for Study Participation

Read sentences in **BOLD** word-for-word

1. **Hello** (*patient name*), **I am** (*investigator or research assistant name*) from **(Washington University School of Medicine Department of Ophthalmology)**.

2. *What is the purpose of the study:*

I am contacting you because you participated in the Ocular Hypertension Treatment Study. It's been 20 years since this study started. We are contacting all participants to find out about their general health and their vision after 20 years. The National Institutes of Health is funding this research study.

This study is important because information about the effects of ocular hypertension and glaucoma after 20 years will help guide patients and doctors.

This study will determine many people have developed glaucoma, how many have mild versus severe glaucoma and how many people have functional limitations because of glaucoma.

3. **Is it okay for me to continue?**

If individual says “no” **STOP, say thank you and do not continue.**

If he/she says yes, then continue.

4. *What will Happen During this Study?*

In this study, we would like to have you come to the (eye clinic) for 1, 2, or 3 study visits. There are no experimental drugs or study treatments

- **You will receive standard tests and measures for people with ocular hypertension or glaucoma.**
- **We will ask you questions about your general health and vision.**
- **We can help you arrange transportation like a taxi and will cover the cost of lunch for you and a companion.**
- **The first visit could take four to six hours. If you prefer, you can do the tests in 2 or 3 shorter visits.**
- **Participants will receive \$50 check after each visit.**

5. (If you are currently being seen at (Clinic name), this study is separate from the eye care you are currently receiving. Whether or not you decide to participate in this study will not affect your eye care.)

6. **Would you be interested in participating in this study?**

- “No”, **STOP, say thank you for his/her time and do not continue.**
- “Yes”, then schedule a clinic visit and transportation.
- “Unsure/maybe”, then offer more time to think about participation and call back later.
- “No, unable/unwilling” ask, **“Would you be willing to answer questions about your health and vision over the telephone?”**
 - If no, **STOP, say thank you for his/her time**
 - If “yes”, Use telephone QOL script, and schedule later

Appendix 2-G Recruitment Script for completion of QOL Survey by Telephone

OHTS: QOL Telephone Recruitment Script

The quality of vision after 20-years from the beginning of OHTS is one of the most important questions to be answered by this new study.

About **40** participants who participated in the Ocular Hypertension Treatment Study at this Clinical Center will be invited back to the clinic for eye examinations and questions about their vision.

Participants who cannot return for eye examinations can provide valuable information by telephone about their visual function such as:

- General physical and mental health
- Driving
- Falling
- Eye discomfort
- Reading, shopping and going out with friends and family

I will send you the surveys and a consent form ahead of time. If you are interested, I will schedule a time that we can go through the surveys together by telephone. Or you can sign the consent and fill out the survey ahead of time if you choose. It should take about 30 minutes to an hour to complete. You are free to skip any question that you prefer not to answer.

You can also authorize release of your visual field tests and OCT scans since the last OHTS visit. Personal information like your name will be removed and your de-identified visual fields will be reviewed by glaucoma experts. I can send you a form to authorize release of your visual field tests?

Would you be willing to release your visual field and OCT tests for evaluation?

Yes ___ (Coordinator initials: _____ Date: _____)

No ___ (Coordinator initials: _____ Date: _____)

What if I have questions?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: PI name (PI telephone) or coordinator (Coordinator name and telephone). I will send you complete contact information if you have questions, concerns, or complaints about your rights as a research participant.

I would like to set up a conference call to go over the survey on your vision in the next few weeks. Will this be “OK”?

“Yes” ___ schedule interview

“No” ___ but follow-up later

“No” ___ and no follow-up later, complete “Decline Interview form”

(Coordinator initials: _____ Date: _____)

If “Yes”, schedule day, date, time for call:

Day _____ MM/DD/YY: ___/___/___ Time: ___ AM or ___ PM

Appendix 2-H Sample Cover Letter for Completion of QOL Survey by Telephone

Departmental Letterhead

(Cover letter for Telephone Consent for QOL Survey and Release of Visual Field Tests)

Date: mm/dd/yy

Dear (OHTS Participant name):

Thank you very much for agreeing to participate in the 20-year follow-up study of the Ocular Hypertension Treatment Study (OHTS by telephone. The medical care of patients with ocular hypertension and glaucoma has been improved world-wide as a result of OHTS.

The OHTS study coordinator, Ms. Pistorius, will answer any questions you may have and to go over the surveys. She will call you at the telephone number below on:

Your telephone number: (area code-xxx-xxxx)
Day of week, month, day, year at XX am/pm.

If any change in the time or date of the call is necessary, please contact Ms. Pistorius at 314-747-5590.

Please sign the enclosed form for release of visual field tests and OCT scans. Please return the signed form using the self-addressed, stamped envelope.

If you have further questions about being a research participant in this study please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445 or email hrpo@wusm.wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, <http://hrpo.wustl.edu>. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

Sincerely,

Anjali Bhorade, M.D., MSCI
OHTS Clinical Center Investigator
314-362-3937 (CAM clinic)

Appendix 2-I Release of Visual Field Tests and OCT Scans



Washington University Physicians[®]
 Washington University School of Medicine in St. Louis

**Authorization for Release of
 Health Record Information**

I hereby authorize **Washington University Physicians** to transfer, release or obtain information on:

 (Name of Patient) (Date of Birth) (Last 4 digits of Social Security #)

OBTAIN FROM:	DISCLOSE TO:
(Physician/Institution)	(Physician/Institution/Patient)
(Attention)	(Attention)
(Address)	(Address)
(Address)	(Address)
(City, State, Zip)	(City, State, Zip)
(Phone) (Fax)	(Phone) (Fax)

For the purpose of: Ocular Hypertension Treatment Study 20-year Follow-up

Data related to ocular hypertension and glaucoma from your last OHTS visit (_____ date) to date;
 specifically as listed below:
 1. Visual Fields
 2. OCT Images (Optical Coherence Tomography)

- This request is a free and voluntary act by me. I understand that I may revoke this authorization at any time by sending a written notice of revocation to:

Washington University
Health Information—Release Services
Campus Box 1219
4240 Duncan Ave., Suite 301
St. Louis, MO 63110
Office Phone: 314-273-0453 Fax: 314-273-0465
- The revocation will not apply to information already released in response to this authorization.
- I understand that if I choose not to give this permission or if I cancel my permission, I will still be able to receive any treatment or benefits that I am entitled to, as long as this information is not needed to determine if I am eligible for services or to pay for the services that I receive.
- I understand that once my information is used and/or disclosed pursuant to this authorization, it may no longer be protected by federal privacy regulations and may be subject to re-disclosure by the recipient(s).

Authorization is valid either for 90 days from the date of signature (if not otherwise specified) OR as specified by selecting the option below:

- This authorization expires on the following date _____
I have read and understand this consent and I have signed it voluntarily.**

(Signature of Patient or Parent/Legal Representative)

(Date)

(Relationship to Patient)

(Witness)

(Date)

(Patient's Address, City, State, Zip)

(Certified copy of appointment of legal guardian or personal representative and death certificate of deceased patient must be attached)

Appendix 2-J Sample Note to File to document LAR assistance with Quality of Life Questionnaires

Study Name: Ocular Hypertension Treatment Study 20-Year Follow-Up
PI: Anjali Borhade, MD
IRB Number: 201507107

Date: mm/dd/yyyy

NOTE TO FILE

I called participant # _____ and spoke with the legally authorized representative *insert name of LAR*, who assisted me with asking the participant the questions contained in the OHTS quality of life questionnaires.

Signature

Insert OHTS Coordinator or Interviewer Name

Date

Appendix 2-K Sample E-Mail to HIPAA Privacy Officer

The Ocular Hypertension Treatment Study (OHTS) 20-year follow-up is an observational study of 1,636 participants who were originally enrolled in 1994-1996 in a randomized clinical trial conducted to determine whether ocular hypotensive medication to lower intraocular pressure in ocular hypertensive individuals prevented/delayed the onset of primary open angle glaucoma. The Washington University site IRB # for the original study is 201107109. The participants were followed between the years 1994 – 2008.

In 2012-2013, OHTS conducted a feasibility study to determine the level of participation in the OHTS 20 year follow-up study. Clinical Centers were asked to contact OHTS participants to determine their willingness to return for examination. 309 deaths have been confirmed among the 1,636 participants who were originally enrolled in OHTS. Thus, there are 1,327 participants presumed survivors.

Goals of the OHTS 20-year follow-up study (IRB 201507107) are to determine how many people developed glaucoma, how many have mild versus severe glaucoma and how many people have functional limitations because of glaucoma. OHTS 20-year follow-up includes the largest, best studied, inception cohort of patients to develop POAG under observation. We will also develop 20-year prediction models to help clinicians identify patients who are at high/low risk for developing glaucoma and who are likely/unlikely to lose visual function rapidly.

Because OHTS is the only study with a sufficiently large cohort of ocular hypertensive participants to estimate the 20 year risk of developing POAG, collecting clinical data from the deceased participants will be instrumental to enable clinicians and patients to make personalized, evidence-based clinical management decisions of ocular hypertension. In addition, OHTS has the largest inception cohort of patients who developed POAG under observation ever reported. OHTS is uniquely positioned to document the incidence of functional limitations due to POAG, a question that has significant public health implications.

Please let me know if more/less information is required for HIPAA compliance of obtaining data on deceased participants.

3. Eligibility and Exclusion Criteria

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3.1 Introduction

The goal in the OHTS 20-year follow-up study (Phase 3) is to examine all participants randomized to OHTS Phase 1. This includes participants who did not enroll in OHTS Phase 2 as well as participants who dropped out and those who may be unable to complete reliable visual fields and/or provide gradeable optic disc photographs.

Effort should be made to complete all tests and measurements. An attempt should be made to complete a test even if a participant may be unable to provide gradeable results (e.g. unreliable visual fields due to cognitive impairment, lens opacification, inability to fixate). Results should be sent to the respective Reading Center with an explanation for incomplete/poor quality data. Almost all participants will be able to complete some of OHTS Phase 3 tests including quality of life surveys which are an important outcome in OHTS Phase 3.

3.2 Eligibility for OHTS 20-Year Follow-up (Phase 3)

All participants enrolled in OHTS Phase 1 are eligible to participate in OHTS Phase 3.

Earnest effort should be made to enroll participants who...

a. Are unable/unwilling to return to the OHTS Clinical Center for examination

Every effort should be made to retrieve information on the participant's current visual status, medical history and quality of life. Clinical Centers should request participant's consent for a quality of life telephone interview, release of ocular medical records, including Humphrey 30-2 Sita standard visual fields, from their eye care clinician since their last OHTS visit to date. A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

b. Were lost to follow-up or dropped-out

Participants who dropped out or were lost to follow-up should be encouraged to participate in OHTS Phase 3 - even if they have not been seen for years for study visits. Their participation will reduce potential bias and increase validity of the study. The Clinical Center should request the Coordinating Center for services of a professional service to retrieve current contact information and vital status.

c. Developed POAG in one or both eyes

It is particularly important to enroll participants in OHTS Phase 3 who developed POAG previously in OHTS Phase 1 or 2 because they will provide important information about early visual field and optic disc change in POAG, the rate of progression of glaucomatous damage, the rate of conversion to POAG in fellow eyes and the association of POAG with self-reported functional limitations.

d. Developed a medical condition during follow-up in OHTS that would have excluded them from OHTS initially.

Some participants have developed a medical condition (e.g. diabetic retinopathy) that would have excluded them from enrolling in OHTS initially. These participants are eligible for OHTS Phase 3. These participants will provide information of the effect of ocular and systemic co-morbidities on self-reported functional limitations.

e. Are unable to perform reliable visual fields

These participants should be enrolled in OHTS Phase 3. Self-reported functional limitations, as well as other Clinical Center tests and measures will be very informative in this group.

f. Are unable to provide useable optic disc photographs

These participants should be enrolled in OHTS Phase 3. Self-reported functional limitations, as well as other clinical tests and measures will be very informative in this group.

4. Participant Education and Informed Consent

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4.1 Introduction

In an effort to enroll all OHTS participants, considerable attention is given to education of the participant and family members so that they have a good understanding of ocular hypertension, glaucoma, the clinical tests and measures, and the importance of 20-year data on the OHTS cohort. Participant education is a key element in the informed consent process. The participant and family member(s) should receive in person or by mail the OHTS Phase 3 flyer that describes the study and gives the link to the study website. Each participant has already made an impact on clinical management of ocular hypertension in the United States and world-wide. Their continued involvement and support continues to be vitally important.

The informed consent process provides confirmation that the participant participated in a discussion of the study. The rationale for written informed consent is not solely legal or bureaucratic but includes description of the tests and measures and the goals of the study. The informed consent process protects the participant as well as the scientific integrity of the study. If the participant is unable/unwilling to return for examination when queried, the participant can provide verbal consent for completion of quality of life surveys by telephone and for release of OCT scans and VF tests since their last OHTS visit. Templates for consent forms are in MOP Chapter 2 Study Design Appendices. A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

4.2 Participant Education

The Clinical Center Investigator and the Clinical Center Coordinator must explain to participants about ocular hypertension, glaucoma, the OHTS Phase 3 tests and measures and the importance of release of records since their last OHTS visit to understand interim changes in their ocular hypertension and glaucoma. For participants unable/unwilling to return for examination when queried, there is the option for a telephone quality of life survey and release of OCT scans and VF tests since their last OHTS visit. Clinical Centers should make every effort to have available the services of interpreters for individuals who do not speak English. Discussion with the participant should include the following:

- Ocular hypertension is a common condition occurring in some 4% to 7% of the population over age 40 in the United States.
- Ocular hypertension may be a forerunner of open-angle glaucoma; however, only a small proportion of people with ocular hypertension develop glaucoma during their lifetime.
- Glaucoma is a condition which can cause loss of vision and even blindness in some individuals.

- In OHTS Phase 3, the participant will complete 1 to 3 visits that will include a comprehensive eye examination consisting of visual fields, optic disc photos, OCT scans, Pelli-Robson contrast sensitivity, refraction, intraocular pressure, visual acuity, blood pressure, slit-lamp examination, ophthalmoscopy, gonioscopy, medical history and quality of life questionnaires (section 5.2).
- A patient may agree to participate in all, some or none of the components of OHTS Phase 3. The consent process includes consent to OHTS Phase 3 examinations, release of OCT scans/VF tests since their last OHTS visit from OHTS Clinical Centers and non-OHTS sites and release of Medicare records if they have not already consented to this. Templates for consent forms are in MOP Chapter 2 Study Design Appendices.

Participants who are unable/unwilling to return for examination due to family crises, illness or vacation, may be able to complete a visit at a later time. Or they may provide verbal consent to complete quality of life surveys via telephone interview and to release OCT scans and VF tests since their last OHTS visit. Consent for participation in the telephone interview will be documented at the time of the interview.

A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

4.3 Informed Consent

Investigators at each Clinical Center are responsible for conducting the consent process. The participant should be given in person or mailed the OHTS Phase 3 study flyer. The Clinical Center Investigator should describe study procedures, discuss the risks and benefits and alternatives to participation, and discuss the voluntary nature of participation with the potential subject. Clinical Center Investigator will answer all questions and review the study a second time to insure that the patient has a reasonable comprehension of the study and its goals. The patient should be asked to sign the consent form only after all questions have been answered to his or her satisfaction.

After the educational discussions outlined above in 4.2, the Clinical Center Investigator asks the participant to sign the consent forms (OHTS Phase 3 examinations and Release of OCT scans/VF tests since their last OHTS visit). A participants may agree to all, some or none of the consent options. Participants are told that they can withdraw from the study at any time and that withdrawal will not interfere with their ability to obtain follow-up care. Participants are informed that they will receive up to \$100 for the cost of transportation, \$50 stipend and \$25 for meals for two people at each visit.

In signing the OHTS phase 3 examination consent form, the participant agrees to complete 1 to 3 visits and associated tests and measures. In signing the Release of Records consent form the participant agrees to let OHTS have access to their de-identified OCT scans/VF tests since their

4-4 Participant Education

last OHTS visit to date. If a participant prefers to think about the study at home, he or she is encouraged to do so. Additional questions can be answered in person or via telephone. A Spanish language translator will be made available to explain the study and the consent forms.

Consent to participate in OHTS Phase 3 must be signed before testing or collection of any study data. The consent for release of records must be signed before data is retrieved. Failure to obtain written informed consent, for any reason, makes the participant ineligible until written consent is obtained.

One copy of the signed consent is supplied to the participant and one is filed with the study records in the Clinical Center. To protect participant confidentiality, copies of the signed consent form are not sent to the Coordinating Center. Signed consent forms are audited at clinic site visits to confirm that they have been signed and are in proper order. The consent form must be stored in HIPAA compliant secure files separate from research data.

4.4 Informing Participants of Study Results

One of the most satisfying aspects of participating in a research study is the opportunity to improve the quality of care for others with the same ocular condition. Clinical Centers are responsible for maintaining current contact information via postal mail, e-mail or social media for OHTS participants who wish to receive study updates and new results.

5. Visits and Examinations

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5-2 Visits and Examinations

5.1 Introduction

Data for OHTS Phase 3 come from the following sources:

1. Tests and measures performed by OHTS certified personnel at Clinical Centers
2. Participant-completed quality of life surveys
3. Retrieved electronic OCT scans and visual field (VF) tests since the last OHTS visit up to date from OHTS and non-OHTS clinics for:
 - a. Participants who developed POAG in OHTS 1 or 2 or are found to have developed POAG in OHTS 3
 - b. Participants who are unable/unwilling to return for examination;
 - c. Participants who have died since March 2009 (end of OHTS 2).

Participants may need one to as many as three visits in an OHTS Clinical Center to complete Phase 3 tests and measures. One visit is sufficient if the participant is able to complete all study measures and all measures are reliable and normal. Participants who have unreliable or possibly abnormal test results may require as many as three visits. Participants, who developed visual field POAG in OHTS previously or are suspected to have developed visual field POAG in OHTS Phase 3 will need 3 visual fields. Participants who developed disc POAG in OHTS previously or are suspected to have developed disc POAG in OHTS 3 will need 2 sets of stereo photographs.

5.1.1 Tests and Measures Requiring OHTS Certification

At least one Clinical Center personnel must be OHTS certified to perform the functions below.

Functions requiring OHTS certification	Certification Procedure	MOP Section
Clinical Center Investigator Clinical Center Coordinator	<ul style="list-style-type: none">• OHTS Phase 3 Protocol knowledge• Satisfied by attendance at FIG meeting or• Certification by Coordinating Center	7.16
Visual field testing	Testing & certification by VFRC	5.10, 11.8
Optic disc photography	Testing & certification by ODRC	5.11, 12.2.1
OCT	Testing & certification by OCTRC	5.12, 13.7
IOP, ETDRS, Pelli-Robson contrast sensitivity	Grandfathered if previously OHTS certified	
IOP	Certification by Coordinating Center	5.6.1, 7.13
ETDRS	Certification by Coordinating Center	5.3, 7.10
Pelli-Robson contrast sensitivity	Certification by Coordinating Center	5.4.1, 7.11
Ophthalmoscopy, gonioscopy, SLE	<ul style="list-style-type: none">• OHTS Phase 3 Protocol knowledge• Satisfied by attendance at FIG meeting or• Certification by Coordinating Center	5.8, 7.3
Blood Pressure	Certification by Coordinating Center	5.9.1, 7.16
REDCap data entry	Certification by Coordinating Center	5.15, 7.17

5.2 Schedule of Tests and Measures

Core Schedule of Tests and Measures (Level 1 Data)

<ul style="list-style-type: none"> Assessments should be completed within 6 mos. More than one visit may be needed to complete all <u>core tests and measures</u> 	Neither eye is POAG
Consent Forms	
Consent for OHTS Phase 3 Examination	
<ul style="list-style-type: none"> All pts. consent to release electronic OCT scans taken since their last OHTS visit For pts. diagnosed with visual field POAG in OHTS Phase 1 or 2 or newly diagnosed in Phase 3, consent to release <u>both</u> electronic OCT scans and VFs from OHTS or non-OHTS clinics since their last OHTS visit 	X
For pts. unable/unwilling to come into clinic Verbal consent for telephone QOL survey & written release of electronic OCT scans, VF tests, and medical history summary since their last OHTS visit	(X)
Quality of Life Surveys (QOL)	
Ocular Symptom Checklist	X
NEI-VFQ, SF-36, Functional Measures	X
Clinical Tests and Measures (FV Form)	
Updated ocular/systemic medical history, height and weight, history, medications and smoking	X
Blood pressure	X
Refraction	X
Snellen VA at each visit	X
ETDRS Best corrected visual acuity	X
Pelli-Robson Contrast Sensitivity	X
Humphrey program 30-2 SITA Standard visual fields (VF) *Retest for abnormality or unreliability required per protocol or VFRC	(X)*
Optical Coherence Tomography (OCT) RNFL & Macula	X
External eye examination at each visit	X
Slit-lamp examination at each visit	X
Corneal Hysteresis	X
Applanation tonometry at each visit	X
Dilated ophthalmoscopic exam/indirect ophthalmoscopy	X
2 sets of the “best quality possible” stereoscopic optic disc photographs for each eye	2 stereo pairs per eye
Gonioscopy	X

Level 2 and/or 3 Data, Examination and Measures

Assessments should be completed within 6 months of Core Tests and Measures	
Level 2 or 3 Data as Required by a Reading Center or for Assessment of POAG Status	
Repeat Clinical Tests and Measures (RV Form)	
Snellen VA at each visit	X
Humphrey program 30-2 SITA Standard visual fields (VF) *Retest for abnormality or unreliability required per protocol or VFRC	(X)*
*External eye examination at each visit	X
*Slit-lamp examination at each visit	X
*Direct ophthalmoscopic examination	X
Applanation tonometry at each visit	X
2 sets of the “best quality possible” stereoscopic optic disc photographs for each eye (if required by Reading Center) *Retest for poor quality photographs if required by the ODRC	2 stereo s per eye

*Only dilate if repeat photographs are required

5.2.1 Timetable for Transmitting Data to Resource Centers

Data from Tests	Days from test date to transmission to Resource Centers	Days to Resource Center feedback to Clinics
Visual Fields	14 days Transmit data to VFRC	VFRC 14 days
Optic Disc Photographs	14 days Transmit data to OHTS Coordinating Center	ODRC 14 days
OCT scans	Monthly uploads Transmit data to OHTS Coordinating Center	OCTRC not applicable, limited feedback on image quality
Case report forms entered in REDCap	7 days from test date	Coordinating Center Immediate auto editing

5.2.2 Refraction

Refraction is required on Visit 1 and is particularly important for visual field testing. Refraction may be performed by any certified OHTS personnel – no specific certification for performing refraction is required. Refraction protocol is from the Diabetic Retinopathy Vitrectomy Study/refraction protocol.

5.2.3 Refraction Technique

Any standard visual acuity chart or computer screen may be used to determine the best lens correction in each eye. The right eye is refracted first, then the left eye.

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 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 phoropter for the subjective refraction. However, for visual acuity testing the lenses from the final phoropter 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.

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- 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.

- **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 one 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, on the other hand, 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 quarter 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. The entire process is repeated for the left eye and the lens corrections are recorded on the worksheets for refraction and visual acuity.

5.3 Visual Acuity

ETDRS visual acuity is performed on Visit 1. Only OHTS personnel specifically certified for ETDRS visual acuity can perform ETDRS visual acuity. (See “[ETDRS Visual Acuity](#)”

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Certification", section 5.3.3). Previous certification for ETDRS testing in OHTS Phase 1 or 2 will be accepted as certification for Phase 3.

Snellen visual acuity using a wall mounted chart or monitor screen is performed at Visit 1 and each subsequent study visit. OHTS personnel certified for knowledge of the OHTS Phase 1, 2 or 3 protocols are permitted to perform Snellen visual acuity.

Visual acuity is measured before pupil dilation, tonometry, gonioscopy or any other technique that would affect vision.

5.3.1 Snellen Visual Acuity Technique

Snellen/monitor visual acuity testing is performed at each visit. Clinical Center personnel do not have to be certified to perform Snellen/monitor visual acuity testing.

Snellen visual acuity is measured using a standard wall or projection chart or monitor screen. The same chart must be used for the duration of OHTS 3. The examiner should ensure that the participant is seated comfortably and that the participant's head does not move forward or backward during the test so that the participant's eyes remain at a constant distance from the chart. The participant should be told that the chart has letters only, no numbers. If the participant, forgetting this instruction, reads a number, he or she should be reminded that the chart contains no numbers; the examiner should request a letter in lieu of the number. After careful instruction, refraction and the placement of the proper lenses in the trial frame, the left eye is occluded and testing begins on the right eye. The examiner records the number of the line read with two or fewer errors. The procedure is then repeated for the left eye.

5.3.2 Snellen Visual Acuity Scoring

The examiner records the distance at which the chart is read in the first two boxes. If the line is read perfectly, record the line number in the next three boxes. If three out of five letters are read in a line, the participant is given full credit for that line. For example, if a participant reads 20/25+3, record 20/20. If only two out of five letters are read on a line, the participant is not given credit for that line, e.g. if a participant reads 20/25+2, record 20/25. If the participant's Snellen visual acuity is worse than 20/200 then ETDRS visual acuity does not have to be performed.

5.3.3 ETDRS Visual Acuity Certification

All study personnel performing an ETDRS visual acuity test must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief certification test requested by the Coordinating Center. The test is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Certification for ETDRS visual acuity testing remains in effect as long as performance is satisfactory. Previous certification for ETDRS testing in OHTS Phase 1 or 2 will be accepted as certification for Phase 3.

5.3.4 ETDRS Visual Acuity Technique

ETDRS best corrected visual acuity is performed at visit 1 by OHTS personnel certified to perform ETDRS visual acuity. (See “[ETDRS Visual Acuity Certification](#)”, section 5.3.3). If the participant’s Snellen visual acuity is worse than 20/200 then ETDRS visual acuity does not have to be performed.

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 (1, 2 or R) can be used. The room illumination should be between 7.4 fc – 29.7 fc range registered on the EXTECH 401027 Foot Candle Light Meter. The light sensor (with black cap removed) should be held approximately 1 foot in front of the chart to display the foot candle reading. Be sure you are not creating shadow with hand or body. 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, that the head does not move forward or backward during testing. After careful instruction, refraction and the 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 the ability to concentrate or follow or 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 in lieu of the number.

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 to not proceed until the participant has given 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. Examiner can state: **“Some letters are harder to see than others. If you are not sure go ahead and guess. It’s fine to get some wrong.”** Do not tell them if they make a mistake. 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 that the fellow eye remains covered. Examiner may provide neutral encouragement: *“Uh-huh, uh-huh, good. Go ahead and guess. We need you to go as far as you can, guessing when you are not sure.”* Stop at the end of the row on which participant gets 3 or more letters wrong.

There are several reasons for encouraging participants to guess: (1) participants' statements that they cannot identify a letter are often unreliable; (2) encouraging them to guess helps to maximize the participant's effort; (3) it helps to assure uniformity among procedures performed in different Clinical Centers; and (4) it may help to 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”) before he or she has read aloud the next letter, then the change should be accepted. If the participant changes a response after beginning to read the next letter, the change is not accepted.

After the test of the right eye is completed, occlude the right eye. The test is repeated for the left eye.

5.3.5 ETDRS Visual Acuity Scoring

The ETDRS visual acuity worksheets are for Clinical Center use only and should not be transmitted to the Coordinating Center. The examiner records each letter identified correctly by circling the corresponding letter on the appropriate Visual Acuity Worksheet (Worksheet 1, 2 or R). The examiner records letters read incorrectly and letters for which the participant makes no guesses with a slash or “/”. 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 OHTS Clinical Evaluation Form.

5.3.6 ETDRS Visual Acuity Testing Discontinuation

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

5.4 Pelli-Robson Contrast Sensitivity

Pelli-Robson Contrast Sensitivity is performed at visit 1 by personnel OHTS certified to perform Pelli-Robson Contrast Sensitivity test. (See Pelli-Robson Contrast Sensitivity Certification, section 5.4.1).

There is evidence that contrast sensitivity is affected early in the glaucomatous process. The Pelli-Robson Contrast Sensitivity chart consists of 8 lines each containing 6 Sloan letters (2 sets of triplets) that stay the same size but decrease by about 40% in contrast sensitivity successively. The letters range in contrast from about 96% to 1%.

The OHTS protocol for Pelli-Robson Contrast Sensitivity testing was developed from similar protocols used in the Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Occupational Therapy Functional Vision Study.

5.4.1 Pelli-Robson Contrast Sensitivity Testing Certification

Study personnel performing Pelli-Robson Contrast Sensitivity testing must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief certification test requested by the Coordinating Center. The test is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Certification for contrast sensitivity testing remains in effect as long as performance is satisfactory. Previous certification for Pelli-Robson testing in OHTS Phase 1 or 2 will be accepted as certification for Phase 3.

5.4.2 Schedule for Contrast Sensitivity Testing

Pelli-Robson Contrast Sensitivity Test is performed after refraction and visual acuity testing and before tonometry or dilation or any other technique that would affect vision.

5.4.3 Pelli-Robson Contrast Sensitivity Chart Placement and Illumination

There are two Pelli-Robson charts, one for the right eye and one for the left eye. Each has a different letter sequence but is otherwise identical.

The participant should be seated 1 meter (39.5 inches) from the chart.

The charts should be hung or mounted so that the center (the top of the 4th row of letters) will be approximately 45 ± 5 inches from the floor. The chart must be level and perpendicular to the floor.

The Pelli-Robson charts may be mounted to the wall or to the **back** of an ETDRS light box with the top of the Pelli-Robson charts aligned with the top of the light box, lining up both, so the charts are level when viewed by the participant. If an easel or other prop is utilized, the charts must be not only level but also perpendicular to the floor. The charts should not be available for viewing by the participant before testing.

The Pelli-Robson charts should be illuminated as uniformly as possible, so the luminance of the white areas range from 18.4 fc – 36.9 fc registered on the EXTECH 401027 Foot Candle Light Meter. The light sensor (with black cap removed) should be placed on the white area of the center and 4 corners of the vision chart. The sensor lays flat on the chart with the sensor facing out toward the source of light to be monitored. Be sure you are not creating shadow with hand or body. Illumination is confirmed by a light meter reading in the white area of each corner and in

the center of the chart; the variance between any two of these measurements should be ≤ 7.0 fc from the lowest reading to the highest reading. It is important that the illumination of the chart remains the same throughout the study. (See 5.4.7 Care and Use of Light Meters.) It is very important that the light **not** vary due to windows near the measurement area (i.e., a bright sunny day vs. a dark day) or any conditions which could cause the light to vary between exam days. Glare should be avoided, and if extra light/lamps are needed to achieve the proper illumination care should be taken to avoid glare and the participant should not see the lamps themselves or any mirror-like reflections of the lamps on the surface of the chart. A lighting log (OHTS Confirmation of Pelli-Robson Protocol: CP) is required to be completed monthly, recording the date of measurement, certification initials, illumination at all 4 corners and center of the chart, supplemental lighting information and storage procedure.

5.4.4 Pelli-Robson Testing Technique

The participant must be seated in a sturdy backed chair not on wheels at 1 meter (39.5 inches) from the chart. Use a 1 meter non-flexible measuring device to insure a 1 meter distance from the front of the participant's eye to the front of the chart. The participant must be instructed that they cannot move backward or forward in their seat as this would affect study results. The **test will be performed with trial frames** on the participant containing the appropriate distance refraction with +0.75 diopters added for 1 meter testing. It is advisable to **change** the power of the spherical lens in the trial frame by +0.75 rather than just **adding** +0.75 sphere to the trial frame as stacking lenses often adds undesired glare to the chart.

Each eye is tested separately using the designated chart for the right eye (starting with triplet H-S-Z) and the left eye (starting with triplet V-R-S). The fellow eye must be occluded by using a tissue or a patch under the trial lens occluder. It is acceptable for the participant to turn their head from side to side, up or down or view eccentrically to try to visualize the letters, so care must be taken to fully occlude the non-study eye. It can take several seconds to see the very faintest letters, so subjects should not be rushed.

Examiner can begin testing by telling the participant:

“On this chart, the letters stay the same size, but they get more and more faded towards the bottom. If you are not sure of the letter, go ahead and guess. Sometimes, it helps just to stare at the letter for a moment. It is **OK** for you to move your head left or right, or up and down but do not move your head forward or backward. It can take several seconds to see the very faintest letters, so please take your time.”

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

When the participant hesitates...

Examiner says, “Go ahead and guess. We need you to go as far as you can, guess if you are not sure. Keep looking-sometimes the letter appears even though it is invisible when you first look.”

When the participant has difficulty deciding between 2 letters...

Examiner says, "Try your best to choose, but if they are equal, it is best to guess."

When the participant makes a mistake...

Examiner does not tell them they made a mistake.

Continue until the participant gets 2 of 3 letters in a triplet wrong...

Examiner stops the participant, "Okay, that's great. Now you can stop."

After the test of the right eye is completed, occlude the right eye. The test is repeated for the left eye using the chart starting with triplet V-R-S.

5.4.5 Pelli-Robson Scoring

The examiner records each letter identified correctly by circling the corresponding letter on the Contrast Sensitivity Worksheet. Letters read incorrectly and letters for which no guesses are made are not marked on the form.

If the participant changes a response after beginning to read the next letter, the change is not accepted. If the participant changes a response aloud (e.g. "That was a "C," not an "O") before reading the next letter aloud, then the change is accepted.

Stop when the participant gets 2 of 3 letters in a triplet wrong. Record the score by entering the triplet number adjacent to the triplet of letters in which the participant got 2 of 3 letters correct. For example, the participant reads all three letters in the first triplet for the OS test correctly, e.g., V-R-S; but in the second triplet, the participant correctly reads 1 letter (K) and incorrectly reads the next 2 letters (D-R). Record the value "1" for this eye.

5.4.6 Care of Pelli-Robson Charts

The chart's plastic substrate and special ink were chosen for their great stability and contrast clarity. Do not use the chart if it is marred by visible marks, e.g., fingerprints. If necessary, the charts may be wiped gently with a soft cloth using a highly diluted solution of mild soap or detergent (e.g., ivory liquid) in water; then rinse with clean water.

Avoid exposure of the image to direct sunlight or any UV light source. To prolong the life of the chart, it is suggested that when the charts are not in use, they should be stored facing each other and preferably kept in the cardboard box that they were shipped in as this minimizes the amount of dust and dirt that will fall on the charts. Another suggestion is to have an extra paper covering made to place over the charts except when testing. Sometimes there is an expiration date printed on the top of each chart at manufacture, however, with correct handling and use the life of the chart can be extended. (Please note not *all* charts have an expiration date). If noticeable degradation in the background contrast develops, it is recommended that the chart be replaced.

5.4.7 Care and Use of Light Meters

The light meter is used for checking illumination each time Pelli-Robson Contrast Sensitivity testing is performed. Contrast sensitivity measurement is sensitive to variations in illumination.

The chart (the center and 4 corners) should be illuminated as uniformly as possible, so the luminance of the white areas range from 18.4 fc – 36.9 fc. Illumination is confirmed by a light meter reading in the white area of each corner and in the center of the chart; the variance between any two of these measurements should be ≤ 7.0 fc from the lowest reading to the highest reading. The sensor lays flat on the chart with the sensor facing out toward the source of light to be monitored. Be sure you are not creating shadow with hand or body. It is important that the illumination of the chart remains the same throughout the study.

Each Clinical Center is provided with one EXTECH Instrument, 401027- Foot Candle Light Meter by the Coordinating Center. Once received at the Clinical Center, the care and maintenance becomes the responsibility of that Clinical Center.

Meter Operation

1. Slide the ON/OFF Switch to the ON position.
2. Fold out the meter's rear tilt stand and set the meter on a desktop.
3. Select range "B".
4. Hold the Light Sensor (Black cap removed) with the white lens facing the light source to be measured. The sensor can also be placed on the desktop facing in the direction of the light source.
5. Read the light measurement on the LCD display.
6. If the measurement is less than 200 fc, select the lower "A" range.

Light sensor

1. The light sensor is permanently attached to the meter by a cable.
2. The white domed light sensor lens is a photo diode and resides underneath the protective black cap.
3. The meter automatically zeroes, therefore a zero calibration is not necessary.

Taking light measurements

1. Remove the protective cap from the sensor and place the back of the light meter directly against the Pelli-Robson chart with the white domed light sensor facing toward the source of light to be monitored. Measure lighting of all four corners and the center of the chart.
2. Read the light level on the LCD.

Cleaning and storage

1. The white plastic sensor dome should be cleaned with a damp cloth when necessary.
2. Store the meter in an area with moderate temperature and humidity.

Battery Replacement

The low battery indicator "LO BAT" appears on the LCD display when it is nearing the time to replace the 9V battery. Reliable readings can still be obtained for several hours after the first

appearance of the low battery indicator. To replace batteries:

1. Slide the rear battery compartment cover off of the meter and remove the old battery.
2. Replace the battery and reinstall the compartment cover.

Repair Services

For repair of this EXTECH product, call customer service for details on services available. EXTECH Support Hotline: (877)439-8324.

5.5 Slit-Lamp Examination

Specific slit-lamp certification is not required. However, OHTS Clinical Center Investigators completing slit-lamp examination must have satisfactorily completed certification for knowledge of OHTS Phase 1, 2 or 3 protocols.

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.

5.6 Tonometry

Goldman applanation tonometry is performed at each study visit by an operator and recorder certified to perform OHTS IOP measurements. (See [Tonometry Certification](#), section 5.6.1). If eyedrops to lower IOP were taken in the last 24 hours, record the time of the last dose. This will tell us whether the IOP is a “treated” IOP or not. The tonometer is calibrated every month. It is suggested that a log be kept of calibration measurement and dates.

5.6.1 Tonometry Certification

Study personnel performing tonometry must be certified as to technique and recording of IOP by the Coordinating Center. Certification consists of completing a brief certification test requested by the Coordinating Center. The test is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Certification for tonometry remains in effect as long as performance is satisfactory. Previous certification for tonometry in OHTS Phase 1 or 2 will be accepted as certification for Phase 3.

5.6.2 Tonometry Technique

Two collaborators, an operator and a recorder, both of whom are OHTS certified for the procedure, perform the IOP measurement. Both eyes are tested, with the right eye always tested first. 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. At least two, and sometimes three, consecutive measurements are made to obtain a determination of intraocular pressure.

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A single measurement is made as follows:

- The recorder adjusts the tonometer dial to an initial setting corresponding to 10 mm Hg. The slit lamp magnification is set at 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 may be instilled. The operator should use the same technique each time, be it a paper strip or a pre-mixed eyedrop.
- 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 operator 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 that 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 corneal astigmatism is greater than 3.0 D, the prism is rotated so that the red line corresponds to the orientation of the longer axis of the elliptical applanated area.
- The above procedure is then 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 and recording of the results for IOP.

5.7 Gonioscopy

Specific certification is not required for Gonioscopy. A one-time gonioscopy measurement is performed by a Clinical Center Investigator certified for knowledge of the OHTS Phase 1, 2 or 3 protocols.

Gonioscopy is performed with the participant sitting at the slit lamp. The eye to be examined receives topical anesthesia. A mirrored gonioscopy lens (e.g., the Goldmann single- or three-mirror lens or the Zeiss four-mirror lens or equivalent) is applied to the cornea with appropriate coupling fluid as necessary.

The angle is graded according to the standard Shaffer system and results are recorded:

- **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** — angle less than 10°
- **Closed** — no trabecular meshwork seen without pressure on the lens.

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

5.8 Ophthalmoscopy

Dilated ophthalmoscopy is performed at Visit 1 and is performed by an OHTS Clinical Center Investigator certified for knowledge of the OHTS Phase 1, 2 or 3 protocols. Specific certification for ophthalmoscopy is not required.

The clinical morphology of the optic disc is assessed by direct ophthalmoscopy as well as a stereoscopic examination after pupil dilation with appropriate mydriatics. 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). Exam results are recorded.

5.9 Blood Pressure

Blood pressure measurement is performed at Visit 1 by study personnel certified for blood pressure measurements. (See Blood Pressure Certification, section 5.9.1).

5.9.1 Blood Pressure Certification

Certification consists of submitting data from two non-study participants to the Coordinating Center prior to taking a brief certification test requested by the Coordinating Center to perform OHTS blood pressure measurements. The test is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Previous certification for blood pressure measurements in OHTS Phase 1 and 2 will not be accepted as certification for Phase 3.

5.9.2 Blood Pressure Technique

Record the type of blood pressure monitor to be used if not using the OMRON monitor. The OMRON Upper Arm Blood Pressure Comfit Cuff – 7 Series Model BP760N provides non-invasive determination of systolic blood pressure, diastolic blood pressure, and pulse rate. Several studies suggest that blood pressure may be a risk factor for glaucoma.

Steps in using the OMRON Model BP760N automatic blood pressure monitor are below:

1. In a quiet room, the participant should be seated for 5 minutes in a comfortable chair with feet on the floor.
2. Loosen tight fitting clothing from the upper left arm. All blood pressure measurements should be taken on the left arm unless there is a medical contraindication.
3. Check that the air plug is securely inserted into the left side of the monitor.
4. The left arm should rest comfortably on a table or arm of a chair (do not rest the arm on lap) so that the blood pressure cuff is at the same level as the heart.
5. Place the Velcro cloth of the cuff on the upper arm with the lower edge of the cuff approximately ½ inch – 1 inch above the elbow.
6. The cuff tube should run down the center of the arm in alignment with the participant's middle finger.
7. Wrap the cuff snugly around the upper arm and secure with the Velcro.
8. Instruct the participant to keep the left arm still during blood pressure measurements.
9. Press START/STOP button on lower right corner of the monitor. Cuff automatically inflates to the ideal level and then stops.
10. When the blood pressure measurement is completed, the cuff automatically deflates. The systolic blood pressure, diastolic blood pressure and pulse are displayed.
11. Record systolic and diastolic blood pressures and pulse.
12. Take second blood pressure measurement after 2-3 minutes.

Record the sets of two readings for systolic blood pressure, diastolic blood pressure and pulse rate. The OMRON Model BP760N device displays the blood pressure result in “orange” if your Systolic BP pressure is 135 mmHG or above and/or the Diastolic BP pressure is 85 mmHg or

above. If the results are within the standard range, the blood pressure color indicator will light in “green”. The normal ranges for blood pressure measurements are as follows: Systolic =120 – 140 and Diastolic = 80 – 90. The normal Pulse rate range is 60 – 100 beats per minute. If the Clinical Center Coordinator enters readings that are outside these ranges, the REDCap entry system will ask the Clinical Center Coordinator to confirm the values are correct. The Clinic Coordinator has the option of correcting the values or overriding the alert.

Worrisome levels of blood pressure are defined as any value greater than 140 systolic and/or 90 diastolic. If worrisome levels of blood pressure or pulse are detected, take another set of two blood pressure measurements. For study purposes, record in REDCap the first two measurements. If worrisome levels are entered, the REDCap entry system will prompt the Clinical Center Investigator to consider contacting the participant’s family physician or taking other action in the participant’s best interest if appropriate.

Store the cuff and tubing loosely rolled, not tightly rolled. Avoid storing in extreme hot or cold temperatures, humidity or direct sunlight.

Examples of problems:

Cuff size too small: Cuff fits arm circumferences from 9 inches to 17 inches. If measurement cannot be taken due to cuff size, check “cuff too small” on the form as the reason for missing data.

Cellular phone: Do not use a cellular phone near the blood pressure monitor. It may cause operational failure.

Low battery: If the low battery indicator appears on the display, replace all 4 “AA” size batteries. Match the “+” and “-” ends of the batteries to the battery compartment. Use long-life alkaline batteries. Battery life is approximately 300 uses.

Pulse Rate: Recorded range is 40-180 beats per minute.

Error Messages and Troubleshooting: Please see OMRON Model BP760N Instruction Manual to review any error messages displayed during measurements

5.10 Visual Fields

Visual field testing is a functional measure to determine the development and/or progression of POAG. For this reason, the quality and completeness of visual field testing are crucial to OHTS 3. Visual field testing must be performed by OHTS certified personnel. The Visual Field Reading Center is responsible for completing all OHTS visual field testing certification (see section 11.8). All certified visual field technicians must maintain their certification by performing OHTS visual field tests on a regular basis. Certification will lapse for any technician who does not perform an OHTS visual field test for a period of six months. Previous certification for visual field testing in OHTS Phase 1 and 2 will not be accepted as certification in Phase 3.

All participants complete at least one Humphrey 30-2 visual field test of each eye using SITA Standard at Visit 1. Technicians should test a participant even if he/she may appear “unable” to perform visual field testing (dementia, muscular skeletal problems, poor vision, poor fixation). Results should be submitted to the VFRC with an explanation (on the case report form) from the Clinical Center investigator for poor quality and why retesting would be unlikely to improve data quality.

The VFRC will determine if tests need to be repeated because of poor quality or suspected abnormality. Retests should be completed within 3 months. If the suspected abnormality is confirmed in three consecutive visual fields and the VFRC determines that the abnormality is not artifactual, the VFRC sends all the visual fields for both eyes to the Coordinating Center for Endpoint Committee review. The Endpoint Committee determines if the abnormality is due to POAG.

Participants who developed visual field POAG in OHTS Phase 1 or 2, need to complete 3 visual field tests in the affected eye(s) to determine visual field progression. If the VFRC determines that the visual field loss has progressed, the VFRC sends all visual fields of both eyes to the Coordinating Center for Endpoint Committee review. The Endpoint Committee determines if the abnormality is due to POAG.

5.11 Stereoscopic Optic Disc Photography

Optic disc photography is a structural measure to determine the presence of optic disc conversion to POAG and/or progression of POAG. Therefore, the quality and completeness of optic disc photography are crucial to OHTS Phase 3. Optic disc photography must be performed by OHTS personnel certified by the Optic Disc Reading Center (ODRC) (see section 12.2.1). Previous certification for optic disc photography in OHTS Phase 1 and 2 will not be accepted as certification in Phase 3.

Optic disc photography is performed at least once on all participants. Even if a participant is difficult to photograph (media opacification, inability to dilate, poor fixation), photography should be performed and the image should be submitted to the OHTS Coordinating Center with an explanation (on the case report form) from the Clinical Center investigator for poor quality and why retesting would be unlikely to improve data quality.

The ODRC will determine if photography needs to be repeated because of poor quality or suspected conversion to POAG. Repeat photography should be completed within 3 months. If the suspected conversion is confirmed by two sets of optic disc photographs, the ODRC sends all optic disc photographs of both eyes to the Coordinating Center for Endpoint Committee review. The Endpoint Committee determines if the suspected conversion is clinically significant and due to POAG or not.

Participants who developed optic disc POAG in OHTS Phase 1 or 2, need to complete 2 sets of stereo-photographs in the affected eye(s) to determine the presence of optic disc progression. If the ODRC detects optic disc progression, the ODRC sends all optic disc photographs of both

eyes to the Coordinating Center for Endpoint Committee review. The Endpoint Committee determines if the optic disc progression is due to POAG or not.

5.12 Optical Coherence Tomography (OCT)

OCT will supplement visual fields and optic disc photography in helping the Endpoint Committee determine conversion/progression to POAG as a secondary endpoint.

Optical Coherence Tomography (Spectralis or Cirrus) is performed at least once on all participants on Visit 1. OCT must be performed by OHTS certified personnel. The Optical Coherence Tomography Reading Center (OCTRC) is responsible for completing all certification of OHTS imaging technicians (see section 13.7). Even if a participant is difficult to test, OCT should be performed and the image should be submitted to the OHTS Coordinating Center with an explanation (on the case report form) from the Clinical Center Investigator for poor quality. Retesting for poor image quality will NOT be done.

OCTRC sends OHTS Phase 3 scans of both eyes to the Coordinating Center for Endpoint Committee review for secondary endpoint determination of POAG conversion/progression.

5.13 Retrieval of OCT Scans and VF tests since Last OHTS Visit

It is important to reconstruct the clinical history of participants since their last OHTS visit for the following participants:

- a. Participants who developed POAG in OHTS 1, 2 or are found to have developed POAG in OHTS Phase 3;
- b. Participants who are unable/unwilling to return to the Clinical Center for examination;
- c. Participants who have died since March 2009 (end of OHTS 2).

Participants should be asked to sign a medical release form for their electronic OCT scans and VF tests since their last OHTS visit from OHTS and non-OHTS clinics. The Clinical Center Coordinator is responsible for requesting tests from the participant's private non-OHTS clinician.

The OHTS Clinical Center Coordinator must de-identify records (use OHTS ID and delete patient name/DOB and other identifying information) before transmitting records to the OHTS Coordinating Center. Instructions for transmitting data to the OHTS Coordinating Center are in MOP Chapter 11.7 and to the OCTRC in MOP Chapter 13.9 (Spectralis) and 13.15 (Cirrus).

5.14 Measurement of Quality of Life/Functional Limitations

An important goal of OHTS Phase 3 is to describe vision-specific quality of life and functional limitations after 20 years in participants who have/have not developed POAG. Participants should complete these surveys prior to clinical examination to avoid influence from the clinical examinations. Translators should be sought for foreign language speakers and the survey

administered with the help of the translator. The Clinical Center Coordinator may need to assist participants with poor vision, dementia or muscular-skeletal problems. Participants who are unable and/or unwilling to return for examinations can complete these surveys by telephone. A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

The QoL surveys include the following components:

1. SF-36 (QL).
2. NEI-VFQ-25 (VQ).
3. Nelson Glaucoma Quality of Life Survey to document vision problems specific to POAG (FM).
4. Items from the Owsley Driving Habits Questionnaire (FM).
5. Items from the Coleman Falls Questionnaire to document fear of falling, history of falls and type of injuries due to falling (FM).
6. Symptom Checklist (SY)

All surveys can be found in the file repository in REDCap <https://redcap.wustl.edu/redcap/srvrs/>

User Files		Data Export Files		Editing File	
Filter by file type: ALL					Action
	SF-36 (QL) File name: SF-36_QL_.pdf Date uploaded: 10/21/2015 File size: 76.6 KB				
	NEI-VFQ-25 (VQ) File name: NEI-VFQ-25_VQ_.pdf Date uploaded: 10/21/2015 File size: 84.9 KB				
	Functional Measures (FM) File name: Funtional_Measures_FM_.pdf Date uploaded: 10/21/2015 File size: 133.7 KB				
	Symptom Checklist (SY) File name: Symptom_Checklist_SY_.pdf Date uploaded: 10/21/2015 File size: 49.9 KB				

5.15 Secure Data Entry and Transmission

OHTS Phase 3 will use REDCap (Research Electronic Data Capture) secure web data entry system for data entry at Clinical Centers. REDCap was developed specifically to be in compliance with HIPAA-Security guidelines. All web-based information is encrypted. Individuals who will be using REDCap to query data or to enter data, including Clinical Center Coordinators and Resource Center Coordinators, will need to be certified to use REDCap. Each user will be assigned a unique user ID and password. User rights will be restricted on a role-specific basis e.g., access to study calendar, data import, data comparison, file repository, data

quality checks, graphical data view and statistics. Data entry rights will be set to none, read only, or view and edit.

Certification for REDCap requires familiarity with the short REDCap overview supplied by the Coordinating Center and demonstration of proficiency by performing routine tasks on a mock-up of the OHTS REDCap database. Certification will be granted upon satisfactory demonstration of ability to enter and edit data from forms, to attach and upload files and saving records. Certification will remain in effect for the duration of the study so long as performance remains satisfactory.

5.16 Corneal Hysteresis and Non-Contact Tonometry

Using the Ocular Response Analyzer (ORA)

The OHTS 3 protocol for the measurement of corneal hysteresis by non-contact tonometry was adapted from the African Descent and Glaucoma Evaluation Study (ADAGES) Manual of Procedures, version 7.0, October 2009, and the Ocular Response Analyzer[®] G3 User's Guide (16170-101 Rev. C) and Computer Interface Guide (16170-105 Rev. A).

Non-contact tonometry is also known as the “air puff” test. In addition to IOP, the Ocular Response Analyzer (ORA) provides a measure of the biomechanical behavior of the cornea to absorb and dissipate an applied air pulse force. There is a need to understand the role of corneal biomechanics in providing measures of the elastic and viscous material properties of the eye and how this may be related to glaucoma risk. OHTS 3 clinics collecting “hysteresis” measurements will receive an Ocular Response Analyzer[®] G3 for use during the study and will have the option to purchase the device after OHTS 3 is finished.

Contact the following individuals for questions on the ORA protocol:

- Sayoko E. Moroi, MD, PhD, University of Michigan, smoroi@med.umich.edu, Phone: 734-763-7974 Cell: 734-945-3842
- Mr. Jesse Gilbert, University of Michigan, jessegil@med.umich.edu, Phone: 734-615-0059
- Mr. Eric Cabezas, University of California San Diego, ecabezas@ucsd.edu, Phone: 858 534-8413

5.17 When to conduct ORA testing

Perform ORA after the slit lamp exam and before applanation tonometry.

An instructional video is located at <https://www.hightail.com/download/cUJXU2VwTIF0QTE3SGNUQw>

Definitions & Interpretation of Measurement Values

- IOP_{cc} - Corneal Compensated IOP. A Goldmann correlated IOP measurement that takes the biomechanical properties of the cornea into consideration providing an indication of intraocular pressure that is less influenced by properties such as corneal viscoelasticity and thickness.
- IOP_g - Goldmann-correlated IOP. IOP_g is strongly correlated with the results

obtained from an expertly executed, properly calibrated Goldmann Applanation Tonometer (GAT).

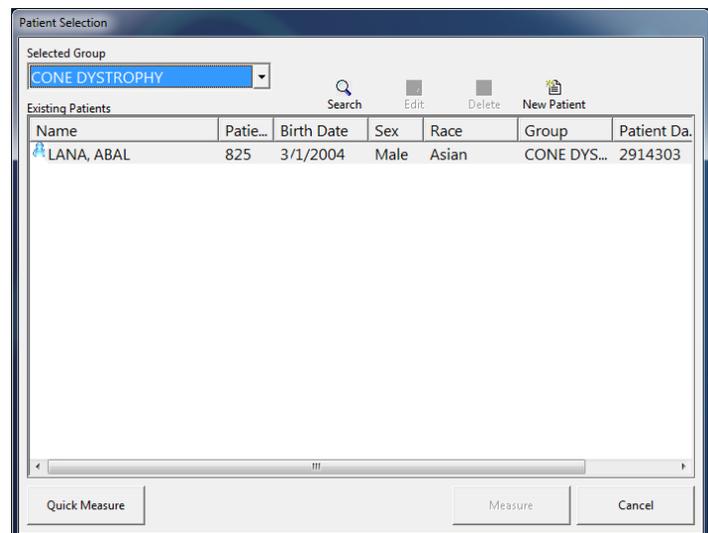
- CH - Corneal Hysteresis is a function of corneal viscoelastic damping that reflects the ability of the corneal tissue to absorb and dissipate energy. It is indicative of corneal biomechanical properties.
- Waveform Score – The Waveform Score is an indicator of measurement reliability on a scale of 0 to 10 (0 being lowest, 10 being highest). The higher the Waveform Score, the more reliable the measurement data. If the Waveform Score is below 3, the measurement will appear orange on the screen. It is recommended that you take an additional measurement.

5.18 New Participant Data Entry/Participant Selection

If you already have existing Patients, the Patient Selection Window will display the list.

The screen capture on the right illustrates the screen as viewed on the lap top.

1. Click the New Patient button to enter a new patient into the database.
2. The New Patient window will appear.
3. When all the information is entered, click OK to save it.
4. The Patient Selection window will appear again, now with the new patient added to the list.
5. Double-click the patient name or click the Measure button to proceed to the Measures Screen.



Notes: All fields indicated by an asterisk (*) are required.

The Patient Number field automatically generates a sequential Patient Number.

Patient Data Field 1 and Patient Data Field 2 are open text fields for additional identification information.

The screenshot shows the 'New Patient' window with the following fields:

- Last Name (*)
- First Name (*)
- Patient Number: 854
- Group: CONE DYSTROPHY
- Birth Date: 1 / 1 / 1965
- Sex: Male
- Race: (Unknown)
- Patient Data Field 1
- Patient Data Field 2

Buttons for 'OK' and 'Cancel' are at the bottom right. A note at the bottom left states '(*) Required fields'.

OHTS 3 ORA - New Participant Entry Key:

Last Name*	OHTS ID
First Name*	OHTS ID
ORA ID*	Automatically Generated
Group*	OHTS3
Birthdate*	mm/dd/yyyy
Sex*	Use pull-down menu to select gender
Race*	Use pull-down menu to select race
Patient Data Field 1	Leave Blank
Patient Data Field 2	Leave Blank

* Denotes required field

5.19 Alignment & Measurement

From this screen, operators may choose to enter the MAIN MENU, or begin the measurement process. To measure, move the Forehead Rest fully to the left or right until it locks into position if it is not already in this position.



Slide headrest left or right

If the forehead rest is not in position, the icons will be inactive, and the message in the image below will appear on the instrument panel of the ORA device interface. This screen shot is NOT from the laptop.

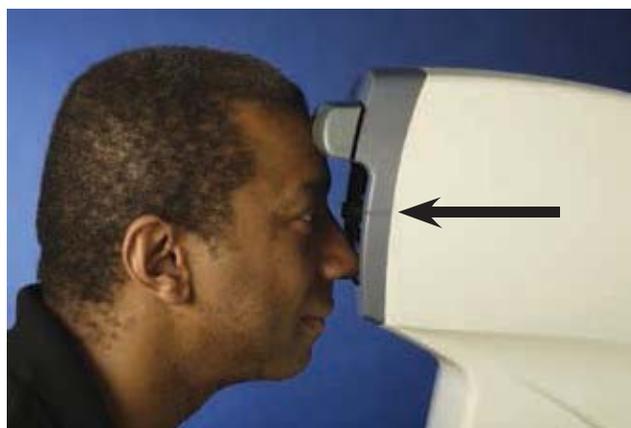


The side that is ready to measure will become blue, indicating the unit is ready to measure that eye.

A properly positioned participant will easily see the fixation cues. The fixation target is a green light, located inside the air tube, surrounded by a ring of red lights. In order to take a measurement, participants must be fixating on the green light. If a participant is able to see any of the lights (red or green) then participant position is adequate. If any red lights can be seen, the automatic alignment system will bring the green fixation target into view. The measurement will be made automatically.

5.20 Correct Participant positioning

Set the height of the table so the canthus marks on the sides of the instrument are level with the participant's eyes.



Canthus Mark

Participants should lean forward slightly so that the center of their forehead rests in the middle of the forehead pad. The participant's head should contact the headrest straight-on; perpendicular to

the front of the instrument (not turned to the side). Ensure the participant's chin is not too far from the front of the instrument, or the alignment system may not be able to reach the eye.



Proper Participant Alignment (Chin Close to Unit)



Improper Participant Alignment (Chin Moved Away From Unit)

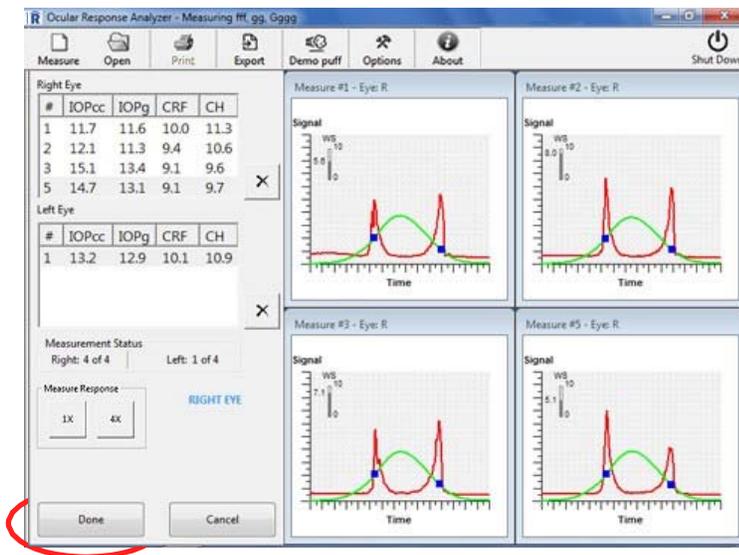
Observe the photo on the right. Notice the distance between the participant's chin and the front of the instrument. The instrument is too low, causing the participant to rest his head in a downward-facing manner. In this instance, the participant may not be able to see the fixation target, and the alignment system may not be able to reach the patient's eye.

5.21 Taking the ORA Measurements

1. Clean the instrument headrest with an alcohol wipe.
2. Participant should remove contact lenses
3. Tell Participant "Nothing will touch your eye and you will feel a gentle puff of air."
4. Enter a new Participant or select an existing Participant from the Patient Selection Window.
5. Click the Measure Icon.
6. The instrument will prepare for a measurement.
7. Start with the right eye.
8. Slide the headrest to one side and then ask the participant to put their head against the headrest and look at the green light. (See Correct Participant Positioning in Section 5.20)
9. Click the 4X Measure Response icon and the ORA will take 4 measurements.

Notes: To ensure fast and accurate results operators should instruct the patient to blink a few times and hold both eyes open immediately before measurement. Remind the participant to look directly at the green light and hold steady.

Corneal pathology or corneal surgery can cause the WS to be 5 or lower. Please note in the comment field on the ORA REDCap module



Measuring the Fellow Eye

After completing the measurements on participant's right eye, slide the headrest fully to the other side and reposition the participant for measurements on the left eye.

Once the participant is repositioned, simply click the 4X Measure Response button again. When the first measurement for the left eye is taken, the measurement signal will appear on the screen.

When the desired number of measurements has been obtained for both eyes, the operator must click the Done button to proceed to the Results Window.

The ORA machine will automatically create an "Intelligent Average" measurement using the 4 measurements taken.

5.22 Recording the ORA Measurements in REDCap

The ORA machine will automatically create an "Intelligent Average" measurement using the 4 measurements taken. To obtain the "Intelligent Average" for recording in REDCap, complete the following steps:

1. Use the 4X Measurement Response button on the Measurement Screen (the machine will automatically highlight the 3 best scores and use those to create the intelligent average)
2. Save and close record
3. Re-open record; the intelligent average provided by the machine will now be bolded
4. Record the intelligent average measurement in REDCap

5.23 Backup of ORA Database

- 1) Perform full backup of the ORA database **at least once a month or per your institutional standards**. The ORA laptop can be connected to a network via an Ethernet cable and standard windows networking protocol.
- 2) From the main screen, click on the **Tools Menu** and select **Options**.
- 3) Under the **General tab**, you will find the file locations for the ORA Database and Backup.
- 4) Set your desired paths or keep the default locations. Set the backup frequency for 30 days or less.

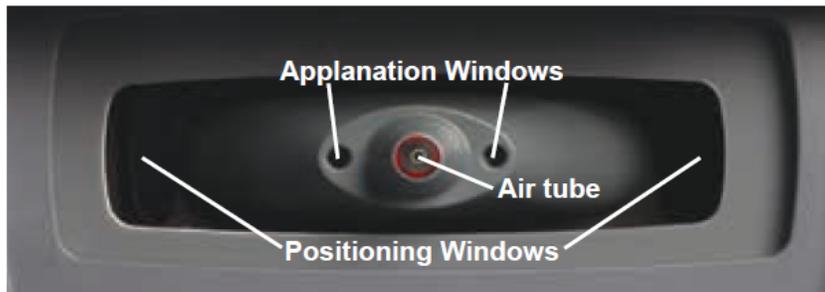
- 5) Click **OK**.

5.24 Entering data into REDCap

1. You may use the ORA Corneal Hysteresis Case Report Form to enter data to facilitate data entry into REDCap.
2. After your center has completed OHTS participants, an encrypted USB drive will be sent for you to download your entire OHTS3 database for further analysis of the raw data. A self-addressed, postage paid return envelope will be provided.

5.25 Instrument maintenance

1. Every 30 days, the instrument on-screen display prompts an Airtube cleaning message. This message causes the ORA®G3 and laptop to be non-responsive.
2. You have three options:
 - a) Turn off the ORA®G3 and restart it;
 - b) Cancel the cleaning mode which will reset the 30-day counter; or
 - c) Push the Select icon and proceed with cleaning.



Positioning Windows

- c1) The Airtube nose will advance.
- c2) Clean the applanation windows and positioning windows with a long handle cotton-tip swab moistened with lens cleaner or alcohol (isopropyl or ethanol).
- c3) Remove remaining dust or particles with dry, compressed air at less than 90 psig (620 kPa).
- c4) Clean the Airtube by sliding a pipe cleaner in and out to remove contaminants.
- c5) Remove the pipe cleaner from the Airtube
- c6) Push the Select icon which will trigger air puffs to clear the Airtube.
- c7) The Airtube unit will retract to normal position

ORA Corneal Hysteresis

OHTS participant ID:

Date of measurement: / /
mm dd yy

- Technician/coordinator should use the 4X Measurement option for conducting the test.
- The machine will highlight the 3 best scores and use those to create the intelligent average.
- Technician/coordinator should save and close record.
- Technician/coordinator should re-open record. The intelligent average score will be **bolded**.
- Technician/coordinator should record the **bolded** measurement in REDCap.

1. ORA measurement done: OU OD OS Not Done

If not done, reason:

2. Which ORA instrument: ORAG-3 Other

If other, describe:

3. Please take ORA measurements:

	OD		OS
Corneal Compensated IOP (IOPcc)	<input type="text"/> <input type="text"/>	. <input type="text"/> mm Hg	<input type="text"/> <input type="text"/> . <input type="text"/> mm Hg
Goldman Correlated IOP (IOPg)	<input type="text"/> <input type="text"/>	. <input type="text"/> mm Hg	<input type="text"/> <input type="text"/> . <input type="text"/> mm Hg
Corneal Hysteresis (CH)	<input type="text"/> <input type="text"/>	. <input type="text"/>	<input type="text"/> <input type="text"/> . <input type="text"/>
Waveform Score (WS)	<input type="text"/> <input type="text"/>	. <input type="text"/>	<input type="text"/> <input type="text"/> . <input type="text"/>

Comments:

Measurement taken by:

6. Treatment

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6.3	OHTS Phase 1 Stepped Medical Regimen	6-2
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6.5	OHTS Phase 2 Treatment and Follow-up.....	6-3

6.1 Introduction

OHTS Phase 3 is strictly observational and consists of tests and measures to determine visual and functional status of participants after 20 or more years after their enrollment in OHTS Phase 1. There is no specified treatment in the OHTS Phase 3 protocol.

6.2 OHTS Phase 3 No Protocol for Treatment

There is no specified treatment in the OHTS Phase 3 protocol. Treatment is at the discretion of the participant and his or her clinician. There was a treatment protocol in OHTS Phase 1 and 2, which is described below.

6.3 OHTS Phase 1 Stepped Medical Regimen

OHTS Phase 1 was a randomized trial to determine if ocular hypotensive medication was safe and effective in preventing the development of primary open angle glaucoma (POAG) in individuals with ocular hypertension. Half of the participants were randomized to receive commercially available topical ocular hypotensive medication and half were randomized to observation.

The treatment goals for both eyes in participants randomized to receive medication were:

- (1) Intraocular pressure \leq 24 mm Hg
and
- (2) A 20% reduction in intraocular pressure from the average of the Qualifying IOP and Baseline IOP. The 20% reduction was not necessary if IOP \leq 18 mm Hg. Medical therapy was changed and/or added until both goals are met or until the patient was receiving maximum tolerated topical medical therapy. Patients not meeting treatment goals despite maximum tolerated topical medical therapy continued to be followed in the trial. For the purposes of this trial, maximum topical medical therapy consisted of a beta blocker, an adrenergic agent, a standard miotic agent, a topical carbonic anhydrase inhibitor and a prostaglandin analogue.

6.4 OHTS Phase 2

The OHTS randomized trial definitively demonstrated that topical ocular hypotensive medication was effective in preventing POAG, but did not answer one important question, “When should treatment be initiated?” In large part the answer depends on whether there is a penalty for delaying treatment. To answer this question, participants in the observation group who had completed 7 years of follow-up without ocular hypotensive medication started ocular hypotensive medication while the participants in the medication group continued medication. Eighty-eight percent (1,366 of the 1,558 surviving participants) signed a new consent form to participate in OHTS Phase 2 in 2002.

6.5 OHTS Phase 2 Treatment and Follow-up

Treatment and follow-up in OHTS Phase 2 was the same as in Phase 1. However, in OHTS Phase 2, all participants who had been randomized to observation during OHTS Phase 1 were offered ocular hypotensive medication. Treatment goals for both eyes of participants originally randomized to observation were the same as for participants in the medication group as outlined in 6.3. Participants in the medication group continued on their medication regimen and participants in the observation group started their medication regimen. The same schedule of tests and measures as well as the ascertainment of the primary outcome was used in Phase 2.

7. Training, Certification and Performance Monitoring

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7.1 Introduction

It is important that all study personnel are familiar with the OHTS Phase 3 protocol and proper study procedures. In addition, prior to becoming eligible for OHTS certification, all investigators and clinical center staff must have training in protecting the rights and welfare of human subjects involved in clinical research, and in complying with HIPAA regulations. Current certificates documenting the successful completion of Human Subjects Training must be submitted to the Coordinating Center by all members of the investigative group prior to OHTS certification.

The initial step in the process of insuring quality data according to a standardized protocol is proper training and certification of all study personnel. Data from non-certified technicians will not be accepted.

7.2 Tests and Measures that Require OHTS Certification

Standardized study protocols are used for most tests, measures and examinations in OHTS Phase 3. At least one Clinical Center personnel (and a back-up if possible) must be OHTS certified to perform the functions below. One person can be certified for multiple functions.

Functions requiring OHTS certification	Certification Procedure	MOP Section
Clinical Center Investigator Clinical Center Coordinator	<ul style="list-style-type: none"> • OHTS Phase 3 Protocol knowledge • Satisfied by attendance at FIG meeting or • Certification by Coordinating Center 	7.16
Visual field testing	Testing & certification by VFRC	5.10, 11.8
Optic disc photography	Testing & certification by ODRC	5.11, 12.2.1
OCT	Testing & certification by OCTRC	5.12, 13.7
IOP, ETDRS, Pelli-Robson contrast sensitivity	Grandfathered if previously OHTS certified	
IOP	Certification by Coordinating Center	5.6.1, 7.13
ETDRS	Certification by Coordinating Center	5.3, 7.10
Pelli-Robson contrast sensitivity	Certification by Coordinating Center	5.4.1, 7.11
Ophthalmoscopy, gonioscopy, SLE	<ul style="list-style-type: none"> • OHTS Phase 3 Protocol knowledge • Satisfied by attendance at FIG meeting or • Certification by Coordinating Center 	5.8, 7.3
Blood Pressure	Certification by Coordinating Center	5.9.1, 7.16
REDCap data entry	Certification by Coordinating Center	5.15, 7.17

7.3 Clinical Center Investigators Certification

Clinical Center Investigators and back-up Investigators can be certified for knowledge of the OHTS Phase 3 protocol by attendance at the Full Investigative Group meeting or by telephone by the Coordinating Center.

New Clinical Center Investigators are furnished with a copy of the Manual of Procedures (MOP) which is also available at vrcc.wustl.edu. Clinical Center Investigators must demonstrate knowledge of the study protocol to be certified. Certification will be performed via telephone by a Central Coordinator at the Coordinating Center. The telephone certification will include, but not be limited to, knowledge of the OHTS 3 protocol for examination procedures, visual acuity measurement, IOP measurement, and study endpoints. The study protocol is described in MOP Chapter 2, Study Design of OHTS Phase 3.

7.4 Clinical Center Coordinators Certification

Clinical Center Coordinators and back-up Coordinators can be certified for knowledge of the OHTS Phase 3 protocol by attendance at the Full Investigative Group meeting or by telephone by the Coordinating Center.

New Clinical Center Coordinators and back-up Coordinators are furnished with the MOP and must be familiar with all aspects of the study. Central Coordinators from the Coordinating Center will review the protocol with Clinical Center Coordinators by telephone. Clinical Center Coordinators must demonstrate knowledge of the study protocol to be certified. Telephone certification will include, but not be limited to, knowledge of the OHTS 3 protocol for examination procedures, refraction, ETDRS visual acuity measurement, Pelli-Robson Contrast Sensitivity, IOP measurement, blood pressure measurements, study endpoints and scheduling of visits. The review may include participant-based examples so that the Clinical Center Coordinators can think through the protocol in participant-oriented terms. The study protocol is described in Chapter 2, Study Design of OHTS Phase 3.

7.5 Optic Disc Photography Certification

Photographers previously certified for OHTS Phases 1 or 2 are required to recertify for OHTS Phase 3.

The stereoscopic optic disc photography certification for photographers is supervised by the Director of the Optic Disc Reading Center (ODRC). This process is detailed in Chapter 12.2.1 Optic Disc Photography. Briefly, photographers and back-up photographers are supplied with the ODRC chapter of the MOP. They read this material and review the protocol with the ODRC Coordinator. The educational material covers photographic technique, proper logging in and storage of photographs, and transmitting photographs to the OHTS Coordinating Center.

The photographer takes two stereo pairs for 2 non-study eyes, of two participants: Participant 1: right eye – two stereo pairs; left eye – two stereo pairs, and Participant 2: right eye – two stereo

7-4 Training, Certification and Performance Monitoring

pairs; left eye – two stereo pairs and submits them to the OHTS Coordinating Center . If these photographs pass quality standards per ODRC protocol, the ODRC certifies the photographer.

Certification may be rescinded if the ODRC determines that the photographer’s performance is unacceptable and does not improve after consultation and review by the ODRC. The stereoscopic optic disc photography protocol is described in detail in Chapter 12 Optic Disc Reading Center.

7.6 Perimetry Certification

The Visual Field Reading Center (VFRC) recommends that each Clinical Center have at least two visual field technicians certified to perform visual fields. Technicians and back-up technicians previously certified for OHTS Phase 1 or 2 are required to recertify for OHTS Phase 3.

Certification of technicians to perform visual field testing is supervised by the Coordinator of the VFRC. This process is detailed in Chapter 11(11.8) Visual Field Reading Center. Briefly, visual field technicians and backups are supplied with the VFRC chapter of the MOP. The technician reads this material and reviews the protocol with the VFRC Coordinator. The technician submits visual fields from two non-study patients to the OHTS Coordinating Center. If these visual fields meet quality standards per VFRC protocol, the Coordinator of the VFRC certifies the technician. All certified visual field technicians must maintain their certification by performing OHTS visual field tests on a regular basis. Certification will lapse for any technician who does not perform an OHTS visual field test for a period of six months.

7.7 Optical Coherence Tomography (OCT) Certification

The OCT Reading Center (OCTRC) recommends that each Clinical Center have at least two imaging technicians certified for OHTS OCT imaging. Certification of technicians is supervised by the OCTRC. To become certified for OHTS Spectralis or Cirrus imaging, the imaging technician must complete a telephone certification with the OCTRC. After satisfactory telephone session, the technician must submit images on two non-study volunteers as described in the OCT protocol, Chapter 13 (13.7) to the OCTRC via the Coordinating Center by flash drive or internet. Certification will be awarded if the images are of satisfactory quality.

All certified technicians must maintain their certification by obtaining OHTS Spectralis or Cirrus images on a regular basis. If there is a lapse of longer than 6 months without taking images, the technician must go through a re-certification process.

7.8 Refraction

Specific OHTS certification for performing refraction is not required. Refraction is required on Visit 1 and is particularly important for visual field testing. Refraction may be performed by any OHTS personnel certified for protocol knowledge. Refraction protocol is from the Diabetic Retinopathy Vitrectomy Study/refraction protocol. Refraction Technique is described in 5.2.2.

7.9 Snellen Visual Acuity

Specific OHTS certification for performing Snellen visual acuity is not required. Snellen visual acuity using a wall mounted chart or monitor screen is performed at Visit 1 and each subsequent study visit. Any OHTS personnel certified for the OHTS protocol or any OHTS test/measure are permitted to perform Snellen visual acuity. Snellen visual acuity testing technique is described in 5.3.1.

Visual acuity is measured before pupil dilation, tonometry, gonioscopy or any other technique that would affect vision.

7.10 ETDRS Visual Acuity Certification

OHTS Phase 1 and 2 certification for ETDRS testing will be accepted for certification in OHTS Phase 3. All new OHTS study personnel performing an ETDRS visual acuity test must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief certification test requested by the OHTS Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Certification for ETDRS visual acuity testing remains in effect as long as performance is satisfactory. ETDRS visual acuity testing technique is described in 5.3.3.

7.11 Pelli-Robson Contrast Sensitivity

OHTS Phase 1 and 2 certification for Pelli-Robson contrast sensitivity will be accepted for certification in OHTS Phase 3. New OHTS study personnel performing Pelli-Robson Contrast Sensitivity testing must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief certification test requested by the OHTS Coordinating Center. The test must be judged as satisfactorily completed by the Coordinating Center. Certification for contrast sensitivity testing remains in effect as long as performance is satisfactory. Pelli-Robson Contrast Sensitivity testing technique is described in 5.4.1.

7.12 Slit-Lamp Examination

Slit-lamp examination is performed by an OHTS Clinical Center Investigator certified for knowledge of the OHTS protocol in Phase 1, 2 or 3 or attendance at the Full Investigative Group meeting. Specific OHTS slit-lamp certification is not required. The slit lamp protocol is described in section 5.5.

7.13 Tonometry

OHTS Phase 1 and 2 certification for tonometry will be accepted for certification in OHTS Phase 3. New OHTS study personnel performing tonometry must be certified as to technique and recording of IOP by the Coordinating Center. Certification consists of completing a brief certification test by the OHTS Coordinating Center. The test must be judged as satisfactorily

7-6 Training, Certification and Performance Monitoring

completed by the Coordinating Center. Certification for tonometry remains in effect as long as performance is satisfactory. Tonometry technique is described in 5.6.2.

7.14 Gonioscopy

A one-time gonioscopy measurement is performed by a Clinical Center Investigator certified for knowledge of the OHTS protocol in OHTS Phase 1, 2 or 3 or attendance at the Full Investigative Group meeting. Specific certification is not required for gonioscopy. Gonioscopy protocol is described in section 5.7.

7.15 Ophthalmoscopy

Dilated ophthalmoscopy is performed at Visit 1 is performed by an OHTS Clinical Center Investigator certified for knowledge of the OHTS protocol in Phase 1, 2 or 3 or attendance at the Full Investigative Group meeting. Undilated ophthalmoscopy is performed on all additional visits. Specific certification for ophthalmoscopy is not required. Ophthalmoscopy is described in section 5.8.

7.16 Blood Pressure

Certification consists of submitting data from two non-study participants to the Coordinating Center prior to taking a brief certification test to perform OHTS blood pressure measurements. The test must be judged as satisfactorily completed by the Coordinating Center. Previous certification for blood pressure measurements in OHTS Phase 1 and 2 will not be accepted as certification for Phase 3. The blood pressure protocol is described in 5.9.

7.17 REDCap Data Entry

OHTS Phase 3 will use Research Electronic Data Capture (REDCap), a secure, multi-user web based interface for entering, storing and managing clinical and administrative data. Certification for REDCap requires familiarity with the short REDCap overview supplied by the Coordinating Center and demonstration of proficiency by performing routine tasks on a mock-up of the OHTS REDCap database. Certification will be granted upon satisfactory demonstration of ability to enter and edit data from forms, to attach and upload files and saving records. Certification will remain in effect for the duration of the study so long as performance remains satisfactory.

7.18 Clinical Centers

The physical facilities of the Clinical Center must include waiting rooms, examination rooms, visual field rooms, Optical Coherence Tomography imaging rooms and photography rooms, all of which are accessible to handicapped individuals. An appropriately equipped Clinical Center has, in good working order, ophthalmoscopes, tonometers (including calibration device), ETDRS and Snellen Eye Charts, Pelli-Robson Contrast Sensitivity charts, OMRON blood pressure monitor, Extech light meter (401027-foot candle light meter-2000), a fundus camera capable of taking stereoscopic disc photos (If a Clinical Center has a sequential and a simultaneous camera, the simultaneous one will be used). The make, model and serial number of the fundus camera is

provided to the ODRC, spectral domain optical coherence tomography imaging (specifically a Spectralis or a Cirrus instrument) and an OHTS certified Humphrey program 30-2 visual field perimeter (HFA II &/or HFA Iii).

A fully staffed Clinical Center includes a Clinical Center Investigator (back-up Investigator), a Clinical Center Coordinator (back-up Coordinator), a photographer (back-up photographer), imaging technician (back-up imaging technician), a visual field technician (back-up visual field technician). Each Clinical Center has a back-up for each position, although one person can serve more than one function and can back up more than one position. **Back-up personnel must be certified to perform their functions.** Certification code is recorded on the case report form for study examinations and measures requiring certification. Only study data collected by study certified personnel in good standing are accepted for inclusion in analyses.

7.18 Performance Monitoring

The Coordinating Center, VFRC, OCTRC and ODRC continuously monitor the quality of data from Clinical Centers. If problems arise, the resource center contacts the Clinical Center Coordinator, the Clinical Center Investigator, Coordinating Center and if necessary, the Study Chair and Executive/Steering Committee. Most problems are solved by telephone. If problems persist, a member of the Coordinating Center (and other personnel as indicated) will site visit the Clinical Center. The site visit generates a plan of action with a specific timetable.

Reports of Clinical Centers and satellite performance are prepared quarterly to monitor the following high priority indices:

1. Completion of scheduled follow-up visits (goal $\geq 90\%$ of scheduled visits).
2. Percent of useable and reliable visual fields in both eyes per protocol (goal $\geq 90\%$ of scheduled tests).
3. Percent of useable optic disc photographs in both eyes (goal $\geq 90\%$ of scheduled tests).
4. Percent of imaging scans of good quality in both eyes per protocol (goal $\geq 90\%$ of scheduled tests).

In addition to the above, secondary indices of performance are monitored by each resource center as follows but not limited to:

Coordinating Center:

- Percent of target sample with follow-up visits scheduled
- Percent of participants lost to f/up who are contacted and scheduled
- Percent of participants consenting to each study component
- Percent of scheduled visits completed
- Percent of repeat tests completed for conversion/progression
- Percent of OCT images & VF tests retrieved from OHTS and non-OHTS clinics, de-identified and transmitted
- Visit data entered within 7 working days of visit (goal $\geq 80\%$)
- Queries resolved within 10 days (goal $\geq 75\%$)
- Forms are query free (goal $\geq 80\%$)

7-8 Training, Certification and Performance Monitoring

Optic Disc Reading Center:

- Photos received within 7 days of photography date (goal $\geq 90\%$)
- Quality retakes requested (goal $\leq 15\%$)
- Gradable photos taken at patient visit (goal 90%)
- Gradable photos taken and received at ODRC (goal 90%)
- Quality retakes received within 3 months of patient (goal ≤ 2 late retakes)
- Confirmation retakes within 3 months of patient visit
- Feedback to Clinical Center within 7 days of receipt

Visual Field Reading Center:

- Percent of visual fields retrieved from OHTS and non-OHTS, de-identified and transmitted to the VFRC by Clinical Centers
- Fields Received within 7 days (goal $\geq 90\%$)
- Test Parameters (goal $\geq 95\%$ with ≤ 5 error points)
- Patient Data (goal $\geq 80\%$ with ≤ 5 error points)
- Reliability (goal $\geq 90\%$)
- Quality retakes received within 3 months of patient visit
- Confirmation retakes within 3 months of patient visit
- Feedback to Clinical Center within 7 days of receipt

The OCT Reading Center:

- Monthly export Images/data received monthly (goal $\geq 90\%$)
- Percent of OCT scans retrieved from OHTS and non-OHTS, de-identified and transmitted to the OCTRC by Clinical Centers
- Percent of OCT scans for OHTS Phase 3 that are useable

Performance reports are distributed for review to Clinical Centers and their satellites, Reading Centers, Executive/Steering Committee and the NEI Project Officer. If problems are noted, a variety of actions are considered from telephone calls to site visits. These measures include a plan of action and a timetable for addressing the problem.

7.19 New Personnel

Personnel changes will occur during the course of the study. The certification process for new personnel is indicated above. Certification of new personnel occurs on an as-needed basis.

7.20 Cross-Training

Individuals who are cross-trained (i.e., coordinator, technician and photographer) must be certified for all appropriate tasks according to study protocol.

7.21 Clinical Center Site Visit

Clinical Centers will be site-visited as deemed necessary for specific problems that may arise as determined by the Study Chair, Coordinating Center, request of the Clinical Center Investigator, Optic Disc Reading Center (ODRC), Optical Coherence Tomography Reading Center (OCTRC), Visual Field Reading Center (VFRC) and/or the National Eye Institute (NEI).

Site visits will be conducted to:

1. Verify accuracy of consent forms.
2. Clarify the protocol to clinic personnel.
3. Conduct a random audit of primary source documents including study participant records, visual fields, OCT imaging scans and optic disc photographs.
4. Confirm adherence to study protocol.
5. Insure the Clinical Center has adequate resources for the proper conduct of the study including for example, desk space for the Clinical Center Coordinator, computer with high speed internet access, phone, fax and copier, secure cabinets for storage of study charts, photography equipment, HFAII and/or HFA Ili Humphrey Visual Field Analyzer. The study should also have adequate time allocated for study personnel.

A written site visit report is provided to the Clinical Center. Copies are also distributed to the Executive/Steering Committee, ODRC, OCTRC, VFRC, and the NEI Project Officer. The site visit reports are reviewed and plans and deadlines are set if substantive problems are uncovered.

8. Statistical Issues and Analyses

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8.0 Statistical Issues and Analyses

8.1 Availability of Participants for 20-year follow-up

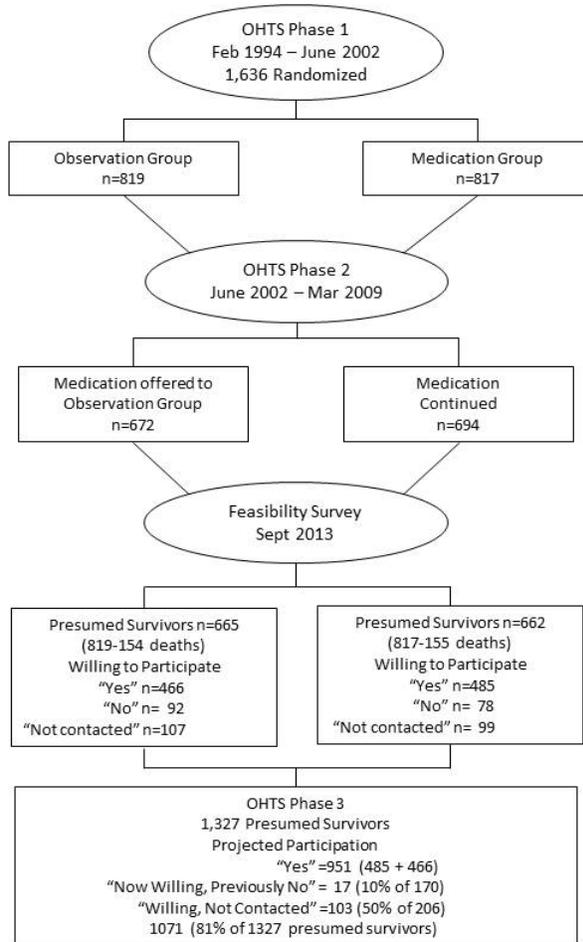
Our target is to retrieve some or all OHTS Phase 3 data from at least 80% of the surviving participants. In 2012-2013, Clinical Centers were asked to contact OHTS participants to determine their willingness to return for examinations. Of the 1,327 presumed survivors, Clinical Centers were able to contact 84% (1,121 of 1,327). Of the participants who were contacted, 85% (951 of 1,121) verbally agreed to participate in the follow-up study and 15% (170 of 1,121) were unable/unwilling to participate when queried.

Of the 206 participants who were not contacted by Clinical Centers, we expect to contact and enroll 50% (103 of 206) using Battelle Memorial to retrieve current contact information and vital status. Of the 170 participants who were unwilling/unable to participate when queried, we expect to enroll about 10% (17 of 170) by reducing barriers to participation and by providing incentives for participation. Transportation can be a major barrier to study participation in a cohort with a median age of 75 years of age.

The study will arrange transportation and cover up to \$100 towards transportation for each visit. In addition, a \$50 stipend (as permitted by the local IRB) and \$25 food allowance will be provided for each of up to 3 visits.

To maximize flexibility of scheduling around vacations, illness and family crises, the study has a 24 month window for scheduling follow-up visits. Thus, enrolling at least 80% (1,071 of 1,327) of the surviving participants in the OHTS 20-year follow-up study is attainable (Figure 1). For participants unable/unwilling to return for examinations, telephone interviews by professional interviewers will be conducted for surveys of quality of life and functional limitations. This will reduce participation bias and insure quality of the survey data collected.

Figure 1: Flow Diagram of Projected Phase 3 Participation Rate



8.1.1 Potential Participation Bias

High and/or biased loss to follow-up is a major concern for the 20-year follow-up study. The median age at the 20-year follow-up visit will be 75 years. Mortality in the OHTS cohort, which was monitored annually from 1994 to 2009, was consistently lower than age-adjusted expectation. The 309 confirmed deaths from 1994 to September 2013 were equally distributed by randomization group (Medication group 154 deaths, Observation group 155 deaths). Participation bias was examined by comparing participants who were contacted and agreed to participate in the 20-year follow-up study (n=951) versus all “others”, which included those who were not contacted or unable/unwilling to participate (n=376). We found little or no evidence of bias between those who agreed “yes” to participation vs. “Others” with regard to demographic factors or five baseline predictive factors for the risk of developing POAG (Table 1). A higher percentage of participants who developed POAG were willing to participate (77%) than participants who had not developed POAG (70%). The participation rate of 67% among the 341 surviving African-American participants was slightly lower than the 73% among other participants.

Table 1. Comparison of Participants Agreeing “Yes” to Participation (n=951) vs. “Others” (n=376)

	Participation in 20-year follow-up			
	“Others”		“Yes”	
	N	%	N	%
Randomization				
Medication	177	26.7	485	73.3
Observation	199	29.9	466	70.1
POAG endpoint?				
No	323	29.6	769	70.4
Yes	53	22.6	182	77.4
Self-Reported Race				
Other Race	265	26.9	721	73.1
African American	111	32.6	230	67.4
Gender				
Male	145	27.0	393	73.0
Female	231	29.3	558	70.7

Baseline Predictors for the Development of POAG	Participation in 20-year follow-up					
	“Others”			“Yes”		
	N	Mean	Std	N	Mean	Std
Baseline Age	376	53.6	9.2	951	54.0	8.8
Baseline predicted 5 year risk	283	0.13	0.11	936	0.11	0.10
Mean Baseline IOP	376	24.7	2.7	951	25.0	2.7
Mean CCT	283	568.2	37.6	936	575.7	38.1
Mean Baseline Vertical CD Ratio	376	0.40	0.20	951	0.39	0.19
Mean Baseline PSD	376	1.90	0.22	951	1.90	0.20

8.2 Aim 1a Sample Size: 20-year Cumulative Incidence of POAG

Follow-up in 2015-2016, will increase median follow-up from 13 to more than 20-years and post-POAG follow-up in participants who developed POAG from a median of 4.8 years to more than 10 years. At the last data freeze March 2009, 279 participants had developed POAG in one or both eyes.

To project the 20-year cumulative incidence of POAG and its 95% confidence boundaries, we fit parametric Weibull survival models to the sample of 1,619 of 1,636 randomized participants with at least 2 visits for endpoint ascertainment (Figure 2 and 3). These models included 5 baseline predictors (age, central corneal thickness, vertical cup-disc ratio, intraocular pressure and visual field pattern standard deviation) and used outcome data from both OHTS Phase 1 and 2.

The parametric estimate of the 20-year cumulative incidence of POAG was 29% (95% CI of 25%-33%) or 460 (95% CI of 400 – 530) participants. To be conservative for the purpose of estimating statistical power, we used the lower 95% confidence boundary of cumulative incidence estimates i.e., 25% and 400 participants (279 incident cases prior to 2009 data freeze and 121 incident cases after the 2009 data freeze thru Phase 3). The definition of POAG is based on the same information and protocol used in OHTS Phase 1 and 2.

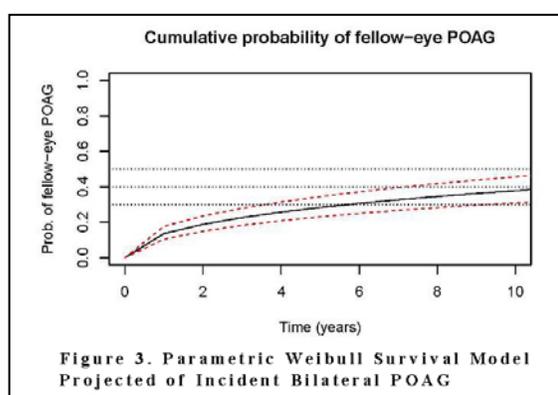
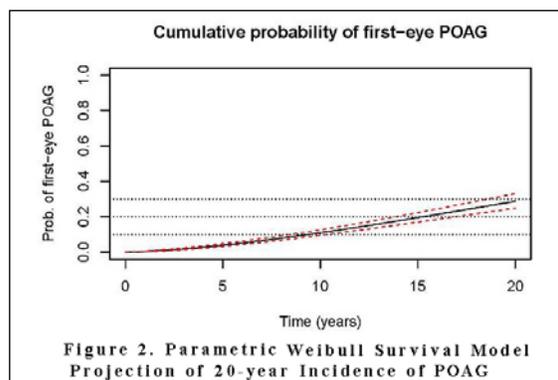


Table 2. Observed 13-Year Event Rates and Projected 20-Year Event Rates

	13+ year Median f/up 2008-2009	Projected 20+ year Median f/up 2015-2016
Year since POAG diagnosis (median)	4.8 years	10 years
N of POAG (pts.)	279 pts.	400 pts. ¹ 95% CI of 400-530
N of bilateral POAG (pts.)	83 pts.	120 pts. ¹ 95% CI of 120-180
Visual Field POAG	204 eyes of 175 pts.	293 eyes of 253 pts. ²
Transition from Disc POAG to Visual Field POAG (eyes)	55 eyes	103 eyes ²

¹ Estimated from Weibull survival models

² Linear projection from 13 year OHTS data.

8.2.1 Aim 1a Analysis Plan: 20-year Cumulative Incidence of POAG

The 20-year cumulative incidence of POAG overall (Figures 2 and 3) and by the original randomization groups (e.g., Medication group treated from randomization versus Observation group treated 7 years after randomization), will be estimated using Kaplan-Meier product limit methods. The 20-year cumulative incidence of POAG among self-identified African American participants will be described by Kaplan-Meier product limit method and compared to other OHTS participants using the log-rank test. The incidences of visual field (VF) POAG and Disc POAG, as well as the corresponding 95% confidence intervals, will be estimated.

Given the older age of participants and the 20-year follow-up period, incidence estimates of POAG could be biased by competing risks such as mortality and ocular co-morbidity. Gray's sub-distribution method will be used as a sensitivity analysis to assess the potential influence of competing risks in the above analyses. Since more than 5 years have elapsed since the last OHTS visit, the date of POAG onset will be unknown for eyes newly diagnosed as POAG in OHTS Phase 3. Survival models with interval censoring time¹ will be used to estimate the 20-year prevalence of POAG by the updated endpoint criteria.

8.2.2 Aim 1b Sample Size: 20-year Estimates of POAG Severity

Measures of "severity of POAG" include progression of unilateral POAG to bilateral POAG, progression from optic disc POAG to VF POAG and severity of visual field loss as measured by mean deviation and its slope. In 2015-2016, the median post-POAG follow-up will be more than 10 years. The parametric estimate of the 10-year cumulative incidence of progression from unilateral POAG to bilateral POAG is 38% (95% CI of 31-46%) (Figure 3). Assuming that a total of 400 participants will develop POAG over 20 years (Section 8.2.1), a cumulative total of 152 participants (95% CI of 120-180) of these participants are expected to develop POAG in the fellow eye. We use the lower 95% boundary of 120 participants who develop bilateral POAG for a conservative estimate (Table 2).

We will estimate and compare the slope of mean deviation over time across different POAG subtypes (VF, disc or both). Based on the OHTS Phase 1 and 2 data², showed that the slope of mean deviation over time in all POAG eyes had a mean and standard deviation of -0.26 ± 0.36 dB/yr. They also found that the slope of mean deviation in eyes reaching both VF and Disc endpoints (-0.42 ± 0.46 dB/yr) were significantly worse than eyes reaching VF endpoint alone (-0.29 ± 0.31 dB/yr) or Disc endpoint alone (-0.12 ± 0.19 dB/y). In OHTS Phase 3, we are more interested in the magnitude of the slope of mean deviation than whether such a difference exists. The increased sample size (N= \sim 400 POAG pts or \sim 520 POAG eyes) and the availability of the additional VF data over a 10+ year period will provide higher precision to estimate the change of mean deviation over time. For example, the number of VF's available among participants who developed POAG includes 15 pre-POAG VF's (median) and 12 or more post-POAG VF's (9 VF's in OHTS Phase 1-2 and 3 VF's in Phase 3). In addition, non-protocol visual fields performed after the last OHTS visit to date will also be retrieved and used if the VFRC

determines that the VF's are of adequate quality. We will also estimate the slope of mean deviation in both pre- and post-diagnosis periods (see below).

8.2.3 Aim 1b Analysis Plan: 20-year Estimates of POAG Severity

Severity of POAG includes the estimation of the cumulative proportion of eyes progressing from optic disc POAG to VF POAG, proportion of participants progressing from unilateral POAG to bilateral POAG and unilateral VF POAG to bilateral VF POAG and the degree of visual field loss as measured by mean deviation and its slope.

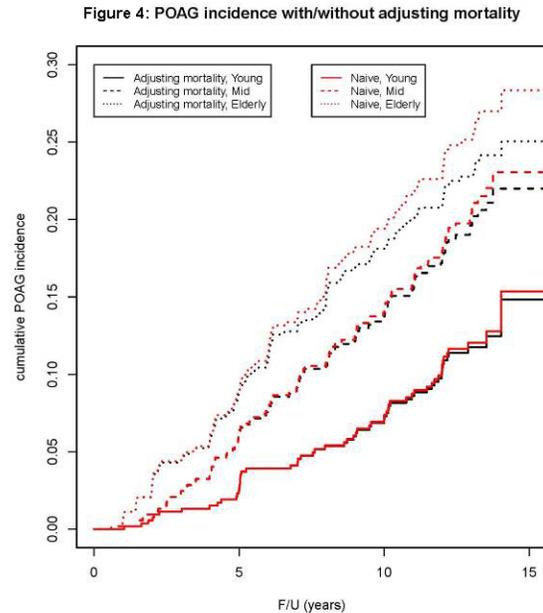
For analysis of progression from optic disc POAG to VF POAG, unilateral to bilateral POAG, unilateral VF POAG to bilateral VF POAG, the first event defines time0. For participants who developed POAG in one eye, the median time to develop POAG in the fellow eye, as well as the median time of transition (if any) from Disc-POAG to VF-POAG, will be estimated using Kaplan-Meier product limit method.

For analysis of visual field loss, we will use OHTS VF's up to and including the Phase 3 examination. The rate of change of mean deviation will be used to measure glaucomatous visual field loss over time in each eye. Data after reproducible visual field loss due to non-glaucomatous conditions, as determined by the Endpoint Committee, will be censored. Many studies have shown that change in mean deviation could be adequately described using a linear trend over time³. However, linearity may be a concern in the OHTS 20-year follow-up because of long VF series in both pre- and post-diagnosis periods. In OHTS Phase 1 and Phase 2, participants who developed POAG have a median number of 15 pre-POAG VF's and 12 post-POAG VF's. Hence, a piece-wise linear (bi-linear) model will be used to handle the potential issue of non-linearity, and the slope of change in mean deviation and its 95% confidence interval will be estimated in pre- and post-diagnosis periods respectively.

Participants who developed POAG will be compared to those who did not develop POAG to control for normal aging in this ocular hypertensive cohort using a 2-slope linear mixed model. For participants who developed POAG, the trajectories of MD over time will be aligned at the date of diagnosis (i.e., time0). For participants who did not develop POAG, "time0" will be set as the median time to diagnosis among those who converted POAG. In this manner, the time periods of slopes for those with and without POAG will be comparable. We will compare differences in slope of mean deviation among POAG subtypes (VF, Disc, or both), as well as between initial randomization groups (Observation versus Medication). We acknowledge that choosing "time0" for non-POAG participants is relatively arbitrary. A potential alternative could be a nested case-control study, i.e., comparing cases (POAG) versus age-matched controls (non-POAG). However, since many analyses^{2,4} have shown that the level of MD is stable over time in non-POAG participants, we anticipate that it would be adequate to align all non-POAG participants to a common "time0".

8.2.4 Aims 1a and 1b: Anticipated Results and Pitfalls

A potential challenge is the competing risk of mortality and ocular co-morbidity such as diabetic retinopathy or cataract. In the presence of high prevalence of competing risks, the cumulative incidence of POAG could be over-estimated. In OHTS, 309 participants have died and 262 died prior to POAG diagnosis, and 93 eyes from 70 participants were discontinued in OHTS Phase 1 and 2 from further VF and optic disc photography by the Endpoint Committee due to ocular/systemic co-morbidity (stroke, diabetic retinopathy, cataract, BRVO, trauma, angle closure glaucoma, etc.). A preliminary analysis was performed using Gray's sub-distribution method (Fine and Gray, 1999) to assess the impact of competing mortality on POAG. We first stratified OHTS participants into low, medium, and high tertiles based on their age at randomization. Figure 4 showed the cumulative incidence of POAG with and without adjusting competing mortality in each tertile respectively.



We see that the influence of competing mortality in each tertile is minor throughout OHTS Phase 1 and 2. However, since the proposed study extends duration of follow-up for an additional 7-8 years, Gray's sub-distribution method will be used as a sensitivity analysis to assess the impact of both competing mortality and ocular/systemic co-morbidity.

8.3 Aim 2a Statistical Power: Prediction Model for the 20-Year Risk of Developing POAG

A power analysis was performed for categorical predictors using 2-sample chi-square test. Prediction models will utilize all data from all randomized participants. Table 3 reports the statistical power for a 2-sided 0.05 alpha for a sample of 1,600 participants (assuming 400 participants with POAG), for prevalence of predictive factors from 0.05 to 0.45 and relative risk of 1.3 to 2.0. Based on prevalences from the 2009 data freeze, we project statistical power > 0.80 for detecting the effect of, for example, myopia (prevalence 53%, RR 1.3), self-reported history of diabetes (28%, RR 1.3), optic disc hemorrhage (11%, RR 1.6), self-reported history of statins (35%, RR 1.3), beta blockers (37%, RR 1.3).

Overall, we anticipate sufficient statistical power to detect influential predictive factors. We anticipate that more power could be achieved because the time-to-event analysis allows us to use information more efficiently, i.e., considering not only the total number of POAG cases but also the exact timing of POAG.

Table 3. Statistical Power for Predictive Factors with Prevalence of 0.05 to 0.45 and Relative Risk of 1.3 to 2.0

Relative Risk								
P0	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.05	0.244	0.342	0.471	0.597	0.708	0.799	0.869	0.918
0.10	0.395	0.594	0.764	0.881	0.948	0.980	>0.99	>0.99
0.15	0.560	0.785	0.919	0.977	>0.99	>0.99	>0.99	>0.99
0.20	0.707	0.905	0.980	>0.99	>0.99	>0.99	>0.99	>0.99
0.25	0.825	0.967	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.30	0.909	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.35	0.987	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.40	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.45	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Statistical power for detecting continuous factors predictive for the development of POAG was estimated using a 2-sample t-test, assuming a cumulative 20-year incidence of 400 POAG cases and 1,200 non-POAG and two-sided alpha of 0.80 and 0.90. Estimated statistical power is 0.80 for detecting an effect size of 0.16 SD or greater and 0.90 for an effect size of 0.19 SD or greater, where SD represents the standard deviation of a given continuous factor. Statistical power will be higher for factors measured more than once during follow-up.

8.3.1 Aim 2a Analysis Plan: Prediction Model for the 20-Year Risk of Developing POAG

The OHTS web-based prediction model for the development of POAG continues to be the primary vehicle for translation into evidence-based medicine. We will assess new clinical factors that might improve the prediction model (see below). In addition, we are including changes in the value of baseline predictors over follow-up. This will enable the clinician to refresh the patient's risk status dynamically.

An important objective of the 20-year prediction model is to better understand the dynamic nature of disease risk (e.g., identifying and quantifying the covariate effects over time). For this reason, the 20-year prediction model will be developed in 2 steps. First, we will use Cox models to select potentially time-dependent factors predictive of POAG development. Baseline and intercurrent risk factors to be tested include systolic and diastolic perfusion pressure, sleep apnea, body mass index, history of diabetes, axial length, optic disc hemorrhage, IOP (treated/untreated), variability of IOP, systemic medication usage (statins, beta blockers, ACE inhibitors) and potential genetic markers. Next, a dynamic prediction model will be constructed under a latent class analysis framework to answer questions such as “what's the probability that a patient will develop POAG within 20 years given his/her accumulated history of clinical information at X years?”

Both baseline predictors (measured at randomization) and intercurrent factors (post-randomization data) will be considered in the 20-year prediction model. In the univariate

analysis, the discriminative ability of each intercurrent factor will be summarized graphically using the concordance index (C-index) for time-dependent covariates⁵. The linearity of each continuous predictor will be evaluated using restricted cubic splines and the proportionality of hazard function will be assessed graphically using scaled Schoenfeld residuals. Multivariable Cox model with time-dependent covariates and backward selection procedure will be used to select factors predictive of POAG development. In the above analysis, Gray's sub-distribution method will be used if needed to adjust the influence of mortality and other competing ocular diseases.

Although Cox model is a powerful tool to identify potential predictive factors, it is often problematic to make individualized prediction in the presence of time-dependent covariates⁶. Therefore, after intercurrent predictors have been selected, a dynamic prediction model for POAG development will be constructed using a joint latent class model^{7,8}. Changes of intercurrent predictors over time will be described by a few subgroups (latent classes) with distinct trajectory patterns, and these subgroups will then be associated to both baseline covariates (as antecedents) and the time to develop POAG (as consequence)⁹. Such a joint modeling approach allows us to assess the evolution between longitudinal predictors and time to POAG simultaneously and thus uses information more efficiently, resulting in less biased estimates. The overall performance of the model will be validated internally using 10-fold cross-validation. Performance of the 20-year prediction will be compared to the existing 5-year prediction. The added value for each of the new predictors in the 20-year model will be assessed. Since C-index (the overall performance measure) is known to be insensitive to small improvements, re-classification measures¹⁰ will also be used for this purpose. The 20-year prediction model will be calculated using the original definition and the updated definition of POAG (which includes OCT).

Two additional analyses will also be performed in Aim2a, using baseline predictors only. The first one will examine whether participants who developed bilateral POAG and who are more likely to report functional limitations, can be differentiated from those who develop only unilateral POAG over follow-up. Logistic regression with ordinal outcome will be used to identify baseline factors predictive of bilateral POAG and the accuracy of the prediction model. The second analysis will explore factors predictive of OHT subjects who are likely free of POAG over the 20 plus year follow-up period and thereby possibly their life time. The proposed study will extend the follow-up to a median of 20 plus years. Since median age at randomization was 55, the proposed study will generate a unique dataset that includes individuals who have ocular hypertension but nearly lifelong freedom from POAG. The survival model with long-term survivors¹¹ will be used to identify baseline factors predictive of subjects free of POAG over 20 years, while accounting for competing risks such as mortality and other ocular diseases. The 20-year follow-up duration is significant because it approaches the life expectancy of patients in their 60's and 70's.

8.3.2 Aim 2b Statistical Power: Prediction Model of Glaucomatous Visual Field Progression

Aim 2b uses only data from eyes diagnosed with visual field (VF) POAG. OHTS is among the few studies with a cohort of patients who have a clearly annotated POAG conversion time. In

the subgroup of patients who developed glaucomatous visual field loss, visual field progression is determined by the Visual Field Reading Center and is attributed to POAG by the Endpoint Committee to rule out non-glaucomatous causes of progression. Glaucomatous visual field loss over time will be measured by the rate of change in mean deviation. The availability of this large longitudinal cohort provides a unique opportunity to characterize the patterns of VF progression over time in patients with newly diagnosed POAG and to assess the association between VF indices and other clinical predictors.

At the time of the 2009 data freeze, 204 eyes of 175 participants had developed VF POAG. The sample of VF's for these 204 eyes includes 15 visual fields before VF POAG (median) and 12 or more visual fields after VF POAG (median). In addition, non-protocol visual fields performed after the last OHTS visit to date may be included in analyses if the VFRC determines the VF's meet quality criteria. We project a total of at least 300 eyes will have developed VF POAG by Phase 3 (Table 2). Demirel et. al.¹² reported a SD of 0.2 dB/year in mean deviation in OHTS Phase 1 and 2 data, therefore we would have adequate power to detect clinically meaningful differences. For a factor with 10% prevalence, for example, we will have 80% power at 2-sided 0.05 significance level to detect a difference of 0.54 SD, where SD represents the standard deviation of slope in MD.

8.3.3 Aim 2b Analysis Plan: Prediction Model of Glaucomatous Visual Field Progression

In Aim 2b, we will first align mean deviation (MD) profiles from all eyes that developed VF POAG to the date of diagnosis (time zero). Then a linear mixed-effect model will be used to estimate the change of MD over time, as well as to assess its association with baseline and intercurrent factors. To stabilize the estimate of VF progression, three visual fields will be performed over 1-2 visits in Phase 3 in eyes that previously developed VF POAG in Phase 1 or 2. Visual field progression attributed to non-glaucomatous causes by the Endpoint Committee will be censored. Because of heterogeneity in the rate of change in MD prior to and after POAG diagnosis and we will use piece-wise linear models to handle non-linearity of MD change over time. The rate of change will be estimated in pre- and post-diagnosis periods separately. The mixed model accounts for the potential correlation among MDs measured from the same eye as well as between eyes from the same individual. The above mixed-effect model accounts for disease heterogeneity by allowing each eye to have its own random intercept and slopes. However, the mixed-effects model may fail to detect differences affecting a small proportion of participants because it focuses more on average systematic trend. For this reason, we will also use a latent class analysis, similar to that of Medeiros et. al.¹³, to describe the rate of MD change and to identify factors predictive of VF progression. Latent class analysis (LCA) can provide information that complements conventional linear mixed model by classifying individuals into subgroups (latent classes) based on distinct patterns of changes over time. Based on a simple unconditional LCA (i.e., without any covariates), Figure 5 (right panels) show a preliminary data analysis of MDR from 202 POAG eyes of 173 participants who had at least 4 post-POAG VF's, with time 0 being the diagnosis of VF POAG. The LCA recognized 3 subgroups.

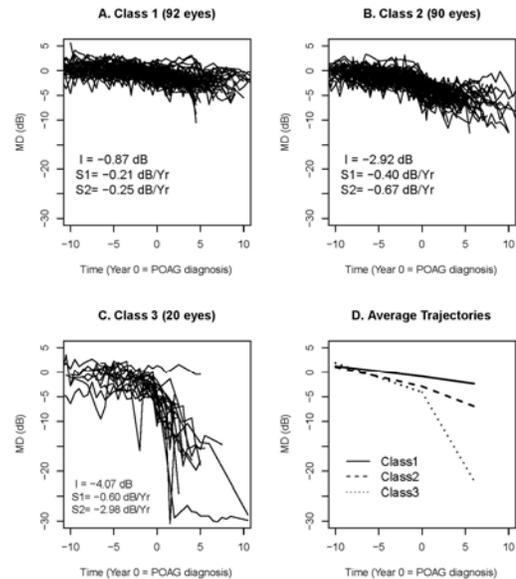
Figure 5

A. 92 (46%) eyes with mean MD of -0.87 dB at diagnosis (intercept) and mean post-diagnosis slope of -0.25 dB/year, (Figure 5A)

B. 90 eyes (44%) with mean MD of -2.92 dB at diagnosis and mean post-diagnosis slope of -0.67 dB/year (Figure 5B)

C. 20 eyes (10%) with mean MD of -4.10 dB at diagnosis and mean post-diagnosis slope of -2.98 dB/year (Figure 5C)

These LCA classifications are based on 4.8 years of VF's after diagnosis. Visual field data 10 plus years after diagnosis will provide a better understanding of consistency of change in visual fields in the life-time of participants.



8.3.4 Aims 2a and 2b: Anticipated Results and Pitfalls

Compared to conventional prediction models with time-to-event endpoint, a dynamic prediction model under joint latent class model (JLCM) possesses some unique advantages and has been used increasingly in the prognosis of chronic diseases such as prostate cancer^{7,8,14}. However, one potential challenge is that JLCM may become too complex and computationally prohibitive in the presence of multiple (≥ 4) longitudinal predictors. If this happens, the prediction model will be developed using landmark models instead¹⁵. A landmark analysis consists of fitting a serial of simple Cox models only to the subjects still at risk, that is, computation of the predictive distribution at a certain time given the history of event and covariates until that moment. It has been shown that the longitudinal effects could be well approximated by a serial of landmark models when the effects of covariate are not very strong and the baseline hazard function is not too “bumpy”^{15,16}. A thorough simulation study will also be performed to test the proposed prediction under various “what-if” conditions.

8.4 Aim 3 Sample Size: Frequency and Severity of Self-Reported Functional Limitations

The OHTS Phase 1, 2 and 3 datasets will capture 20 plus years of general and vision-specific quality of life surveys completed at regular intervals corresponding to clinical visits. Most participants already have more than 3 surveys to support longitudinal analyses. Ninety-eight percent (1,598 of 1,636) of all randomized participants have ≥ 3 SF-36 surveys which were administered annually from randomization until 2002 and then at close-out. Sixty-six percent (1,078 of 1,636) of the participants have ≥ 3 NEI-VFQ surveys which were administered every 2 years from 2001 through 2008. Seventy-two percent (1,184 of 1,636) have at least one Functional Measure Battery that includes the Nelson Glaucoma Survey plus questions from the Owsley Driving Survey and the Coleman Falls Survey. The primary comparison of interest is

between participants who did/did not develop POAG. Participants who did not develop POAG serve as concurrent controls for co-morbidity and normal aging. Among the 279 participants who developed POAG by the 2009 data freeze, sufficient data are available to examine longitudinal changes in QoL outcomes after the onset of POAG. Eighty-nine percent (248 of 279) have at ≥ 1 VFQ after POAG diagnosis in OHTS Phase 1 or 2 and 58% (163 of 279) have ≥ 1 VFQ ± 18 months of the POAG diagnosis to serve as a “baseline”.

To determine whether differences QoL between POAG (either disc POAG and/or VF POAG) and non-POAG participants might be detected in OHTS Phase 3, we compared SF-36 and NEI-VFQ and Functional Measure Battery score of POAG and non-POAG participants at their last OHTS Phase 2 visit. We classified scale scores of the SF-36 and NEI-VFQ by whether the scores were below vs. at/above the normative age-decade median to capture the construct of “worse” than age-specific function. A comparison of means/medians of the two groups could miss differences since the majority of participants, whether they did/did not develop POAG, reported no functional limitations. Despite the fact that most of the participants who developed POAG, diagnosed by visual fields and/or by optic disc photography, would be classified as “early” loss (mean of -1.22 ± 3.0 dB in the better eye)¹⁷ at their last OHTS visit, there was evidence of greater self-reported functional limitations and difficulty among participants who developed POAG. Additional follow-up will reveal whether these differences increase over time.

Table 4. Comparison of Vision Specific Quality of Life and Functional Limitations Between Participants who did/did not Develop POAG (Disc or VF POAG). Data from Last OHTS Phase 2 Visit

Nelson Glaucoma N (%) participants reporting “some”, “quite a lot” “severe” difficulty or “gave up” because of vision.	Not POAG (n, %)	Disc or VF POAG (n, %)	Chi-Square P-Value
Walking After Dark	88(9.7%)	31 (13.6%)	0.0852
Seeing at Night	145 (15.5%)	48 (20.4%)	0.0684
Walking on uneven ground	133(14.3%)	43 (18.2%)	0.1348
Walking on step/stairs	67 (7.3%)	24(10.2%)	0.1380
“moderately” or “very” fearful of falling	86 (9.6%)	30 (13.3%)	0.1001
NEI-VFQ N (%) pts. below the normal age reference group mean score¹⁸.			
VFQ-25 Driving (Ref mean=87)	202 (19.7%)	57 (23.6%)	0.1774
VFQ-25 Peripheral Vision (Ref mean=97)	191 (16.9%)	59 (21.9%)	0.0556
VFQ-25 Color Vision (Ref mean=98)	107 (9.5%)	38 (14.1%)	0.0257
VFQ-25 Role Difficulties (Ref mean=93)	318 (28.1%)	98 (36.2%)	0.0087

To reduce the complexity of multiple outcome measures for estimating statistical power, we selected the driving subscale of the NEI-VFQ as an “indicator” variable because of its contribution to utility loss associated with POAG¹⁹. The driving subscale together with 5 other subscales (“needing help”, “unable to leave home”, “accomplishing less”, “unable to read”,

“unable to see to the side”) were associated with a utility loss comparable to bilateral blindness²⁰. A power analysis was performed for the association between POAG status and driving subscale using 2-sample chi-square test. Based on Table 4, we project that 25% of non-POAG participants would report driving difficulty at 20 years. The projected sample size (N=~400 POAG versus ~1200 non-POAG) using all data to date will allow us, with 90% power at 2-sided 0.05 significance level, to detect a minimum difference of 8.5% (25% versus 33.5%) or relative risk (RR) of 1.34 –within the range of minimum clinically significant difference between POAG and non-POAG participants. Table 5 presents the minimal detectable RR in assessing the association between potential predictors and self-reported functional limitations given the prevalence of a predictor (P1), the proportion of participants positive for the predictor, and the event rate in "controls" (P0), the proportion of certain functional limitation in participants negative for the predictor. We anticipate that more power could be achieved in the analysis because all the outcomes are measured repeatedly over time and the longitudinal data analysis will allow us to use information more efficiently.

Table 5. Minimum Detectable Relative Risk of Self-Reported Functional Limitation for 90% Power and 2-sided Alpha=0.05 given P0=Proportion of Functional Limitation (0.05 to 0.70) in Participants who do not have the Risk Factor and P1=Proportion of Participants (0.05 to 0.45) who have the Risk Factor

		P0						
P1	0.05	0.10	0.20	0.30	0.40	0.50	0.60	0.70
0.05	3.08	2.31	1.81	1.59	1.46	1.36	1.29	1.22
0.10	2.44	1.93	1.58	1.43	1.34	1.27	1.21	1.17
0.15	2.20	1.77	1.49	1.36	1.28	1.23	1.18	1.14
0.20	2.06	1.68	1.43	1.32	1.25	1.20	1.16	1.13
0.25	1.96	1.63	1.40	1.30	1.23	1.19	1.15	1.12
0.30	1.92	1.59	1.38	1.28	1.22	1.18	1.14	1.11
0.35	1.88	1.57	1.36	1.27	1.21	1.17	1.14	1.11
0.40	1.86	1.55	1.35	1.26	1.21	1.17	1.13	1.10
0.45	1.84	1.55	1.34	1.26	1.20	1.16	1.13	1.10

8.4.1 Aim 3 Analysis Plan: Frequency and Severity of Self-Reported Functional Limitations

Data analysis for Aim 3 will focus on the driving difficulty (primary outcome), while the impact of POAG on other self-reported functional limitations will also be assessed as secondary outcomes. One common challenge in such a self-reported QOL data is the relatively large variability in self-reported functional limitations which may lead to misclassification of whether the participant reports functional limitations consistently or sporadically. This issue could be significantly alleviated in OHTS Phase 3 because multiple measures over time are available for most participants. For example, participants showing persistent difficulties would more likely to be the “true cases” as comparing to those only reporting functional limitations occasionally. Rasch analysis will be performed to test item fit and differential item functioning.

The frequency and severity of self-reported functional limitations (SF-36, NEI VFQ, Nelson glaucoma survey, number of falls, vehicle accidents, Owsley Driving Survey) will be compared in participants after developing POAG to participants who did not develop POAG to differentiate functional limitations associated with normal aging and co-morbidity. Self-reported functional limitations will be correlated with Humphrey 30-2 mean deviation, ETDRS visual acuity and Pelli-Robson Contrast Sensitivity and socio-demographic factors. We will examine the association of the rate and duration of visual field loss on self-reported functional limitations.

For each subscale and the overall score, its change over time and the association with POAG status will be initially investigated using a linear-mixed model or generalized estimating equation (GEE), to account for the potential correlation among repeated measurements from the same participant. In these models, the mean evolution of a specific response is described using some function of time, and patient-specific deviations from this mean evolution are introduced by random intercepts and random slopes, allowing for different baseline values and different rates of change for each participant. Similar to the analysis of slope of change in mean deviation in Aim 1, all participants will be aligned to the date of diagnosis (POAG) or a comparable time (non-POAG) to facilitate an easy interpretation for the estimated intercepts. A high proportion of participants who developed POAG already have at ≥ 1 VFQ, with 58% (163 of 279) and 89% (248 of 279) during pre- and post- diagnosis periods, respectively. And 77% (214 of 279) have at least one SF-36 within ± 18 months of POAG diagnosis. In the linear mixed model, VFQ scores will be considered the dependent variable, while the development of POAG will be included as a fixed-effect covariate. Time will be included as a continuous predictor and the 2-way interaction between time and POAG status will also be included in the model to evaluate whether there is a significant difference in longitudinal VFQ over time between those with and without POAG.

Since more than 30 secondary endpoints will be assessed, the critical P value for association should be corrected for multiple testing. Bonferroni correction is likely too conservative, given some degree of correlation is expected among different subscales. Therefore, bootstrap re-sampling methods²¹ will be used to control the *false discovery rate* (FDR)²². The bootstrap re-sampling methods is an appealing approach in that the correlation structure (i.e., repeated measurements) of the data can be incorporated into the adjustments. In addition, this method has been implemented in the statistical package SAS (i.e., PROC MULTTEST).

8.4.2 Aim 3: Anticipated Results and Pitfalls

We have selected a focused approach to the analysis of vision-specific quality of life and self-reported functional limitations. We choose driving limitation as our primary outcome for Aim 3 because of its importance to utility loss in POAG. Subscales of the NEI-VFQ, SF-36, Nelson Glaucoma Survey, falls and Owsley Driving survey will be secondary functional outcomes. One potential issue is scoring of the driving subscale for participants who report giving up driving due to vision. In the presence of missing values for “driving difficulty”, an alternative for scoring the driving subscale is based on Lisboa²³ who defined abnormal QOL as the presence of a score less than 50 on any 1 of the 10 vision-related subscales of the NEI VFQ-25 (excluding the ocular pain subscale). This corresponds to approximately 2 SDs below the scores previously described for a normal reference population.

Although the above linear mixed model provides a powerful tool for assessing the longitudinal change over time, it often assumes that individual trajectories are smoothly distributed around the average or systematic trends. In some fields, particularly psychological and behavioral development, this assumption may not be satisfied. For example, a great majority of participants may have little or no “abnormality” with scores at the top of the scale over the whole follow-up, while a small fraction of participants may report scores near the scale floor over the follow-up. When outcomes are markedly heterogeneous in a small sub-group, a typological representation (i.e., a small number of groups) may be more appropriate. We will use latent class analysis to classify participants into a few subgroups and to identify potential predictors. Specifically, participants will be classified into a few subgroups (latent classes) based on the unique patterns of longitudinal change over time. The distributions of patient demographic and clinical characteristics across these subgroups will be compared using chi-square test and 1-way ANOVA (for baseline factors such as age, gender, CCT, etc.) or GEE and 2-way ANOVA (for intercurrent factors such as mean deviation during follow-up, disc hemorrhage) as appropriate. The uncertainty in the status of subgroups will be accounted for using 1000 bootstrapping resampling methods²⁴. Once the participants are classified into a few subgroups, a conventional logistic regression analysis can be performed to identify factors predictive of participants who consistently self-report functional limitations.

8.5 Handling of Missing Data

The rate of missing data has been low throughout OHTS. At the last DSMC report, April 2007, prior to initiation of close-out procedures, 86.9% of the participants had kept their last visit and visit completion rate was identical between randomization groups. Outcome evaluation was consistently high with 99% of the participants having evaluable visual fields and 94% of the participants having evaluable stereoscopic optic disc photographs. In OHTS Phase 3 every effort will be made to have high rates of visit completion and evaluable outcome assessment. Clinical Centers will be encouraged to test participants even if may seem improbable that the participant can provide reliable data due to cognitive impairment or ocular co-morbidity. However, despite our best efforts, some data will be missing. Baseline and follow-up demographic and clinical characteristics of surviving participants who do/do not complete Phase 3 examinations will be compared for evidence of participation bias. Missing data for analyses will be tabulated. If more than 5% of the expected data from surviving participants are missing, key analyses will be performed not only with the observed data from OHTS Phase 3 follow-up, but also using multiple imputation methods²⁵⁻²⁷.

We plan to retrieve data after the last OHTS visit and before OHTS Phase 3 from OHTS Clinical Centers and non-OHTS clinicians. Data to be retrieved include visual fields, IOP, ocular and medical history. Ocular history retrieved from medical records, including hypotensive medical treatment and glaucoma surgery, is likely to be more accurate than patient recall. The key outcome measure to be collected from interim data is visual field testing. The Visual Field Reading Center will determine if retrieved visual field tests are evaluable for analyses. Mixed models of slope of change in mean deviation are robust to sporadic “missing” data, but we are aware that availability and frequency of visual field testing may be associated with patient demographic and clinical characteristics. We will examine potential for bias in the availability of interim visual field data and frequency of testing by comparing baseline and follow-up

characteristics of participants. Quality of IOP data will be assessed by examining variability between IOP measures over time in the same eye and comparing mean and variances of IOP among clinics.

A potential challenge is the handling of POAG cases occurring since the participant's last OHTS visit and OHTS Phase 3. In OHTS Phase 1 and 2, the date of POAG diagnosis was determined by the "date of the first optic disc photography and/or visual field that determined the Endpoint Committee's decision". However, the onset date is likely to be unknown for the ~ 120 new POAG cases expected in the 7-8 years between the last OHTS visit and the OHTS Phase 3 visit. For this reason, the 20-year cumulative incidence of POAG will be estimated using methods for interval censoring survival data¹, though POAG onset date might be estimated for many participants from intervening disc photographs and/or visual fields.

8.6 Statistical Power of OHTS Phase 3 Compared to Population-Based Incidence Studies

One might be concerned that a limitation of OHTS is low statistical power to answer the specific aims posed compared to large population-based studies. However, the large sample sizes of population-based studies do not necessarily give them greater statistical power.

While the total sample size of the OHTS is small compared to population-based studies, OHTS has a larger number of incident POAG cases than any population-based study and all available data from baseline is used for cases and controls. Using the harmonic mean ($n' = 2n_A n_B / (n_A + n_B)$), it is possible to estimate the statistical power of studies with normal equally varying samples of cases and controls of different sample size²⁸. We computed the harmonic mean for OHTS and for population-based studies that reported incident open-angle glaucoma. At the last data freeze in 2009, OHTS had 279 participants who developed definite POAG in one or both eyes and 1,357 controls. Using the harmonic mean, the effective sample size of the OHTS is equivalent to 462 cases and 462 controls and, if we assume 121 additional incident POAG cases by 2015/16 (projection based on parametric model, MOP Chapter 8 "Statistical Issues and Analyses"), this would increase the effective sample to 604 cases and 604 controls. In Table 6, the effective sample size of OHTS is compared to population-based studies reporting incident open-angle glaucoma. These comparisons assume that all other factors affecting statistical power are constant across studies.

Table 6. Effective Sample Size of OHTS Phase 3 compared to Population-Based Incidence Studies of POAG/OAG

Study	N Sample	Percent African Ancestry	N Incident “Probable” or Definite POAG/OAG	Years after Baseline	N’ Equivalence to 2 groups of cases and controls of equal size
OHTS Phase 1 & 2	1,636	25%	279	13	462
OHTS Phase 3 2015-2016	1,636	25%	400	20	604
Blue Mountain Eye Study Kawasaki, 2013²⁹	2,417	<1%	82	10	158
Los Angeles Latino Eye Study, 2012³⁰	3,772	Not included	87	4-5	170
Ponza Eye Study Cedrone, 2012³¹	411	Not reported	15	12	29
Beijing Eye Study Wang 2012³²	3,251	0%	23	5	46
Rotterdam Study Ramdas, 2011³³	3,939	0%	108	9.7	200
Barbados Eye Studies Nemesure, 2007³⁴	3,222	93%	125	9	240
Visual Impairment Project Mukesh, 2002³⁵	2,594	0%	62 39 possible 13 probable 10 definite	4.5	121

The large number of incident POAG cases gives OHTS more statistical power than larger population-based incidence studies to identify risk factors associated with the development of POAG and associated functional limitations.

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9.1 Introduction

The organizational structure of the Ocular Hypertension Treatment Study (OHTS) links the following resource centers together in a productive network:

- Clinical Centers (CLC)
- Coordinating Center (CC)
- Visual Field Reading Center (VFRC)
- Optic Disc Reading Center (ODRC)
- Optical Coherence Tomography Reading Center (OCTRC)
- Study Chair's Office
- National Eye Institute (NEI) Program Office

9.2 Clinical Centers

Each Clinical Center is responsible for contacting and scheduling study participants who were previously randomized and followed in OHTS Phase 1 and/or 2 to complete OHTS Phase 3 visits. Participants may need 2-3 visits to complete all tests and measures required in OHTS Phase 3. Each Clinical Center has at least one OHTS certified individual for each of the following functions: Clinical Center Investigator, Clinical Center Coordinator, optic disc photographer, visual field technician and imaging technician. Each position requires a back-up person, although an individual can serve more than one role and can back up more than one position. A detailed description of the responsibilities and procedures related to the Clinical Center may be found in Chapter 14.

9.3 Coordinating Center (CC)

The CC is a joint effort of the Division of Biostatistics and the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine. A detailed description of the responsibilities and procedures related to the CC may be found in Chapter 16. It is responsible for:

- Development and implementation of the study design;
- Overall scientific and ethical conduct of the trial;
- Training and certifying Coordinating Center personnel, Clinical Center Coordinators and Investigators in protocol knowledge, clinical tests and measures including IOP, refraction, ETDRS visual acuity testing, contrast sensitivity testing and automated blood pressure;
- Coordinating activities of the Clinical Centers, VFRC, OCTRC and ODRC;
- Maintaining study personnel directory and database of IRB approvals and certified study personnel;
- Receiving, editing, processing, analyzing, and storing study data from Clinical Centers and Reading Centers;
- Implementing and maintaining quality assurance and control procedures;
- Monitoring performance of Clinical Centers and Resource Centers and taking corrective action as needed with the Study Chair and the Executive/Steering Committee;

- Preparing performance reports for review by Clinical Centers and Executive/Steering Committee;
- Preparing presentation and publications;
- Archiving study documents and datasets and de-identifying datasets for resource sharing.

9.4 Visual Field Reading Center (VFRC)

The VFRC is located in the Department of Ophthalmology & Visual Science at the University of Iowa Hospitals & Clinics, Coralville, IA. A detailed description of the responsibilities and procedures related to the VFRC may be found in Chapter 11. The VFRC is responsible for:

- Developing and maintaining written protocol for visual field testing;
- Training and certifying VFRC personnel, monitoring for secular trend and inter-grader agreement;
- Training and certifying Clinical Center visual field technicians;
- Receiving all Humphrey visual fields;
- Grading the fields according to criteria described in the VFRC MOP;
- Transmitting grading results to the Clinical Center and Coordinating Center;
- Monitoring data quality from Clinical Centers and taking corrective action as needed with the Study Chair and the Executive/Steering Committee;
- Notifying Clinical Centers for retest if a visual field is not evaluable for analysis due to poor quality;
- Notifying Clinical Centers for retest if a visual field is suspicious for an abnormality;
- Preparing quarterly Clinical Center and semi-annual Reading Center performance reports;
- Preparing narrative description of visual fields for Endpoint Committee review to determine POAG conversion and/or progression;
- Maintaining, documenting and archiving the visual field dataset.

9.5 Optic Disc Reading Center (ODRC)

The ODRC is located in the Department of Ophthalmology at Bascom Palmer Eye Institute, University of Miami, Miami, FL. A detailed description of the responsibilities and procedures related to the ODRC may be found in Chapter 12. The ODRC is responsible for:

- Developing and maintaining written protocol for optic disc stereophotography;
- Training and certifying ODRC personnel, monitoring secular trend and inter-grader agreement;
- Training and certifying Clinical Center photographers;
- Receiving and grading all stereophotographs according to criteria described in the ODRC MOP;
- Monitoring data quality from Clinical Centers and taking corrective action as needed with the Study Chair and the Executive/Steering Committee;
- Transmitting grading results to the Clinical Center and Coordinating Center;
- Notifying Clinical Centers for retake of stereophotographs if stereophotograph is not evaluable for analysis due to poor quality;

9-4 Study Organization

- Notifying Clinical Centers for retake of stereophotographs if stereophotograph is suspicious for abnormality;
- Preparing quarterly Clinical Center and semi-annual Reading Center performance reports;
- Preparing narrative description of stereophotographs for Endpoint Committee review of POAG conversion and/or progression;
- Maintaining, documenting and archiving optic disc dataset.

9.6 **Optical Coherence Tomography Reading Center (OCTRC)**

The OCTRC is located at Hamilton Glaucoma Center in the Department of Ophthalmology at the University of California, San Diego. A detailed description of the responsibilities and procedures related to the OCTRC may be found in Chapter 13. The OCTRC is responsible for:

- Developing and maintaining a written protocol for OCT assessment;
- Training and certifying OCTRC personnel, monitoring secular trend and inter-grader agreement within the reading center;
- Training and certifying Clinical Center imaging technicians;
- Receiving and grading Spectralis or Cirrus OCT scans as described in the OCTRC MOP;
- Maintaining, documenting and archiving imaging dataset.

9.7 **Study Chair's Office**

The Study Chair's Office is located in the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine, St. Louis, MO. A detailed description of the responsibilities and procedures related to the Study Chairman's Office may be found in Chapter 15. The Study Chair'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;
- Patient relations and education;
- Quality control and troubleshooting;

9.8 **NEI Program Office**

The NEI Program Office participates in the general organizational and scientific guidance of the study.

9.9 **Committees and Groups**

The OHTS is supported by the following standing committees and groups:

- Executive/Steering Committee;
- Full Investigative Group;

- Clinical Center Coordinators Group;
- Endpoint Committee.

These committees are expected to function throughout the lifetime of OHTS. Other committees such as writing committees will be formed and dissolved as their tasks are completed.

9.10 Executive/Steering Committee

The Executive/Steering Committee has overall responsibility for directing OHTS activities and formulating policy for the study, except for responsibilities specifically assigned to other committees. Policy decisions proposed by the Executive/Steering Committee are subject to review and approval by the Full Investigative Group.

9.10.1 Executive/Steering Committee Membership

The following individuals are permanent members of the Executive/Steering Committee:

- Michael A. Kass, M.D., Chairperson
- Dale K. Heuer, M.D., Vice-chair
- Eve J. Higginbotham, M.D., Vice-chair
- Richard K. Parrish II, M.D., Vice-chair and Director of the Optic Disc Reading Center
- Mae O. Gordon, Ph.D., Director of the Coordinating Center
- Chris A. Johnson, Ph.D., Director of the Visual Field Reading Center
- Linda Zangwill, Ph.D., Director of the OCTRC
- Donald Everett, M.A., NEI Representative
- Ellen Fischbach, BS, CCRP and Shirley Pistorius, CCRP, COA. Central Coordinators (non-voting)
- Two clinician members elected from the Full Investigative Group, each of whom serves a two-year term
- One member elected from the Clinical Center Coordinators, who serves a two year term. (Each Clinical Center receives one vote in the selection of the Coordinator representative.)

The Study Chair may appoint other individuals to the committee for two-year terms as he deems necessary to assure the scientific quality of the deliberations. Any member missing two consecutive meetings of the Executive/Steering Committee is subject to replacement by the Study Chair. All members must file statements with the Study Chair describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of OHTS.

9.10.2 Executive/Steering Committee Functions

Some of the specific functions of the Executive/Steering Committee are:

- To direct all activities of OHTS;
- To formulate all policy decisions related to the design and conduct of OHTS;
- To assist the Study Chair with the scientific administration of the study;

- To notify the NEI of major changes to the study protocol judged necessary or desirable;
- To ratify major changes to the Manual of Procedures;
- To review all ancillary studies for suitability and all publications from ancillary studies;
- To advise the central units (Study Chair's Office, CC, VFRC, ODRC, OCTRC) on operational matters;
- To resolve problems brought to attention by the directors of the VFRC, ODRC, OCTRC, CC, the clinical investigators, or NEI staff;
- To monitor the performance of all Clinical Centers and to take corrective action as necessary;
- To formulate editorial policy and to monitor adherence to it among the study investigators;
- To establish writing committees for principal papers, to review all written and oral reports for publication and presentation;
- To appoint subcommittees as required for special study functions;
- To dissolve subcommittees and technical committees when their functions have been fulfilled.

9.10.3 Executive/Steering Committee Meetings

The Executive/Steering Committee meets once at the start-up of OHTS. Telephone conferences will be held semi-annually and as needed. Additional meetings may be called by the Study Chair.

9.11 Full Investigative Group

The Full Investigative Group represents all of the operational units participating in the study and is responsible for maintaining a study protocol that is specific, practical, and well understood by all OHTS personnel.

9.11.1 Full Investigative Group Membership

The following individuals are voting members of the Full Investigative Group:

- Michael A. Kass, M.D., Study Chair
- Dale K. Heuer, M.D., Vice-chair
- Eve J. Higginbotham, M.D., Vice-chair
- Richard K. Parrish II, M.D., Vice-chair and Director of ODRC
- Mae O. Gordon, Ph.D., Director of the CC
- Chris A. Johnson, Ph.D., Director of VFRC
- Linda Zangwill, Ph.D., Director of OCTRC
- Donald Everett, M.A., NEI representative
- Ellen Fischbach, BS, CCRP and Shirley Pistorious, CCRP, COA, Central Coordinator/Project Manager
- The principal investigator of each Clinical Center
- The coordinator of each Clinical Center, VFRC, OCTRC and ODRC.

Other staff members of OHTS centers may attend Full Investigative Group meetings as non-

voting members.

9.11.2 Full Investigative Group Functions

The OHTS Full Investigative Group is responsible for:

- Implementing the OHTS protocol at the Clinical Center
- Notifying the Executive/Steering Committee when changes in procedures are required
- Implementing changes in the protocol approved by the Executive/Steering Committee

9.11.3 Full Investigative Group Meetings

The Full Investigative Group meets once at study start-up in conjunction with the Coordinators Group to review the protocol and to insure its successful implementation. Two investigators are elected by its members as voting members of the Executive/Steering Committee. Each Clinical Center has one vote towards each candidate.

9.12 Coordinators Group

The Coordinators Group consists of the coordinators who manage the day-to-day performance of the study at each Clinical Center and coordinators from the Coordinating Center, Visual Field Reading Center, Optic Disc Reading Center and Optical Coherence Topography Reading Center.

9.12.1 Coordinators Group Functions

The primary responsibility of the Coordinators Group is to provide information to the Investigative Group on the logistical aspects of the study, particularly at the working level of individual Clinical Centers. Members of the Coordinator's Group assist in mentoring newly certified OHTS personnel. Recommendations from the Coordinators Group can be made to any of the standing or ad hoc committees of the study.

9.12.2 Coordinators Group Membership

The following individuals are members of the Coordinators Group:

- Central Coordinator of Coordinating Center
- Coordinators from each of the Clinical Centers
- Coordinator of the VFRC
- Coordinator of the ODRC
- Central Coordinator of the OCTRC

9.12.3 Coordinators Group Meetings

The Coordinators Group meets once at study start-up in conjunction with the Full Investigative Group. One Clinical Center coordinator from the Coordinators Group is elected every two years by its members as a voting member of the Executive/Steering Committee. (Each Clinical Center receives one vote in the selection of the representative.)

9.13 Endpoint Committee

The Endpoint Committee determines whether reproducible abnormality/change from baseline or glaucoma progression from the time of POAG diagnosis as documented by the Reading Center(s) is due to POAG or not. A detailed description is provided in Chapter 2.9 and 2.10. Many systemic and ocular conditions other than POAG can cause reproducible visual field loss, optic disc change and/or peripapillary nerve fiber layer thinning.

9.13.1 Endpoint Committee Membership

Members of the Endpoint Committee for OHTS Phase 3 is the same as for OHTS Phase 1 and 2.

- Dale K. Heuer, M.D., Vice-chair, Medical College of Wisconsin, Milwaukee, WI
- Eve J. Higginbotham, M.D., Vice-chair, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
- Richard K. Parrish II, M.D., Vice-chair and Director of the ODRC, University of Miami School of Medicine, Miami, FL

9.13.2 Endpoint Committee Function

The Endpoint Committee determines if a reproducible abnormality/change from baseline or glaucoma progression from the time of POAG diagnosis as documented by the Reading Center(s) is due to POAG or not. The Endpoint Committee members initially independently review ocular and medical history using a secure website. If the initial independent review does not result in consensus, then a second round of review is conducted. If needed, the case is resolved in a monthly conference call.

9.13.3 Endpoint Committee Meetings

The Endpoint Committee meets by teleconference monthly and/or prior to Executive/Steering Committee meetings on an as-needed basis.

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10.0 Study Policies

10.1 Protection of Human Subjects

The protection of OHTS study participants has been and continues to be paramount in the design and implementation of the study. This includes consideration of the risks and benefits of participation, plans for the consent process and criteria for study eligibility and protection of privacy.

All Clinical Center personnel must complete training programs in research ethics, in maintaining the safety of human subjects in clinical research and in complying with HIPAA regulations prior to OHTS certification. Training may be provided by the Clinical Center's approved training program or by the NIH website (<http://phrp.nihtraining.com>). Certificates documenting the successful completion of research ethics, patient safety programs and HIPAA compliance must be submitted to the Coordinating Center by all members of the investigative group prior to OHTS certification.

10.2 Institutional Review Board and Informed Consent

Each Clinical Center must provide the Coordinating Center with a copy of the consent form approved by their local IRB before the Center is certified to enroll participants into the study. The consent form is prepared by each Clinical Center based on a prototype provided by the OHTS Coordinating Center and is submitted to the local IRB for approval. All consent forms must be fully HIPAA compliant. Each participant must provide written informed consent in order to participate in any component of OHTS Phase 3 (Chapter 4 "Patient Education and Informed Consent").

Investigators at each Clinical Center are responsible for conducting the consent process. In OHTS Phase 3, the participant will complete 1 to 3 visits that will include a comprehensive eye examination consisting of visual fields, optic disc photos, OCT scans, Pelli-Robson contrast sensitivity, refraction, intraocular pressure, visual acuity, blood pressure, slit-lamp examination, ophthalmoscopy, gonioscopy, medical history and quality of life questionnaires (section 5.2).

The Clinical Center Investigator should describe study procedures, discuss the risks and benefits and alternatives to participation, and discuss the voluntary nature of participation with the potential subject. The patient should be asked to sign the consent form to participate in OHTS Phase 3 only after the patient has been introduced to the study and had all questions answered to his or her satisfaction (Appendix 4-A).

We will attempt to reconstruct disease progression since the participants' last OHTS visit using OCT scans and/or visual field tests. We are requesting release of OCT scans from all participants since their last OHTS visit from OHTS sites (Appendix 4-B). In addition, we are requesting both OCT scans and visual field tests since their last OHTS from OHTS and non-OHTS clinics for:

- a. Participants who developed POAG in OHTS 1 or 2 or are found to have developed POAG in OHTS 3
- b. Participants who are unable/unwilling to return for examination;
- c. Participants who have died since their last OHTS visit.

OCT scans and visual field tests will be de-identified by Clinical Centers before being transmitted to the OCT Reading Center and Visual Field Reading Center.

Participants who are unable/unwilling to return for examination when queried due to family crises, illness or vacation, may be able to complete a visit at a later time or to complete quality of life surveys via telephone. The Clinic Coordinator will ask for verbal consent for completion of quality of life survey by telephone and for release of OCT scans and visual field tests. A legally authorized representative (LAR) may sign the informed consent and assist a cognitively impaired participant with the telephone Quality of Life surveys if approved by the local IRB.

A copy of the signed/dated consent form(s) must be provided to the participant and the original will be maintained at the Clinical Center in HIPAA compliant secure files separate from research data. The original consent form must be available for inspection during site visits.

10.3 Regulatory Binder

Clinical Centers should keep a regulatory binder to document compliance with GCP (good clinical practices), IRB and regulatory requirements. The following sections should be included:

- IRB Documentation
 - Approval Memos
 - Current Consent
 - Correspondence
- Protocol (Chapter 2 of Manual of Procedures)
- Investigator's CV, Medical License and Human Subjects Training Certificate
- Delegation of Authority Log
- Training & Certifications
- Subject enrollment log
(keep completed log in separate secured location, with note to file indicating location)
- Adverse Events
- Site Monitoring Log and Correspondence
- Current Case Report Forms
- Correspondence
- Other

10.3 Participant Confidentiality

Clinical Centers must take all appropriate measures to protect the confidentiality of OHTS participants. All research data that leave the Clinical Center do not identify the patient by name or contain personal health information. Participants keep the same unique study ID number (that

is not related to their birth date, social security number or name) that was assigned at the time of study enrollment. All study information is kept in password protected accounts and/or locked file cabinets at the Clinical Centers and all resource centers. Patient identities are not disclosed in any publications that may result from this study. Clinical Centers maintain logs of participants names, social security numbers and assigned study ID's, which are kept in the regulatory binder in a locked cabinet separate from research data. Clinical information is not released without written permission of the participant, except as necessary for monitoring by the IRB, FDA, the NEI, the OHRP, or study monitors.

10.4 Patient Costs

Charges for standard clinical care of participants (office visits, tests, imaging, medications) with ocular hypertension or glaucoma are the responsibility of the participant, Medicare or other insurance companies. Charges for research tests and measures are the responsibility of the study. The cost of transportation and meals are provided by the study. If the local IRB approves, the participants will receive a stipend of \$50.00, up to \$100 for transportation and \$25 for meals for each visit. The participant may require as many as 3 visits to complete the protocol. Participants who no longer live in the service area of the OHTS Clinical Center, may be seen at a closer Clinical Center. If needed, the study will cover the cost of airfare and lodging to the closest OHTS Clinical Center. Medicare and insurance companies will be charged for any treatment of side effects that may occur as a result of participation in the study.

10.5 Publications and Presentations Policy

OHTS Phase 3 papers and presentations are defined as those that use data, documents, and procedures or any of the information collected during the study. Publication and/or presentations will be governed by the policies and procedures developed by the Executive/Steering Committee. The Executive/Steering Committee will review all major manuscripts prepared for publication. The review insures that the appropriate analyses and conclusions have been reached and that the publication/presentation complies with NIH policies and guidelines. The Executive/Steering Committee also is responsible for the determining the priorities (timeline and order of preparation) of proposed manuscripts/presentations. Clinical Center Investigators will be reminded on a yearly basis about the publication and presentation policies.

10.5.1 Authorship

All manuscripts from OHTS will list the Ocular Hypertension Study Group as an author. Selected major manuscripts will list only the Ocular Hypertension Study Group as the primary author in a manner consistent with publication policies of the selected journals. Other publications will list the primary author and coauthors and the Ocular Hypertension Study Group. All professional participants of OHTS, including those at the central units and the Clinical Centers, will be listed at the end of each paper and are considered as contributors. For major papers all study personnel, past and present, will be listed with the approval of the Clinical

Center Investigator for whom they worked. Conflicts regarding authorship will be resolved by the Executive/Steering Committee.

10.5.2 Writing Committees

The Executive/Steering Committee will determine potential manuscript topics based on the specific aims, interim analyses and hypotheses. The Executive/Steering committee will select a chair for each writing committee and may offer suggestions of particular members for inclusion on the writing committee based on specific expertise. All Investigative Group members are invited without bias to volunteer for writing committees and to suggest additional topics when appropriate. The final composition of the writing committee is made by the chair of that committee. The chair of the writing committee and the Executive/Steering Committee will select the journal to receive the submission.

If a Clinical Center Investigator has an idea for a manuscript that has not been considered by the Executive/Steering Committee he/she should submit a short description of the proposed paper including data to be reported and timeline for the drafts and submission. The Executive/Steering Committee is responsible for reviewing the proposed papers' merit and deciding if it should be an OHTS publication. This review process is intended to insure the quality of the study publications and may require refinement of the proposal. The Executive/Steering Committee is responsible for determining priorities (timeline and preparation) of proposed papers.

The Coordinating Center will maintain a database that tracks proposed and approved study publications and presentations. A list of approved study publications and presentations will be distributed to all OHTS investigators on a regular basis. If the timeline for a paper has expired with little evidence of progress, the Coordinating Center will contact the chair of that writing committee to assess the situation. The Executive/Steering Committee has the right to dissolve and reformulate the writing committee as needed.

The chair of the writing committee is responsible for coordinating all activities related to that manuscript. This includes arranging conference calls, discussing analytic plans with the Coordinating Center, assigning responsibilities to co-authors, meeting timelines, determining the order of authorship and circulation of drafts to co-authors.

10.5.3 Manuscript Pre-submission Review

Papers prepared for publication must be sent to the Study Chair for review and distribution to the Executive/Steering Committee for approval.

The same process is required for oral presentations that include new information about the specific aims of the study. This process does not apply to presentations of information previously published.

Manuscripts from Ancillary Studies must be sent to the Executive/Steering Committee for review before submission.

The Study Chair 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 Chair's Office to obtain these signatures.

10.5.4 Acknowledgements

Each publication must acknowledge National Eye Institute support as follows:

“This study was supported by grants from the National Eye Institute, National Institutes of Health, Bethesda, MD”, specific “EYnnnnn” grant numbers provided by the Chairman's office or Coordinating Center.

10.5.5 Publications Concerning Methodology

The Executive/Steering Committee encourages the investigators at the Coordinating Center, Visual Field Reading Center, OCTRC and ODRC to publish methods employed at those centers to carry out their OHTS functions. For example, publications from the Coordinating Center may deal with methods used for data management, statistical analysis, quality assurance, or other procedures for which that center has primary responsibility.

Papers concerning methodology developed at the central units may be published in conventional authorship format. However, OHTS centers and investigators and the National Eye Institute must be recognized. Review and approval by the Executive/Steering Committee are required before manuscripts concerning methodology are submitted for publication. The authors are responsible for distributing copies of methodological publications to the Executive/Steering Committee and other OHTS Investigators.

10.6 Protocol Changes

All potential protocol changes will be reviewed by the Executive/Steering Committee. If approved, a numbered memorandum will be sent from the Study Chair to all Clinical Center Investigators and Coordinators. The new information will be incorporated into the Manual of Procedures and the new pages of the MOP will be sent to all Clinical Centers. The coordinators will replace the old MOP pages with the new pages and the online version of the MOP will be updated as well. In some cases, approval from the NEI may be required for protocol changes.

10.7 Publicity

All publicity and press releases on behalf of the OHTS are to have prior approval of the Executive/Steering Committee and the NEI. OHTS Investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chair or to the Information Offices of the NEI. It is recognized that when information is sought from an individual investigator by the local media in his or her community, it is sometimes necessary or desirable for the investigator to handle the request himself/herself. In such an event, the

investigator who gives information should speak as an individual and not as the official representative of OHTS. This fact should be made clear to the media. The information presented should be accurate and reflect the general policy and views of the group. Major findings, press releases and talking points will be prepared by the Study Chair's office after consultation with the Executive/Steering Committee and the NEI, and will be distributed to all OHTS Clinical Center Investigators.

10.8 Ancillary Studies

Ancillary studies may greatly enhance the value of OHTS 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 Executive/Steering Committee. This is necessary before the Ancillary Study begins, whether or not it involves the need for supplementary funds.

10.8.1 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 OHTS participants or
- Additional work to be done by or information to be obtained from the Coordinating Center, Visual Field Reading Center, Optical Coherence Tomography Reading Center or Optic Disc Reading Center.

10.8.2 Reason for Requirement of Approval

Everyone concerned with OHTS is entitled to assurance that no ancillary study will

- complicate the interpretation of OHTS results
- Adversely affect patient cooperation, recruitment or retention
- jeopardize the public image of OHTS
- create a serious diversion of study resources locally, at the Coordinating Center, or at any other of the central units serving the OHTS research group.

10.8.3 Preparation of a Request for Approval for Ancillary Study

The request for approval of an ancillary study should be in narrative form following the standard PHS-398 outline. 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 OHTS participants, such as clinical tests, laboratory tests, psychological testing, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on a patient outside of the

clinic should be described. Detailed discussion must be provided regarding the additional patient burden imposed by the ancillary study (informed consent procedure, extra time, extra visits, etc.). Information should be given concerning the extent to which the ancillary study will require blood or other specimens. If specimens are to be obtained from the patients, mention should be made of all procedures to be carried out on these specimens. If access to OHTS study data is required, the investigator must specify what data are needed, on whom it is needed, and the timetable for access to such data. Access to study data requires approval by the Executive/Steering Committee.

10.8.4 Procedures for Obtaining Ancillary Study Approval

The investigator proposing an ancillary study should send a written request to the Study Chair of OHTS. The Study Chair is responsible for distributing copies to all members of the Executive/Steering Committee. Within a reasonable time, the Study Chair will summarize any questions and/or objections raised by members of the Executive/Steering Committee and will send this summary to the applicant to permit amplification, clarification, and/or withdrawal of the request. The members of the Executive/Steering Committee will review the request again and the Study Chair will then prepare a statement of the Executive/Steering Committee consensus, including any remaining reservations or objections. This statement is forwarded to the investigator who requested approval for the ancillary study. The Executive/Steering Committee is responsible for final approval of ancillary studies.

10.8.5 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 Executive/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 Study Chair and the Coordinating Center. The investigator may not accept the grant or activate the ancillary study until approval has been received from the OHTS Executive/Steering Committee.

10.8.6 Progress Reports of Ancillary Studies

The Principal Investigator of each ancillary study is expected to report to the Study Chair and Coordinating Center at six-month intervals on the progress of the ancillary study. This report may be prepared as a letter. The Study Chair reports on the status of all ancillary studies to the Executive/Steering at each meeting.

10.8.7 Publication of Ancillary Study Results

All manuscripts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the OHTS Executive/Steering Committee before publication or

presentation. Such review pertains to impact on OHTS objectives and to scientific merit. Appropriate acknowledgement of OHTS resources used should be included.

10.9 Study Documents and Data

10.9.1 Study Documents

The Manual of Procedures and copies of the data collection forms used in OHTS will be placed in a suitable repository, such as that maintained by the National Technical Information Service, after approval by the Executive/Steering Committee for access by any interested party. 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 OHTS procedures or methods, as determined by the Executive/Steering Committee.

In general, the following documents may not be released to any group or individual outside the OHTS Research Group:

- Minutes of study meetings
- Performance monitoring reports for OHTS centers
- Executive/Steering Committee reports

10.9.2 Access to Study Data

Access to study data for individual patients is prohibited to unauthorized individuals, whether on file in a Clinical Center or in the CC, VFRC, OCTRC or ODRC. The identity of individual OHTS patients may not be revealed in any public report or presentation.

10.9.3 Access to Study Data

NIH released “Final NIH Statement on Sharing Research Data” (NOT-OD-03-032) on February 26, 2003 which modified “NIH Announces Draft Statement on Sharing Research Data” (NOT-OD-02-035). In accord with NIH guidelines, a summary, de-identified data set will be made available through the OHTS website at the time of publication and through direct inquiries to the Study Chair or Coordinating Center. The OHTS data sets will be largely self-documenting in that an item identifier is embedded within the label for each variable. In addition, key derived variables will also be contained in the data sets.

The rights and privacy of people who participated in the Study will be protected at all times by stripping the data from all identifiers that could lead to disclosing the identity of individual research participants. This commitment to privacy-protected data sharing will be incorporated in all levels of database design.

By the end of the funding period, de-identified SAS data sets and form images corresponding to all data collection forms used, as well as key derived variables, will be put on file with a data repository such as the National Technical Information Service (NTIS).

The full SAS databases (not de-identified) associated with OHTS will be kept on secured computer systems maintained by the Study Chair and by the Director of the Coordinating Center. Researchers may request limited access data sets and will need to enter into a data sharing agreement. Guidelines for the process of requesting such data sets and their content have been put forth recently by NHLBI (Geller, 2004). Access to the OHTS database will be similar to these guidelines. Researchers requesting limited access data sets will bear the cost of their preparation.

10.10 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. All Clinical Centers must be accessible to handicapped people and be able to provide translators for questionnaire data, especially for Spanish speaking participants.

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. For this reason, OHTS enrolled 25% African American participants, a higher proportion than their population distribution.

Appendix 10-A: OHTS Publication and Presentation Form: PP

Today's Date: _____

Type of Publication:

Circle: Presentation; Article; Book Chapter; Abstract; Technical report;

Unpublished analysis, Other: (describe) _____

Title:

Keywords: (Enter up to **15** keywords for this document) _____

Principal Author: _____

Collaborating Authors (Include ALL authors, regardless of OHTS affiliation):

Journal Name: (For a presentation, give name of conference. For a book chapter, give a book title. For unpublished analyses, leave blank).

Circle: 1 = Single Clinic 2 = Multi-Clinic

PROPOSED TIMETABLE

Mo/Yr

- | | | |
|----|---|-----------|
| 1) | Submission of abstract to OHTS Steering Committee | ____/____ |
| 2) | Paper/Analysis Plan signed off by P&P Committee | ____/____ |
| 3) | Draft of presentation/paper signed off by P&P Committee and
Steering Committee | ____/____ |
| 4) | Proposed submission/presentation date | ____/____ |

11. Visual Field Reading Center

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1.0 OBJECTIVE

In ocular hypertensive patients, changes in the visual field can take place that indicate possible glaucomatous damage. Often these changes affect some parts of the visual field while other parts remain unaffected. To analyze visual field conversion and/or progression, automated static perimetry will be performed on Ocular Hypertension Treatment Study (OHTS) participants using the 30-2 SITA Standard test pattern on the Humphrey Visual Field Analyzer (HFA).

These guidelines were developed to standardize techniques for administering the 30-2 SITA Standard test for OHTS. This Manual of Procedures is not intended to replace your Humphrey Field Analyzer manual.

2.0 PARTICIPANT TESTING SCHEDULE

Visual field testing will consist of Humphrey tests of the central 30° field of both eyes using the 30-2 SITA Standard visual field test. **All participants need to be tested and all results should be sent to the Visual Field Reading Center.** Clinical center technicians should attempt to test participants even if they might seem to be unable to perform a reliable visual field, e.g. cognitive impairment. If the Clinical Center Clinician determines that retesting would not improve quality, the Clinician should describe why this is the case in the notes section of the case report form.

2.1 Progression

One visual field (VF) test per eye in OHTS Phase 3 is required for participants who were Ocular Hypertensive at their last visit in OHTS 1 or 2. Some of these participants may have developed a visual field abnormality (i.e., Glaucoma Hemifield Test (GHT) is Outside Normal Limits or Pattern Standard Deviation (PSD) is below the lower 5% probability level), since their last OHTS Phase 1 or 2 visit.

Three Visual Fields in OHTS Phase 3 are required for participants who developed VF POAG in OHTS Phase 1 or 2. Repeat Visual Fields should be completed within one day to 3 months. A second VF can be done on the same day after giving the patient a one hour break. The VFRC will use trend analysis for assessment of visual field progression. Clinical Centers should retrieve all interim VF tests since the last OHTS visit for participants who developed VF POAG in OHTS Phase 1 or 2. This information will help identify the rate of VF progression.

Table 1.0: Testing Schedule

Visual Fields per eye	WHO	NOTE
One (1) Visual Field	Participants who were Ocular Hypertensive at their last visit in OHTS 1 or 2	Some participants may have developed a VF abnormality since their last OHTS visit
Three (3) Visual Fields	Confirmation of New VF Abnormality in the same location and the same index/indices as determined by the VFRC	*Repeat VF Should be done within one day to three months
Three (3) Visual Fields	Participants who developed VF POAG in OHTS Phase 1 or 2	*Repeat VF should be done within one day to three months

2.2 New POAG

Confirmation of a new VF abnormality requires 3 consecutive VF tests with the same abnormality in the same location and the same index/indices as determined by the VFRC. Repeat Visual Fields should be completed within one day to 3 months. If the abnormality is obvious, the Clinical Center is permitted to perform a second VF on the same day after giving the patient an hour break. If the VFRC determines that the 3 consecutive VF tests meet the OHTS definition of a “confirmed” VF abnormality, the endpoint review process is initiated to determine if the VF abnormality is due to POAG. Clinical Centers should retrieve interim VF tests since the last OHTS visit for any participants who newly convert to VF POAG. This information will help determine when conversion to VF POAG occurred. These strict diagnostic criteria for VF POAG conversion greatly increase the accuracy of the diagnosis.

3.0 TECHNOLOGY REQUIREMENTS

- ✓ 30-2 SITA Standard test is the preferred test strategy for OHTS
- ✓ Scanner and Adobe Acrobat to convert the test printouts from the HFA to a PDF
- ✓ 3.5” diskette drive to transfer the data from the HFA to your PC or flash drive for the HFA Iii
- ✓ Java version 7.0 (sometimes referred to as version 1.7). or higher to upload data to the secure VFRC website. See [Submission Upload Protocol Page 3](#) for additional information.

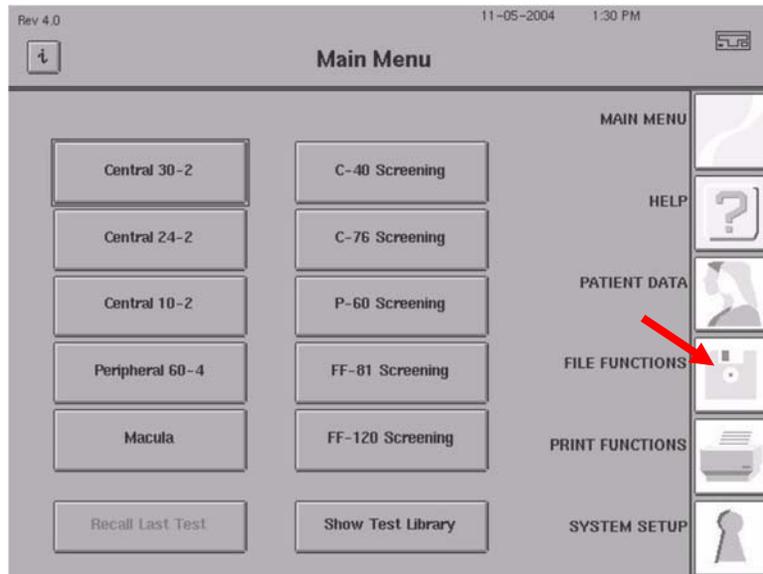
4.0 HUMPHREY FIELD ANALYZER PREPARATION

4.1. Formatting Diskettes

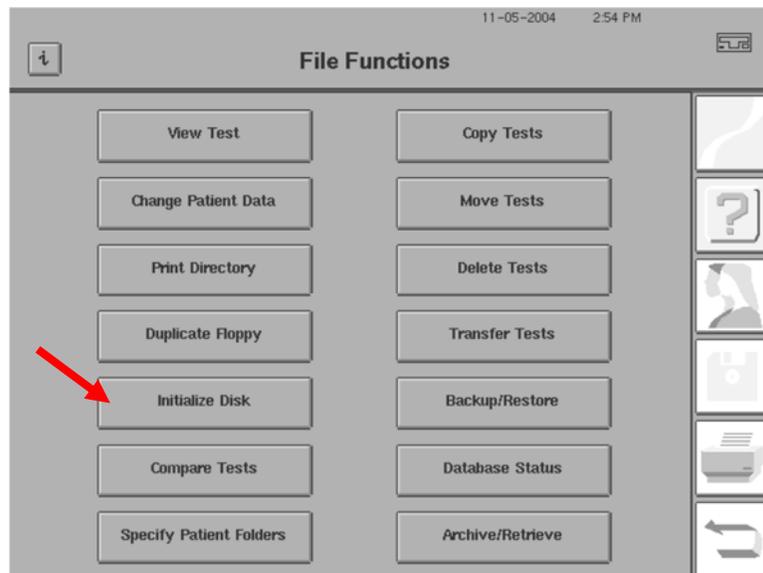
11-6 VFRC

Before you can save test data to a new diskette, you must first format the diskette. You can format multiple diskettes in one setting so that you are not formatting diskettes while the participant is waiting.

1. From the MAIN MENU screen select the “FILE FUNCTIONS”



2. Select “Initialize Disk”
Older HFA models will have “Initialize Floppy” instead of “Initialize Disk”



3. Insert a diskette into the drive.
4. Select “OK” to proceed with the initialization. The screen will display a box with “Formatting in Progress.” Formatting will take approximately 2 minutes. Once done, your diskette will be ready for use.

If your HFA machine can generate the PDF files, it is most likely storing the PDF files somewhere on your Clinical Center’s computer network. Please consult with your IT person to find the location of those PDF files.

If your HFA does not generate the PDF files, you will need to scan them and store them on either a separate diskette or USB/Flash Drive, (**not the one used in the HFA machine**) or on your local machine.

If your HFA has a USB port instead of a diskette drive, you will NOT need to format the USB/flash drive and will skip this step.

5.0 VISUAL FIELD TEST PREPARATION

5.1. General Test Guidelines

Reduce the lighting in the room to a moderate level or the HFA will display a message that it cannot adapt to the background luminance. Perform the visual field tests on each eye of the participant using 30-2 SITA Standard. To maintain consistency throughout the study, test the RIGHT eye first. Use the test parameters below for the 30-2 SITA Standard visual field test.

- ✓ Threshold Strategy..... SITA STANDARD
- ✓ Test Speed.....NORMAL
- ✓ Fixation Target CENTRAL
- ✓ Fixation Monitoring..... GAZE / BLIND SPOT
- ✓ Blue YellowOFF
- ✓ Foveal threshold ON
- ✓ Stimulus Size III
- ✓ Stimulus Color..... WHITE
- ✓ GAZE TRACKING..... ON
- ✓ FASTPAC.....OFF

5.2. Determining The Appropriate Refraction

Depending on the age of the participant, the refraction used at the bowl may be quite different from the participant's best-corrected distance prescription.

5.2.1. Automatic Lens Power Determination by Humphrey Field Analyzer

The HFA can automatically determine the appropriate trial lens to use. Please follow steps 9 - 16 in Section 5.4: Entering Participant Data to automatically determine the lens power.

5.2.2. Manual Lens Power Determination

Depending on the age of the participant, the refraction used at the perimeter bowl may be quite different from the participant's best-corrected distance prescription. Take the current distance prescription and add the amount of sphere indicated by Table 2.0: Goldmann's Table. The only exception to this is if the eye was dilated with neo-synephrine or a cycloplegic. In that case, use the full near correction. If your trial lens set does not contain the exact lens, round up to the nearest 0.25 Diopter (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, then algebraically 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 the participant needs for the test is greater than ± 6.00 D, have the participant wear soft contact lenses, if possible for testing. Participant can complete test when wearing contacts if they correct vision to 20/20 or better. However, you must still enter the best-corrected distance prescription 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 participant data (see [Section 5.4: Entering Participant Data](#)).

Table 2.0 Goldmann's Table

Age	Add
40 – 44	+1.50 D
45 – 49	+2.00 D
50 – 54	+2.50 D
55 and Older or dilated	+3.25 D

Examples:

1. Best-Corrected distance prescription (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

2. Best-Corrected distance prescription (53-year old): **OD +1.00 DS + 0.25 + 065**
OS – Plano +1.50 x 090

Use:

OD +3.50 D

OS +2.50 +1.50 x 090

5.3. Performing The Over-Refracton Procedure

Perform the following over-refraction procedure at the perimeter bowl for each visual field test on an eye with best corrected visual acuity of 20/40 or better; however, do not perform it on eyes with worse visual acuity. Place the trial lens(es) in the lens holder and ask the participant to look at the fixation light in the center of the bowl and the edge of the center hole. Present the participant a +0.50 D lens and then a -0.50 D lens over the calculated spherical correction. Ask the participant to report which is better: (1) a +0.50 D over-correction, (2) -0.05 D over-correction or (3) no over-correction. From the participant's response, determine the proper lens correction.

5.4. Entering Participant Data

Table 3.0: Participant Data

Humphrey Screen	Information Entered
Patient ID	Site ID (2 digits) Participant ID: 5 numeric digits: ^{1,2} Example: A101234
Birth Date	MM-DD-YYYY
Pupil Diameter	OD: e.g., 4 mm OS: e.g., 5 mm
Patient Name	Site ID (2 digits) Participant ID: 5 numeric digits: ^{1,2} Example: A101234
Right / Left Eye Comment	Enter the participant's ⁷ Best-Corrected Distance Prescription Example: -1.50 +1.25 X 075
Visual Acuity	OD: e.g., 20/20 ⁸ OS: e.g., 20/20
Prescription Used (trial lens)	OD: (+ or -) .__ DS (+ or -) .__ DC X __ DEG ⁹ OS: (+ or -) .__ DS (+ or -) .__ DC X __ DEG

¹Be sure to distinguish between zeros and the letter “O” appropriately. Patient ID is 5 numbers assigned to study participants during OHTS phase 1 and 2 (OHTS Phase 3 does not require patient initials).

² Certification: Use **Practice1** for the first technician and **Practice2** for the second technician as the ID when performing certification visual fields. If you need to recertify, use **Practice1A** and **Practice2A** for the ID.

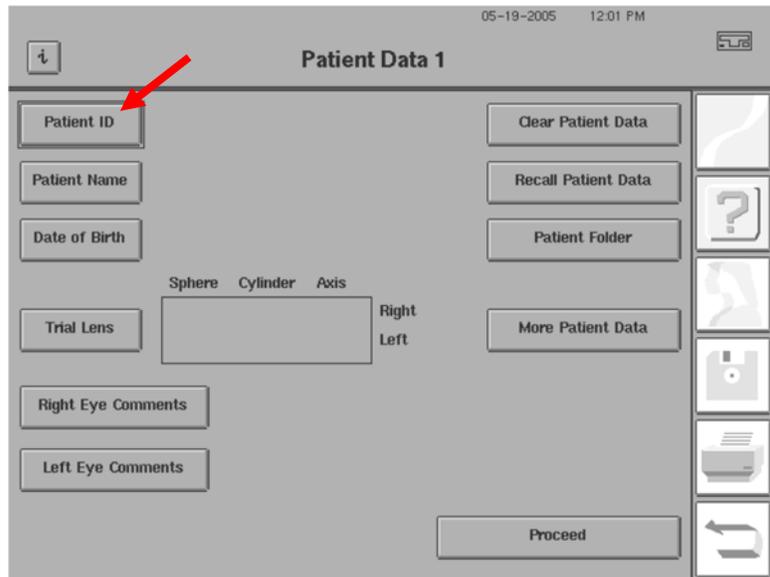
³Your “Site ID” is a 2 character alphanumeric code (i.e. A1 or W1,) that was assigned by the OHTS Coordinating Center. The “Participant ID” consists of 5 numeric digits (i.e. 01234)

⁷Best Corrected distance Rx consists of 14 characters. Enter **3 digits** each for the sphere, cylinder, and axis with decimals for the first two values along with polarity. Enter the letter “X” before the axis. Enter 0.00 for plano. This is the participant’s distance vision correction. **After saving the results of the test on the right eye, and before proceeding with the test on the left eye, you will need to edit the distance Rx in the Participant’s Data (unless it is the same as for the right eye).** *Example: -1.50 +5 X 075*

⁸Click on the “More Patient Data” button to enter the Visual Acuity and pupil diameter.

⁹Enter 3 digits for each, 0.00 for plano. “Rx Used” is the correction that is used for performing visual field testing. Note: **If the HFA calculated the lens power you do not need to enter anything here as the HFA will do it automatically.** NOTE: Data entry instructions for newer HFA 750i are listed below screen shots.

1. Select:
 “Patient ID”



2. Enter:
 Site ID³
 OHTS
 Participant
 ID³
 **(example:
 A101234)**
 Table 3.0:
 Participant
 Data



3. Select: **“Patient Name”**
4. Enter Site ID³
OHTS Participant ID³
(**example: A101234**) Table
3.0: Participant Data
information as described in
[Table 3.0:](#)
5. Select: **“Enter”**

The screenshot shows the 'Patient Data 1' form with a dialog box titled 'Enter Patient Name'. The input field contains 'A101234'. A virtual keyboard is displayed below the input field, and a red arrow points to the 'Enter' key.

6. Select: **“Date of Birth”**
7. Select: **“Enter”**

The screenshot shows the 'Patient Data 1' form with a dialog box titled 'Enter Date of Birth'. The input field contains '09-22-1943'. A virtual keyboard is displayed below the input field, and a red arrow points to the 'Enter' key.

8. Select: **“Trial Lens”**

The screenshot shows a software interface titled "Patient Data 1" with a timestamp of 05-19-2005 12:03 PM. The form contains several input fields: Patient ID (1234), Patient Name (Zeiss, Cor1), and Date of Birth (09-22-1943). Below these are fields for Sphere, Cylinder, and Axis, with a "Trial Lens" button to their left. A red arrow points to this button. To the right of the Sphere/Cylinder/Axis fields are "Right" and "Left" labels. Below these are "Right Eye Comments" and "Left Eye Comments" buttons. A "Small pupil" label is also present. On the right side of the form, there are buttons for "Clear Patient Data", "Recall Patient Data", "Patient Folder", "More Patient Data", and "Proceed". A vertical toolbar on the far right contains icons for help, search, and other functions.

9. Select:
“Manual Trial Lens Input”

This screenshot shows the same "Patient Data 1" form as above, but with a timestamp of 12:06 PM. A dialog box titled "Select One" is overlaid on the form. The dialog box contains three buttons: "Calculate Trial Lens", "Manual Trial Lens Input", and "Cancel". A red arrow points to the "Manual Trial Lens Input" button. The background form is partially obscured by the dialog box.

10. Select : “Pupil Diameter”

The screenshot shows the 'Patient Data 2' interface for a patient named 'Zeiss, Carl' with a date of birth of '09-22-1943'. The interface is split into 'Right Eye' and 'Left Eye' sections. Each section contains buttons for 'Diagnostic Code', 'Procedure Code', 'Pupil Diameter', 'Visual Acuity', 'I O P', 'Horizontal C/D', and 'Vertical C/D'. A red arrow points to the 'Pupil Diameter' button in the Right Eye section. At the bottom, there are 'Return To Patient Data 1' and 'Proceed' buttons. The top right corner shows the date '08-03-1998' and time '2:56 PM'.

11. Enter Pupil Size

12. Select “Enter”

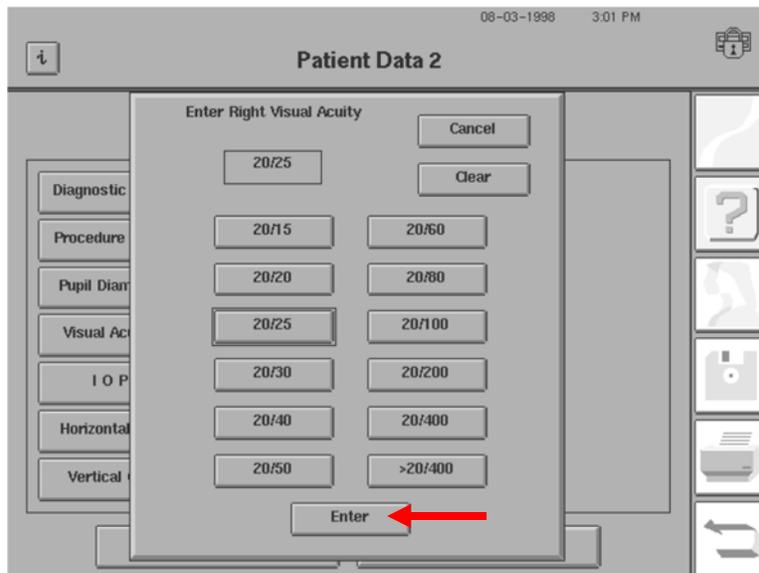
Note: If you are using the Auto pupil feature (750i) you do not need to enter the pupil diameter. For all other models you will need to enter this information.

The screenshot shows the 'Patient Data 2' interface with a dialog box titled 'Enter Right Pupil Size' open. The dialog box has a text input field containing '4.0', a 'Cancel' button, and a 'Clear' button. Below the input field is a numeric keypad with buttons for digits 1-9, a decimal point, and an 'Enter' button. A red arrow points to the 'Enter' button. The background interface is partially visible, showing the 'Right Eye' section with buttons for 'Diagnostic Code', 'Procedure Code', 'Pupil Diameter', 'Visual Acuity', 'I O P', 'Horizontal C/D', and 'Vertical C/D'. The top right corner shows the date '11-06-97' and time '12:01 PM'.

13. Patient Data 2 Screen
Select: “Visual Acuity”

14. Enter the Visual Acuity

15. Select: “Enter”



HFA model 750i: USB/Flash Drive is required to export data

Please contact the VFRC to request a flash drive.

Entering Patient Data- HFA 750i

- Step 1** **Select: 30-2 SITA Standard**
Set parameters according to OHTS Phase 3 Protocol [Section 5.0](#) Parameter Guidelines
- Step 2** Select Right or Left Eye (always test right eye first)
Click: Patient ID
- Step 3** **Family Name:** OHTS ID (example 01234)
DOB: Participant’s Date of Birth
Right Eye Comments: Best Corrected DISTANCE Prescription
Left Eye Comments: Best Corrected DISTANCE Prescription
Click: Patient Data 2
- Step 4** **Enter:** Visual Acuity
Enter: Pupil Diameter
- Start** **You are ready to start Test**

6.0 TEST GUIDELINES & ADMINISTRATION

6.1 Preparing The Participant

Measure the participant's pupils to the nearest 0.5 mm and enter into the HFA. If they are less than 3 mm in diameter, dilate them with 2.5% phenylephrine drops, unless contraindicated. If this is ineffective, dilate with a cycloplegic agent such as tropicamide and wait a full 20 minutes before beginning the test. In the case of cycloplegic, the full near correction should be used (see Section 5.2: Determining the Appropriate Refraction). In addition, enter "P" for phenylephrine, "C" for cycloplegic or "N" for none into the name field after the Tech ID in the participant data screen (see Section 5.4: Entering Participant Data). If a participant's pupil is < 3 mm with the dilating agent, attempt the visual field test and notify the VFRC that the pupil size could not be dilated beyond 3 mm diameter.

Occlude the eye not being examined. For the eye being tested, if the brow is heavy or the upper lid is drooping, tape it accordingly. The entire pupil should be visible when the participant looks at the central fixation target. When in doubt, tape the upper lid. The tape should allow the participant to blink. Allow the participant to adapt to the bowl luminance for three minutes. During this time, familiarize the participant with the test procedure.

Adjust the chin rest and table height to align the pupil in the center of the eye monitor. Make sure the participant's forehead is against the head rest and that he or she is comfortable. Use the knob at the side of the trial lens holder to move the trial lens(es) close to the participant's eye. However, make sure the participant'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 participant's eye as possible (see Figure 1) and by aligning the pupil in the center of the lens (see Figure 2).

Figure 1: Proper Trial Lens Position

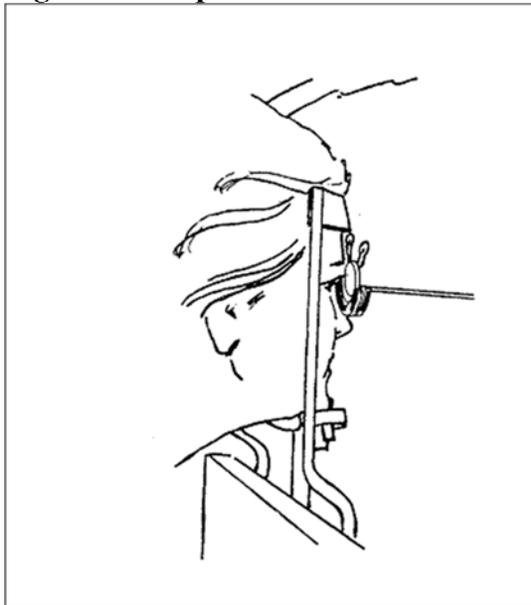
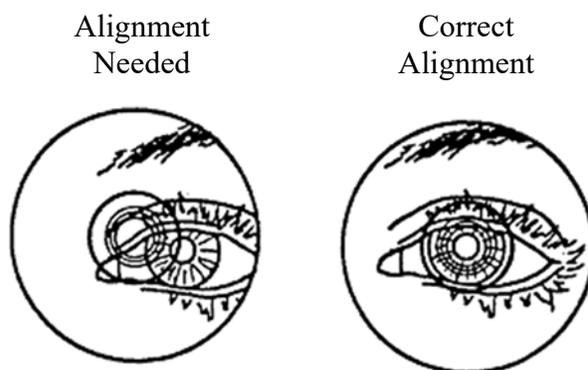


Figure 2: Participant Alignment



Instruct the participant how to perform the Foveal Threshold test, Initial Gaze Monitor set up and Threshold test using the information provided below.

HUMPHREY PARTICIPANT INSTRUCTIONS --- KEEP A COPY AT YOUR PERIMETER!!

6.2. Foveal Threshold Test

All normal participants should have foveal thresholds ≥ 35 . If the foveal threshold is ≤ 35 retest the participant. Some participants may not be able to get a higher foveal threshold. In most situations, only attempt this 2 – 3 times. If you are unable to get a foveal threshold of ≥ 35 , give the participant the instructions again emphasizing that they should press the button each time he/she sees the light and that sometimes the light may be very hard to see.

Give the participant the following instructions:

“Look straight ahead at the four yellow lights. In the center of the lights there will be a flash of light. Sometimes the light will be very dim, very hard to see. Other times the light will be brighter. Each time you see a flash of light, press the button. The test will last about 20 – 30 seconds.”

6.3. Initial Gaze Monitor Set Up

It is important to position the participant as accurately as possible as their position will affect the tracking. Position the crosshairs in the center to slightly below center of the participant’s pupil.

Gaze tracking is another method of monitoring fixation and eye alignment. Follow the instructions in the HFA II screen and the machine’s instruction manual to initialize gaze tracking. If it has not been possible to initialize gaze tracking after two attempts, realign the participant’s eye after tilting the trial lens slightly or lowering it while initializing the gaze tracking (in some instances, a reflection from the lens may cause problems with gaze tracking), and try a third time.

Gaze tracking provides a time line of blinks (downward deflections on the chart) and misalignments (eye and head position, indicated by upward deflections) which is useful for determining if a participant is moving, becoming sleepy, losing attention, drifting eye and head position and many other features that indicate the quality of the test procedure.

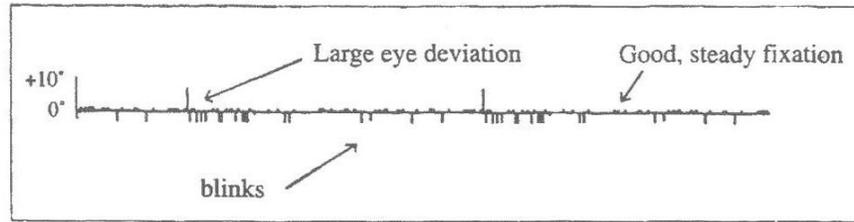


Figure 5.3: Example of a Gaze Graph: Good Fixation with a Large Number of Blinks

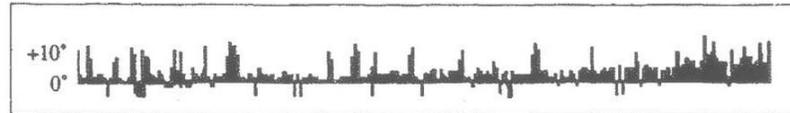
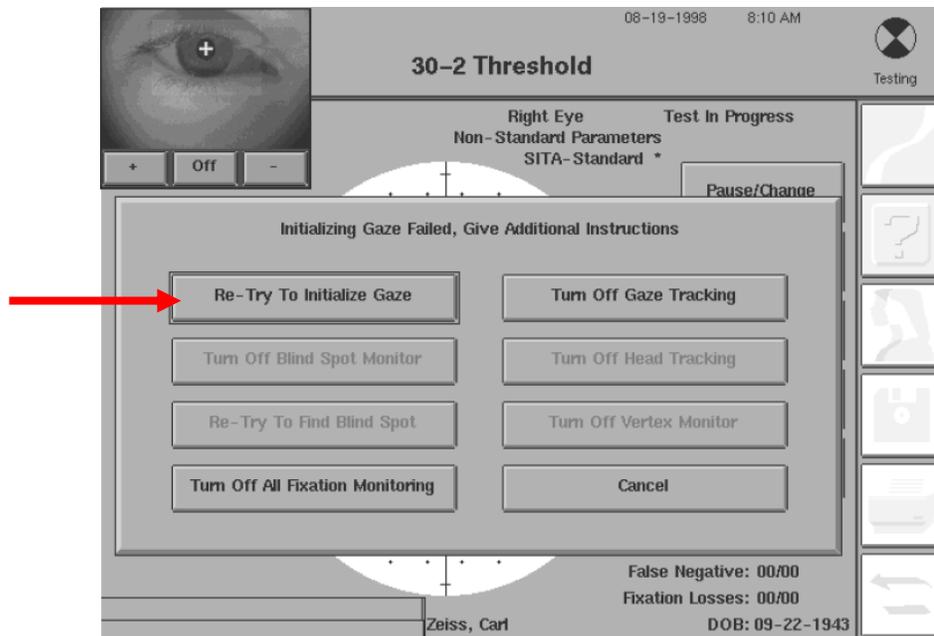


Figure 5.4: Example of a Gaze Graph Indicating Poor Fixation

If the lens is >5 D you may need to fold down the trial lens holder until the gaze monitor is initialized. Make sure to move back the lens holder to the upright position before starting the test. If the “gaze tracking initialization” is unsuccessful, choose “re-try to initialize.”



If you are unable to initialize the gaze monitor after 2 – 3 attempts, turn off the gaze monitor and observe fixation closely on your display screen. Turning off the gaze tracking will not turn off the blind spot monitor. **If you are unable to initiate gaze tracking after 2-3 attempts, be sure to record this in the comments section of the test.**

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 the reliability and unreliability can be accurately judged. If you have to turn off the gaze monitor, make sure to note your observations for the VFRC in the “Right Eye Comments” or “Left Eye Comments” on the “Patient Data 1” screen of the HFA.

Give the participant the following instructions:

“Do you see the single yellow light? Look straight ahead at the single yellow light. You will not need to do anything except stare at that single yellow light for about 20 seconds. You may blink normally.”

6.4. Threshold Test Instructions

Give the participant the following instructions:

“Always look straight ahead at the small steady central light. Other lights will flash one at a time at other positions around the center light. Some lights may be brighter than others light. Press the button when 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.”

6.5. Proceeding With The Test

Follow the instructions shown on the HFA screen under *Operator Assistance*, EXCEPT the reference to hold the button down to rest. It is permissible for the technician to occasionally encourage the participant, if the participant seems to be fatigued or is losing concentration, and to allow the participant 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 participant's criterion for responses during the course of the test but to remain alert to problems that develop.

If the blind spot is not detected during the blind spot location phase of the test after two attempts, restart the test and turn off the blind spot check. Please make a note of this in the Right / Left Eye Comments section for the test. 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. This will occur during the first 60 seconds of the test procedure. If excessive fixation losses are again detected after the second attempt to locate the blind spot, allow the participant to continue through to the end of the testing program. Please make a note of this in the Right / Left Eye Comments section. **DO NOT** allow the participant to stop the test by holding down the response button.

The participant should be given a minimum rest of 5 minutes and a maximum of 15 minutes between the testing of each eye on the HFA. 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 Rx in the patient data before the start of the second test.**

6.6. Saving & Printing the HFA Results

- If you have upgraded to the HFA 750i, you will treat the USB/Flash Drive as if it was the Diskette Drive.
- It is important that you do not put any additional information on the HFA data diskette or flash drive. Doing so will corrupt the diskette or flash drive. The HFA diskette formatting is designed to only accept visual field test results (data).
- **Flash Drive Users:** You will have 2 flash drives for the HFA; **One for data (XML file) and one for Visual Field (PDF) print-outs.** Keep copies of each visual field on diskettes or flash drive at your Clinical Center. To minimize diskette storage problems, you may consolidate the Humphrey diskettes/flash drive files on a "Master" diskettes/flash drive. You will need to place the HFA diskette/flash drive into your PC when it is time to transfer the visual field data to the VFRC website at www.perimetry.com. Details for uploading to our website are provided in the **Protocol for Submission Uploads** (*Protocol for Submission Uploads is located at the end of VFRC Chapter 11 Manual of Procedures*)
- Print out the Single Field Analysis test results at the completion of each test.
- Scan the Single Field Analysis printout and save it as a PDF file so that you can send it electronically.
- Flash Drive Users: Scan the Single Field Analysis printout and save it as a PDF file on to the flash drive OR mail the Visual Field printouts to the Visual Field Reading Center (VFRC) along with the flash drive, containing the Visual Field DATA. (**Remember:** One flash drive is for HFA DATA and one flash drive is for HFA Visual field PDF printouts).

- When saving the PDF files, it is best to save it using the Site ID and Participant ID, date of test, time of test (military format), type of test, and test eye.
For example: A101234 121008 1420 HFA 30-2 OD.pdf
- Please save each individual visual field as a separate PDF. You should have one PDF for the right eye and one PDF for the left eye.
- It is best to use the same naming convention throughout the study so that you can quickly identify which PDF files should be uploaded.
- Keep one printed copy in the participant's file.

6.7 How Many Visual Fields Should be Performed Initially?

For patients who had glaucomatous visual field loss (POAG from a reproducible visual field abnormality consistent with glaucoma) or who now appear to have potentially developed glaucomatous visual field loss, three visual fields should be submitted to the VFRC. It is possible to test more than one visual field per day, but there should be at least ½ hour between visual field determinations for the same eye. Depending on the stamina and endurance of the patients, it is possible to perform 3 visual fields in the same day (provided they are reliable and are not prone to fatigue effects). If it is too much for the patient to perform three visual fields on the same eye in one day, they should be rescheduled for a follow up visit for the remaining visual field(s). If the patient has normal visual fields up to this point (whether or not they were classified as POAG based on optic disc assessment) they are only required to have one visual field test at this time.

6.8 Repeating HFA Visual Field Test for Unreliability, Conversion or Progression

The technician should attempt to test all participants, even if the participant may appear to be unable to perform or complete a reliable visual field due to, cognitive impairment or lens opacification. Transmit the participant's visual field (unreliable or incomplete) to the VFRC with an explanation recorded on the visual field form

6.9 Determination of Visual Field Conversion

As in OHTS Phase 1 and 2, the VFRC for the OHTS has used the criterion of a Glaucoma Hemifield Test (GHT) result that was Outside Normal Limits on three successive occasions, or Pattern Standard Deviation (PSD) that was below the lower 5% probability level on three successive occasions. This procedure was found to be effective for detecting persistent localized glaucomatous visual field loss, and had high specificity as well. If the graders determine that the visual field meets criteria for conversion, the VFRC will notify the Clinical Center and OHTS Coordinating Center that the eye should be retested within 3 months of notification to confirm the abnormality. If this second consecutive follow-up field is abnormal in the same location and on the same indices, the eye must be retested a third time within one day and 3 months of the second VF. If the 3rd retest and the two previous visual fields all show an abnormality in the same location and on the same indices and the VFRC indicates that the visual field loss is not due to artifact, the VFRC will send the Coordinating Center the baseline visual fields and the OHTS Phase 3 visual fields for both eyes along with a brief narrative description for Endpoint Committee review. The Endpoint Committee will decide if the confirmed conversion is due to POAG or not. The Coordinating Center will notify the Clinical Center and the VFRC of the Endpoint Committee decision.

6.10 Determination of Visual Field Progression

Participants who developed visual field POAG previously in OHTS Phase 1 or 2 need to complete 3 visual fields in the affected eye(s) to determine possible visual field progression.

Assessment of visual field progression is a topic that has been extensively evaluated by our laboratory as well as by many other investigators. To date, there is no consensus concerning an acceptable method of determining visual field progression and distinguishing pathologic changes from inter-test and intra-test variability. To date, every multicenter clinical trial in glaucoma and ocular hypertension that has used visual field assessment as an outcome measure has adopted a different method of assessing visual field progression. We performed an analysis of analyzing visual field progression and stability in glaucoma with the same visual field data set, but different evaluation procedures that have been used in multicenter clinical trials. Our findings indicated that there were more than two-fold differences in the ability to determine the time to detect visual field progression for the various progression assessment procedures, that there were tremendous differences in the relationship between sensitivity and specificity for these procedures, and that there was only agreement among the procedures approximately 50 to 60 percent of the time. Several other laboratories have also verified these findings. The most common methods of determining visual field progression are event analysis (change from baseline) and trend analysis (most commonly linear regression). Each of these procedures has its advantages and disadvantages. Event analysis is usually able to detect visual field progression earlier and with a fewer number of visual fields than trend analysis. However, it does not provide a good indication of the rate of progression, and visual field information obtained between the baseline visual field(s) and the current visual field(s) are not considered. Trend analysis provides an indication of the rate of progression, uses all of the available visual field information, but requires a larger number of visual fields to achieve better performance than event analysis. There are other methods that have been attempted such as exponential regression and Tobit analysis (which censors zero sensitivity evaluations), but these are most useful for following participants with advanced glaucomatous visual field loss, which is uncommon in the OHTS participant population. Support Vector Machines, Bayesian strategies, Decision Trees and Random Forests have also been utilized for visual field progression, but they are not techniques that are readily available for glaucoma specialists or general practitioners, so their real-world applicability would be limited. Finally, permutation analysis, a technique that has been available for more than 70 years and has recently been applied to optimize signal-to-noise procedures has recently been applied to visual field analysis. This procedure appears to be more effective in extracting the signal (progression) from noise (variability) in visual field assessment.

For OHTS Phase 3, we will utilize trend analysis because it provides the greatest amount of information and, facilitates translation of study results into clinical practice because of its wide use in clinical practice already. Because participants in the OHTS have performed a large number of visual field examinations in OHTS Phase 1 and 2, there will be an adequate sample of visual fields to satisfy the requirements for trend analysis (linear regression). This will provide a determination of progression at values below the lower 5% probability level, a rate of progression, the confidence limits and residuals for the linear regression, and a prediction of future visual field results. It has been reported that the rate of progression becomes steeper when a participant reaches greater amounts of

glaucomatous visual field loss, so we will utilize a bilinear regression procedure that will provide a rate of initial progression, an inflection point where the rate of progression begins to change, and the final rate of progression. This information will be then sent to the Endpoint Committee. Other methods of assessing visual field progression will also be evaluated in secondary analyses.

If the VFRC determines that visual field progression has occurred, visual fields for the affected eye(s) and the unaffected eye from baseline, the 3 repeat VF's at the time of conversion and 3 current VF's and a brief narrative description are sent to the Coordinating Center for Endpoint Committee review. The Endpoint Committee will determine if the progressive visual field loss is due to POAG. The Coordinating Center will notify the Clinical Center and the VFRC of the Endpoint Committee decision.

7.0 EXPORTING HFA DATA & VF PRINTOUTS TO A FLASH DRIVE

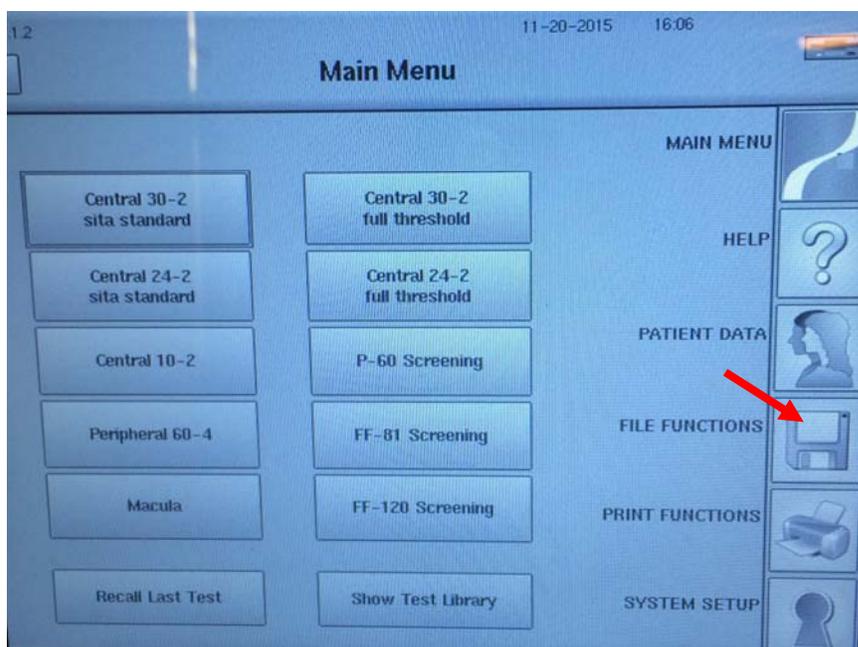
Saving HFA DATA and VISUAL FIELD IMAGES to FLASH DRIVE:

Please remember that you must use a flash drive reserved ONLY for HFA data. If there are any other items on the designated flash drive (even the corresponding PDF), the data may become corrupted and you will not be able to upload to www.perimetry.com.

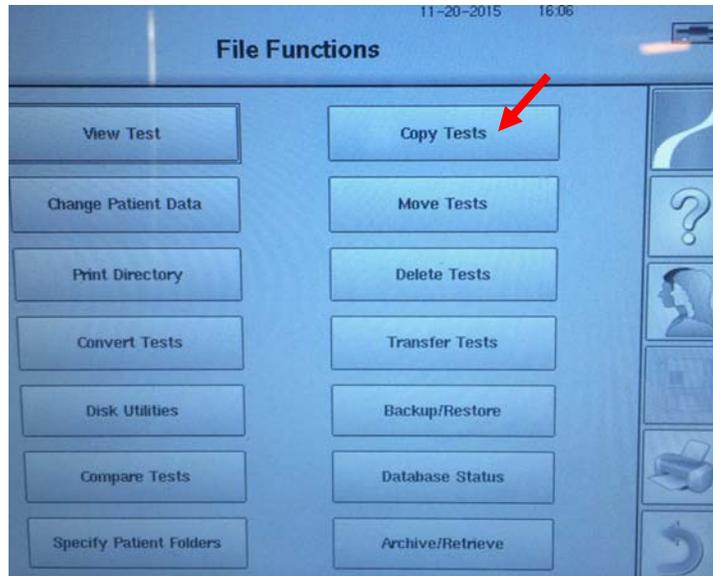
These steps illustrate the process of obtaining data from an HFA 750i. If your HFA machine does not provide these options and you are unfamiliar with the process for copying HFA data from your machine, please contact the VFRC at (319) 467-4539 or at vfrc@uiowa.edu to discuss the proper method of retrieving HFA data from your machine.

Step 1: Connect the flash drive to either USB port 1 or USB port 2. (Note: Flash Drive will appear under "Destination" after connecting to the HFA/USB port). If you're looking at the USB ports, USB port 1 will be on the left and USB port 2 will be on the right.

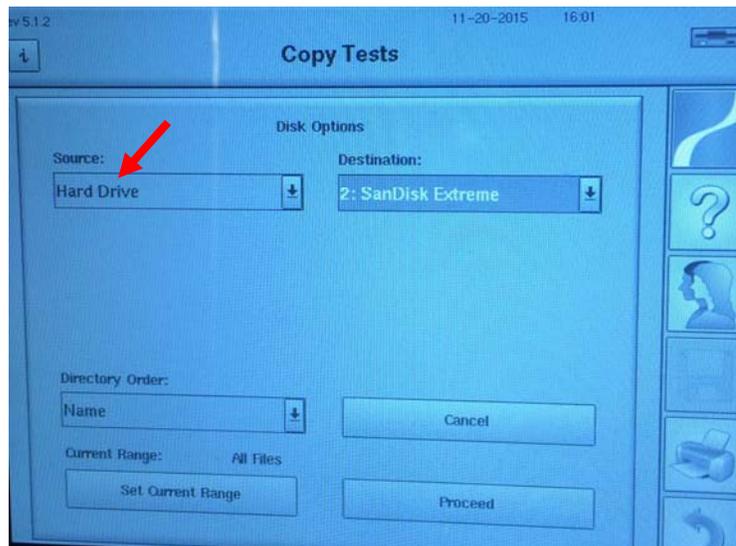
Select: **File Functions**



Select: **Copy Tests**



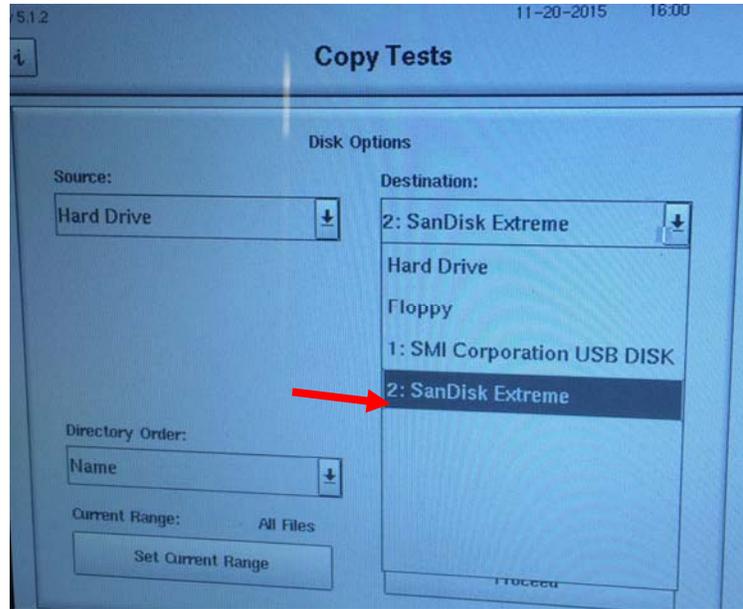
Step 2:
Source: **Hard Drive**



Destination: **HFA 750i**
designated flash “DATA”
drive.

(Example: “SanDisk
Extreme.”)

*Note: The name of the flash
drive will show up
under USB port 1 or
USB Port 2*



Troubleshooting

Can't find your flash drive in the Destination section?

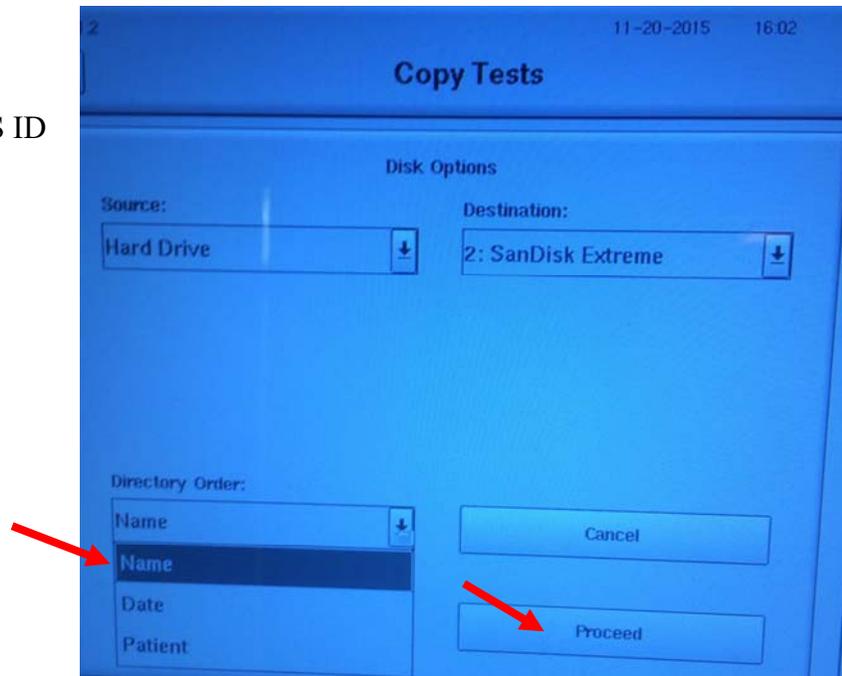
While looking at the File Functions screen, under "Destination" remove flash drive and then re-insert it.

The name of the flash drive will only appear when it's connected to the HFA/USB port.

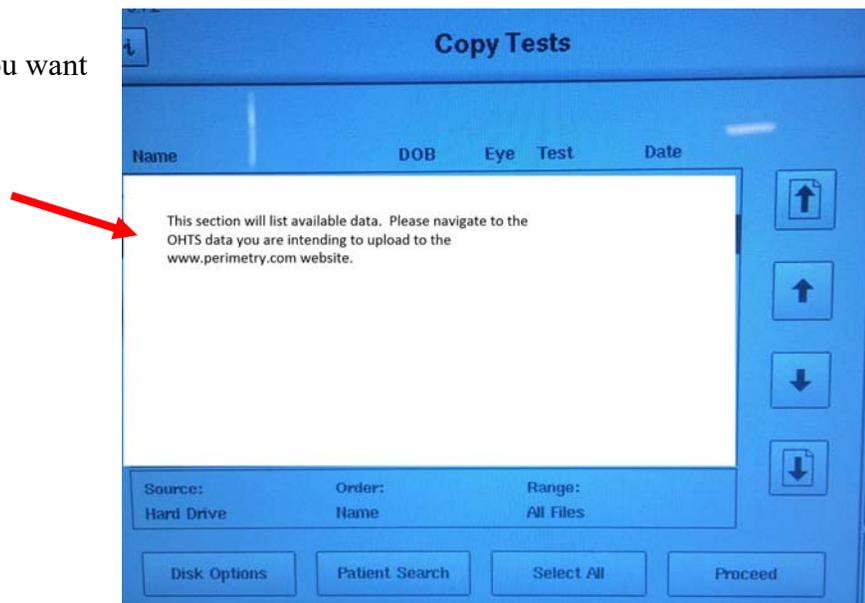
Step 3:

Directory Order: **Name**
(find the subjects OHTS ID number)

Select: **Proceed**



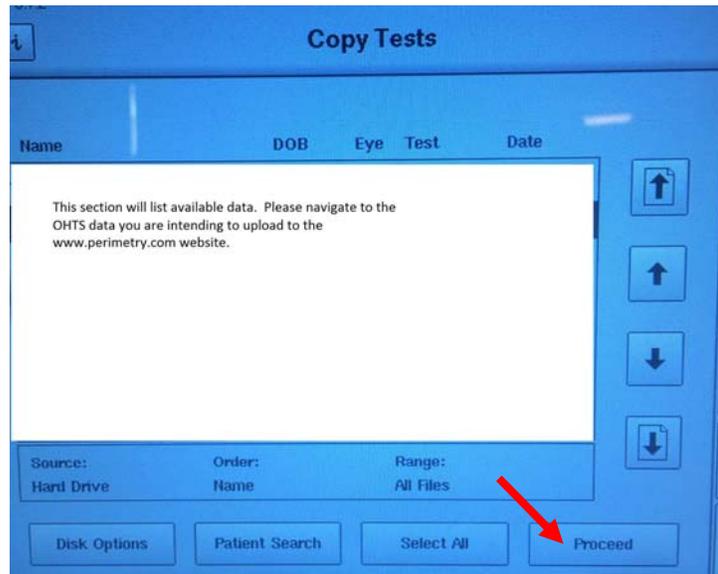
Click on the test to highlight the test you want



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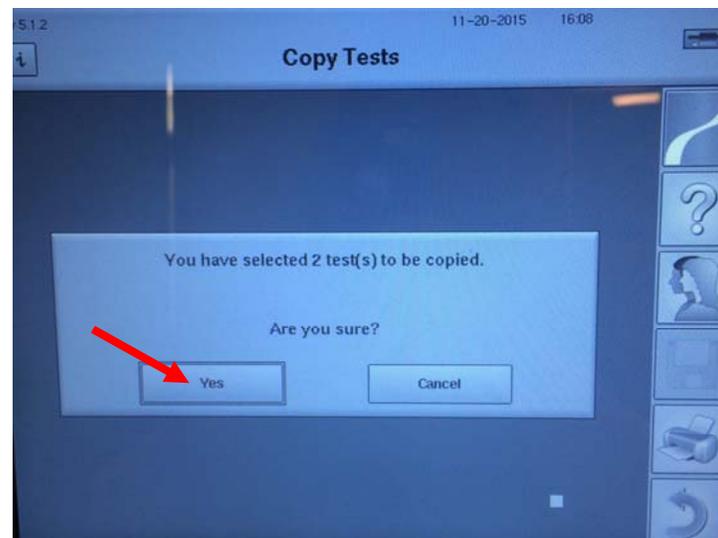
to copy.

Select: **Proceed**

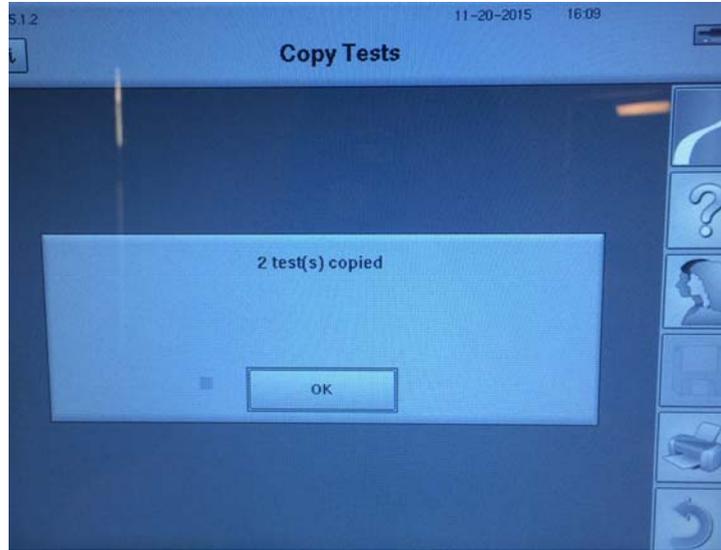


You will then be asked to confirm that you would like to copy the test(s).

Select: **Yes**



You will receive a message that data is now saved to the flash drive.



Step 4:

Print a copy of the Visual Field (both eyes)

Scan the Single Field Analysis printout and save it as a PDF file to your PC so that you can send it electronically along with the HFA Data to the VFRC website at www.perimetry.com.

Copying files from a flash drive to a PC:

Extend the flash drive and insert the metal part into the computer's USB Port.

1. Open **My Computer** and see which drives are shown. Most computers, for example, have a hard disk such as a C: drive and a few removable storage devices such as a floppy drive, a CD-ROM drive, and perhaps a zip drive.
2. Insert the flash drive into the USB port and watch to see where the USB flash drive appears. Most will appear as removable storage, but some will instead appear as hard drives. Note the name Windows is using to refer to the flash drive ("Removable Disk (G :)," for example).
3. **Double-click** on the flash drive to locate the file(s) or folder(s) you want to copy to this computer. Select the **files** or **folders** you want to copy by left-clicking on them. To select more than one, hold down the CTRL key while you click and select all of the files or folders you wish to copy.
4. **Right-click** on the files or folders you have selected and choose **Copy**.
5. Open **My Documents** or the location to which you want to transfer files from the flash drive.
6. Click on the **Edit** menu, and then select **Paste**.
7. When the copying is finished, **do not immediately remove the flash drive from the USB port**. Instead, left-click on the **Remove Hardware** icon located in the System Tray (bottom right corner of screen). A window containing a list of the USB devices will appear. Left-click on the **Safely Remove Mass Storage Device** line that matches your flash drive (for example, **Safely Remove Mass Storage Device - Drive (G :)**).
8. When you see the following message appear in the bottom right toolbar, it is, as it says, safe to remove the flash drive from the USB port; you may close the message or ignore it, as it will close itself automatically:



Saving Visual Field Printouts as a PDF File:

1. On your computer, find the document you want to convert to a PDF file.
2. Click the Microsoft Office Button  (bottom left corner of screen).
3. Point to the arrow next to “Save As”, and then click PDF.
4. In the “File Name” list, type or select a name for the file (see section 6.6)
5. In the “Save as Type” list, click PDF

Make sure to label all images and data (old and new) files according to the OHTS Protocol. When saving the PDF files, it is best to save it using the

- Site ID and Participant ID
- Date of Test
- Time of Test (Military Format)
- Type of Test and Test Eye
- Example: A1012341210081420HFA30-2OD.pdf

8.0 TRANSMISSION OF ALL VISUAL FIELDS TO THE VFRC

3 ways to submit Visual Field Data and Visual Field PDF's

- Preferred way: via VFRC web-based system

We will be using a web-based system to submit visual field tests for interpretation at www.perimetry.com. Each technician and site coordinator will be assigned a unique logon and password. To obtain your unique logon and password, please email the VFRC at vfrc@uiowa.edu and provide your name, email address, site number, and your role in the project (technician or site coordinator). Please note that the site coordinator can send one email for their site, listing all the individuals in need of a unique logon and password, in addition to the required information listed above. All OHTS visual fields, including abnormal and unreliable ones, must be uploaded to our website, www.perimetry.com, or mail diskettes and/or flash drives to VFRC within 14 days of the date taken.

Once you log in to our website at www.perimetry.com, you will have access to study resources. These resources can be located on the ‘Home’ tab, under the ‘Resources’ section. Resources include the Chapter 11 VFRC Perimetry Guide, Protocol for Submission Uploads, OHTS 3 Diskette Labels, and the OHTS 3 Visual Field Information form. You need to keep a copy of the OHTS visual fields (i.e., one diskette and one set of visual field printouts) in an organized and secure manner. To minimize diskette storage problems, you may consolidate the Humphrey diskette files on master diskettes. Be sure to attach a label to each Humphrey diskette you store for the study (see below). On the label, enter your Site ID, Subject ID, and Visit Date (print labels from VFRC website: www.perimetry.com).



OHTS STUDY

Site ID	
Subject ID	
Visit Date	

The flow for submitting test data is listed below; each step is described in detail in the Submission Upload Manual which is located in the study resources section on the www.perimetry.com website:

1. Select the “OHTS 3” Project to upload test data
2. Fill out required Demographic information
3. Select the test data to upload
4. Review the selected test data and information
5. Submit to the VFRC

If an entry is required or the entered data is incorrect, the interface will notify you of the error so you can properly correct it. Note that you will not be able to upload data until all identified errors are corrected.

Test data can be selected for upload by clicking on the ‘Add Tests’ link at the bottom of the upload interface. Clicking that link will open a new window for the upload tool; you will select the test data from that window. Clicking the ‘Add Tests’ link will open the Upload Tool.

The screenshot shows a web interface for 'Submission Upload'. At the top, there are navigation tabs: HOME, UPLOAD, SUBMISSIONS, GRADING, MY ACCOUNT, ADMINISTRATIVE, and LOGOUT DEVAADMIN. The main form contains the following fields:

- Project:** VFRCeasting
- Site:** Administrative
- Technician:** VFRC Testing
- Patient Date of Birth:** 06/04/1982
- Visit:** Baseline
- Unscheduled:** No
- Comments to the Reading Center:** This is a test submit

A red arrow points to the 'Add Tests' button located at the bottom left of the form. Below the form, there is a small disclaimer: 'This website conforms to the United States Health Insurance Portability and Accountability Act, 1996 (HIPAA). Personal health information is protected by 128-bit encryption. Unauthorized entry is punishable by law and will be prosecuted to the fullest extent. No advertising is allowed on this site. Copyright © 2012'.

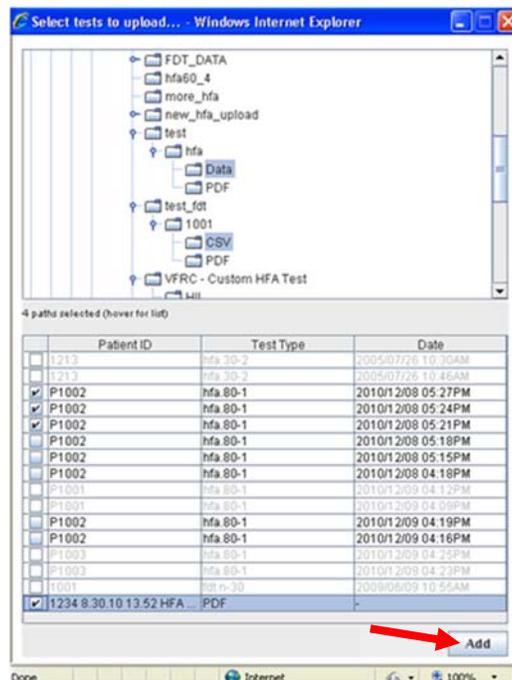
Note: When clicking on the ‘Add Tests’ link, you might be asked to accept a Security Certificate to allow the Upload Tool to run. You must click the ‘Run’ button for the

Upload Tool to open. Please note that some sites might have more strict IT policies that can require further configuration to ensure the Upload Tool can be run; please contact the VFRC if you need assistance with this.



It is important to note that a submission can only contain data from one participant and for one test type. As soon as you select a test for a certain Participant ID and test type, tests for other participants and types will be disabled and cannot be selected. When selecting PDF data to upload, please note that the Participant ID will contain the name of the PDF document you selected, not the actual Participant ID from the perimeter. Also, the date that is listed will correspond to the date that the PDF document was created (or downloaded from the perimeter), not the date that the test was performed.

After you have selected all of the desired test data, click the 'Add' button in the lower right to send the data to the VFRC.



After you have reviewed the selected test data and demographic information, you can submit the data to the VFRC by pressing the 'Upload' button at the bottom of the upload interface. Once the 'Upload' button is pressed, the submission cannot be stopped, please ensure that the correct data and information has been specified before you submit. Once the test data is successfully uploaded and submitted to the VFRC, you will get a listing of the Submission IDs that were created, corresponding to the data you selected for upload. You can retrieve more information about these Submission IDs from the 'Submissions' tab (described in the next section). After your data is successfully uploaded, the upload interface will reset so you can upload more data if desired. If any error occurred while trying to submit your data, you will be informed of the error. If the error relates to any demographic information, you will be asked to correct that information before the upload can proceed. You will not be able to upload any data to the VFRC until all demographic information is correctly specified. For more detailed information regarding submission upload, please reference the Submission Upload Manual which is located in the study resources section on the www.perimetry.com website. If you need help or are unfamiliar with any errors, please contact the VFRC at vfrc@uiowa.edu or (319) 467-4539.

It is important that you upload the data within 14 days of the visual field visit.

8.1. Instructions for Forum and Axxess systems

Forum and Axxess systems change the way you are able to download data files. If your site uses Forum or Axxess, please contact the VFRC to troubleshoot the best method for your site to download and submit data to the VFRC. You can contact us via email at vfrc@uiowa.edu or at 319-467-4539.

9.0 TECHNICIAN CERTIFICATION

Each Clinical Center must have at least two visual field technicians certified for OHTS perimetry. It is the responsibility of each Clinical Center Investigator to ensure that the appropriate personnel are competent in the OHTS perimetry protocol. To obtain certification, a technician must demonstrate an understanding of the correct procedures for all aspects of the OHTS visual field testing. The candidate for VF certification must successfully demonstrate knowledge of the protocol in a telephone session with a VFRC staff member and transmit a set of practice visual fields from **one** non-OHTS study person (two tests-one right eye and one left eye) to the VFRC website at www.perimetry.com or mail diskette or USB/flash drive containing practice visual fields to VFRC (see address below). The candidate for certification is recommended to study this manual, the Submission Upload Protocol, and review the OHTS Perimetry Procedures before making an appointment for a telephone session. To make an appointment, the candidate or Clinical Center Coordinator should contact the VFRC at (319) 467- 4539 or at vfrc@uiowa.edu

**Visual Field Reading Center
University of Iowa
2501 Crosspark Road
B148-MTF
Coralville, IA 52241**

For the telephone session, the candidate may want to use a telephone directly by a Humphrey Field Analyzer, and the candidate will initiate the call to the VFRC staff member. After a satisfactory telephone session, the candidate must submit visual fields performed on both eyes of one non-patient person according to OHTS protocol. These fields should be uploaded to the VFRC website at www.perimetry.com. Certification will be awarded if these are also satisfactory.

All certified technicians must maintain their certification by performing OHTS visual field tests on a regular basis. Certification will lapse for any technician who does not perform an OHTS visual field test for a period of six months. To become re-certified, a technician must send a memo to the VFRC, confirming review of protocol. In addition, the technician must perform a single practice visual field according to protocol, and it should be uploaded to the VFRC website at www.perimetry.com.

To become certified for OHTS visual field testing, a technician must demonstrate competency in the following:

- calibrating the Humphrey perimeter and formatting a diskette
- measuring the pupil size
- adjusting the comfort features for the participant, 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 participant data
- performing a 30-2 SITA Standard visual field test
- being sensitive to participant fatigue -- allowing the participant to rest during the test
- saving and printing the test data
- making a back-up diskette and copying visual field files onto another diskette

Upon successful certification, the VFRC will send a certificate to the Clinical Center Coordinator and the Coordinating Center a certificate of certification for that particular technician. The Clinical Center Coordinator needs to file the certificate in the Regulatory Binder, as a part of the technician's training documents. Once a minimum of two technicians have been certified for this study, the Clinical Center will be considered to have fulfilled the VFRC Certification requirements.

10.0 QUALITY CONTROL OF VF TESTING BY THE VFRC

All visual fields received by the VFRC will undergo quality control assessment procedures prior to visual field interpretations by the grader. A quality control assessment for each HFA visual field will be sent to Clinical Center over the internet via the VFRC website to indicate whether the results are acceptable, a listing of the items that must be corrected, and

whether the test needs to be repeated. All tests should be sent to the VFRC for evaluation, even if the quality is poor.

Each visual field submission will be initially examined by the VFRC Coordinator or designee for compliance with OHTS Clinical Study Procedure Protocols. To reduce the number of errors, it will be the responsibility of the Clinical Center Coordinator to ensure that:

- Each technician is following the guidelines set forth in the Perimetry Guidelines provided by the VFRC and in compliance with the OHTS Protocol
- The technician is monitoring the participant at all times during the visual field tests to ensure compliance with the various tests and to correct or encourage the participant when they are not complying with the test instructions
- Both eyes are tested, using the HFA 30-2 SITA Standard
- Each Clinical Center is to upload their HFA data and corresponding PDF files to the VFRC website at www.perimetry.com using instructions provided in section 7.0, preferably before the participant leaves the Clinical Center

11.0 QUALITY CONTROL OF VFRC READERS

All three visual field readers (CAJ, MW and JLK) have served as readers for previous multicenter clinical trials. Prior to this investigation, all three readers will agree upon written criteria for visual field conversion and visual field progression. Following this, the reviewers will evaluate a common visual field data set of 200 eyes that have undergone longitudinal visual field tests to assess their level of agreement for visual field abnormalities and visual field progression. Cases in which there is disagreement among the readers will be discussed by the readers to refine the interpretation of visual fields and the application of various decision rules and visual field progression algorithms. To be certified for this investigation, all readers must demonstrate a level of agreement that is equivalent to the results obtained during the original OHTS trial (see reference cited below).

To assess the consistency and reproducibility of the within and between reader assessments, a subset of approximately 20-25% of the visual fields submitted to the VFRC will be re-evaluated under masked conditions, in the same manner that was conducted previously for the OHTS investigation. (Keltner JL, Johnson CA, Cello KE, Bandermann SE, Edwards MA, Kass MA, Gordon MO and the Ocular Hypertension Treatment Study Group: Classification of visual field abnormalities in the ocular hypertension treatment study. Archives of Ophthalmology, 2003, 121: 643-650)

All visual field assessments will be performed independently by the readers with no knowledge of the findings reported by the other readers. Each visual field will be evaluated by two readers, and if there is agreement, the determination is complete. If there is disagreement, then a third reader will be requested to provide an evaluation so that the assessment can be adjudicated.

Protocol for Submission Uploads

University of Iowa Visual Field Reading Center
Version 1.4

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Introduction

Welcome to the University of Iowa Visual Field Reading Center (VFRC). We will be using a web-based system to submit visual field tests for interpretation.

Each technician, site coordinator and monitor will be given a unique log in and password. Please keep your log in and password in a safe place and do not share your login or password with anyone else.

Please familiarize yourself with this protocol and the submission upload requirements. If you have any questions or have difficulty accessing the website, please contact the Visual Field Reading center by email at vfrc@uiowa.edu or by phone at (319) 467-4539.

Uploading Submission Data to the VFRC

The following sections will describe the required steps and process for selecting and uploading visual field tests and related documents. Please contact the VFRC with any questions.

The Webscreen system is an online web application and must be accessed via a web browser. The system has been tested on all current versions of the major web browsers (Internet Explorer, Firefox, Chrome and Safari). While other browsers have not been tested, they likely can be used without error. However if you do encounter problems, first please try to use one of the previously listed web browsers.

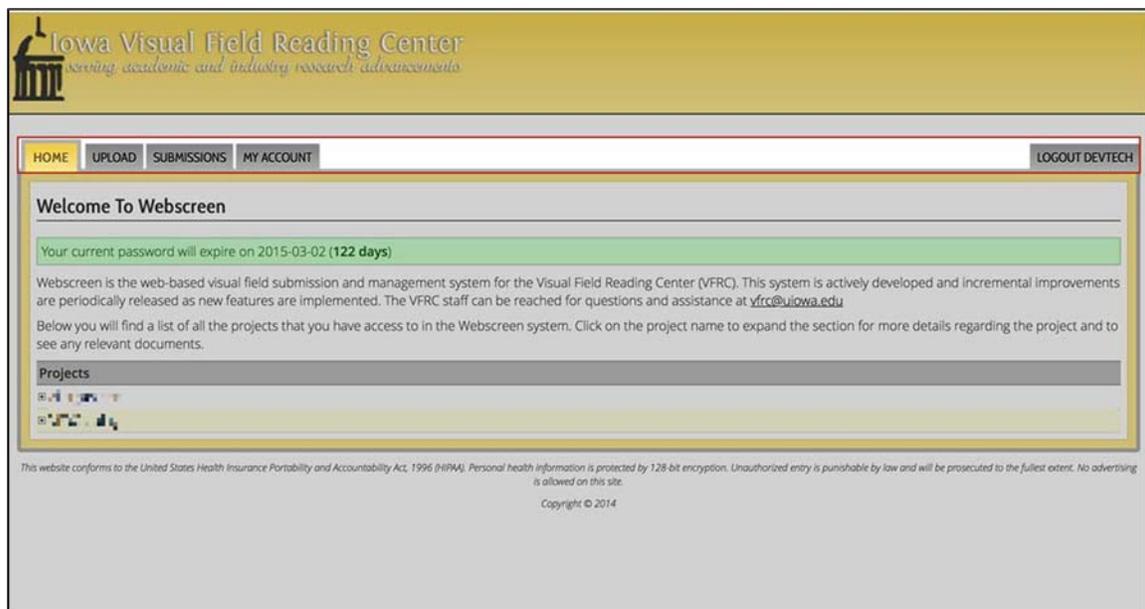
Portions of the upload system utilize the Java Runtime Environment to perform the upload of data. The Java Runtime Environment is a standard component to most operating systems and is installed by default. The minimum required version of Java installed is version 7.0 (sometimes referred to as version 1.7). If you are having problems uploading, please ensure that Java version 7 is installed and properly configured (<http://java.com/>).

Logging In

Accessing any part of the system will first require you to login to Webscreen.

1. Using your internet browser go to the Webscreen address
 - a. <http://perimetry.com>
 - b. The login area is located in the lower left of the page
2. Enter your Username and Password
3. Click the “Login” button
4. If you entered the correct user credentials, you will be taken to the Webscreen home page
5. You will be asked to re-enter your user credentials if there was an error logging in

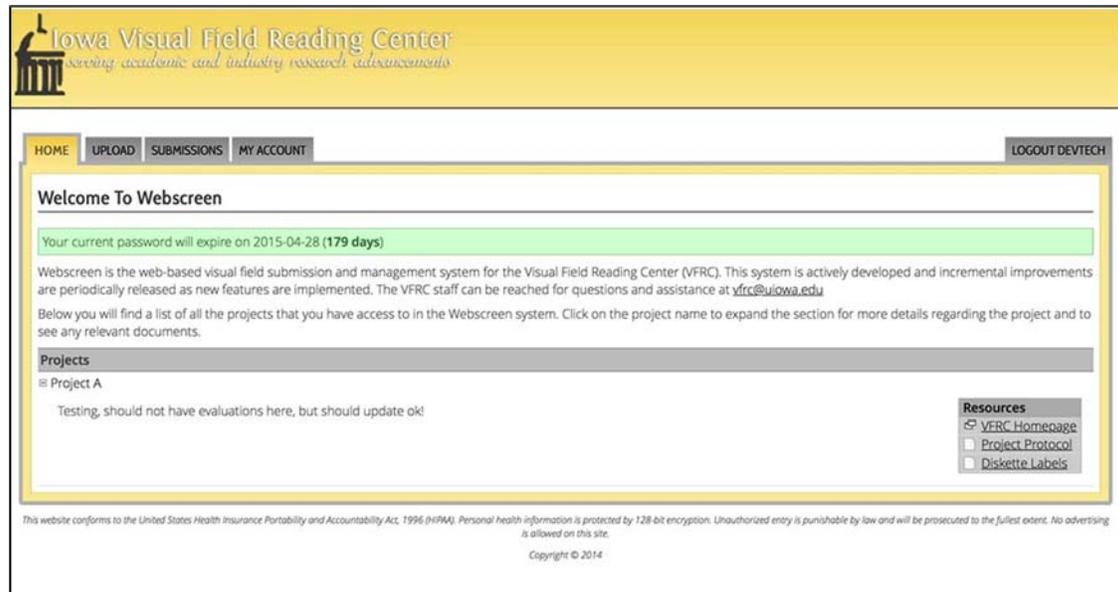
After successfully logging in, you will be taken to the Webscreen homepage. In the Webscreen interface, there is a row of clickable ‘tabs’ that will allow you to navigate to different areas of the Webscreen system. At any time you may click one of those tabs to access a different section of the system.



Navigation 'tabs' in the Webscreen System

The 'Home' Tab

After logging in, you will be on the 'Home' tab. The 'Home' tab will show you a listing of all the Projects your user account has been assigned to. Each Project in the list can be expanded (by clicking anywhere on the Project row) to view a brief description of the Project. In the expanded Project information, you will also be able to see any Project Resource files that have been linked to the project. The Resources are linked by the VFRC administrator and can contain any information that might be useful to the Project; protocols, manuals, training videos, etc. The Project Resources can be opened or downloaded by clicking on the name of the Resource from the 'Resources' table for that Project.



'Home' Tab and expanded Project information showing Project Resources

Changing Your Password

When your user account is created, you will be given a temporary password. This password should be changed when first logging into the VFRC Webscreen system. You can change your password at any time.

Please note that VFRC staff and administrators **cannot** see your password. If you forget your password, you will need to contact the VFRC (by email at vfr@uiowa.edu or by phone at (319) 467-4539) to have it reset.

To change your password:

1. Click the 'My Account' tab
2. Enter the new password in the 'Password' text field
3. Re-enter the new password in the 'Re-enter Password' text field
4. Press the 'Update My Account' button to update your password

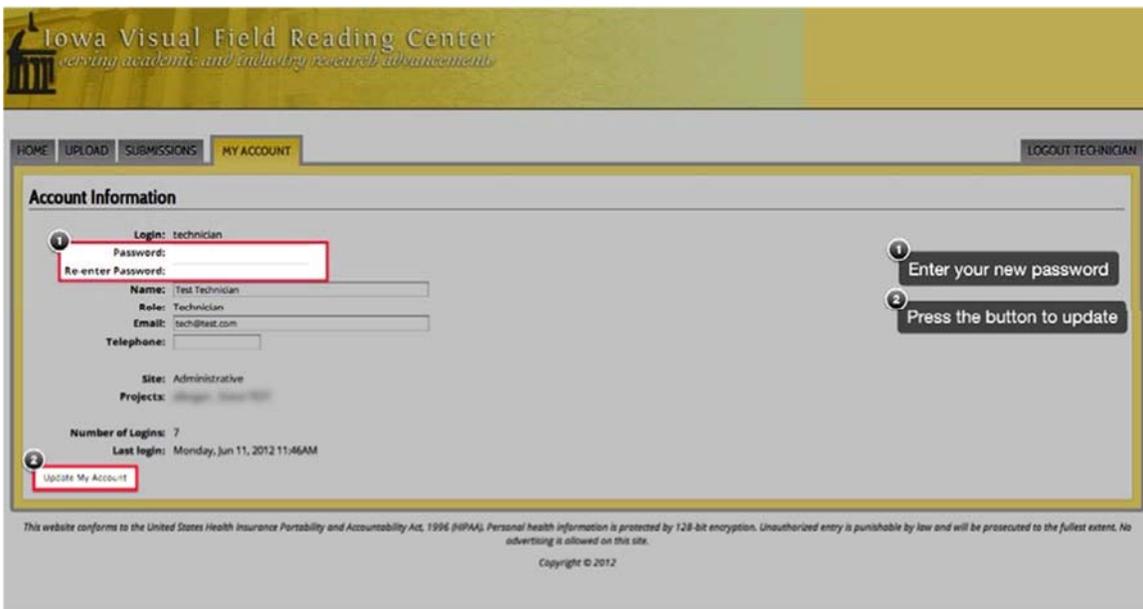
There five requirements that must be met for a password to be valid:

1. The new password must be different than your current password
2. The new password must be different than your username
3. The new password must be at least 9 characters in length
4. The new password must contain at least 1 upper case character
5. The new password must contain at least 1 non alphanumeric character

You will be notified if the password was updated or if there were any errors that occurred. The password entered into both text fields must match. Your new password will be valid for 180 days, after which it must be changed again.



Click the 'My Account' page to change your password



Enter your new password and click the 'Update My Account' button

Iowa Visual Field Reading Center
advancing academic and industry research advancements

HOME | **UPLOAD** | SUBMISSIONS | MY ACCOUNT | LOGOUT DEVTECH

DETAILS | CERTIFICATIONS

Your account profile has been updated

Account Details

Login: devTech
 Password: [redacted]
 Re-enter Password: [redacted]

Your password must be:

- different from your current password
- not your username
- at least 9 characters in length
- contain at least 1 upper case character
- contain at least 1 non-alphanumeric character

Name: Developer Technician
 Role: Technician
 Email: [redacted]
 Telephone: [redacted]
 Email frequency*: Weekly
 Emails will be sent on Sundays at Midnight
 *Note: Your email frequency can be overridden if an Administrator sets a higher frequency for a project

Site: Administrative
 Projects: Project A

Number of Logins: 125
 Last login: Thursday, Oct 30, 2014 8:04PM

[Update My Account](#)

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You will be notified if your update request succeeded or failed

Uploading A Submission

The following is a general overview of the process required to select and upload participant data to the VFRC Webscreen system. This general procedure is accurate regardless of the study you are uploading data for. However, some studies will require additional data to be provided.

The interface to upload test data can be found by clicking on the 'Upload' tab from the navigation tabs. At any time you can click the 'Upload' tab again to restart the process.

The flow for submitting test data is listed below; each step is described in detail in the remainder of this manual:

1. Select Project to upload test data to
2. Fill out required Demographic information
3. Select the test data to upload
4. Review the selected test data and information
5. Submit to the VFRC



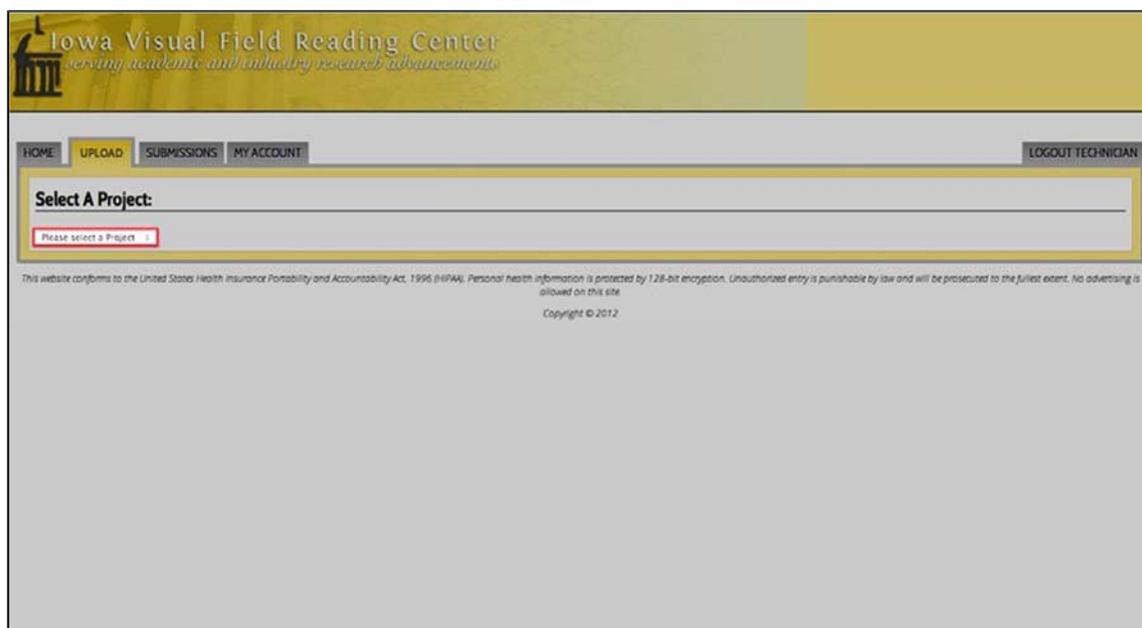
Clicking the 'Upload' tab will take you to the interface to upload test data

Selecting A Project

All submissions need to be associated with a Project (study). After clicking on the 'Upload' tab, the first piece of information you will need to provide is the Project that you would like the data to be uploaded to.

If you have been assigned to multiple Projects, you will be presented with a dropdown that lists all of your accessible projects. Select the appropriate Project from the list.

If you are only assigned to one Project, you will be taken directly to the upload interface and will not have to select the Project. All data uploaded will be assigned to your only accessible project.



The screenshot shows the Iowa Visual Field Reading Center website. The header includes the logo and the text "Iowa Visual Field Reading Center" with the tagline "serving academic and industry research advancements". Below the header is a navigation bar with links for "HOME", "UPLOAD", "SUBMISSIONS", "MY ACCOUNT", and "LOGOUT TECHNICIAN". The main content area features a "Select A Project:" label above a dropdown menu. The dropdown menu currently displays "Please select a Project". Below the dropdown menu, there is a small disclaimer: "This website conforms to the United States Health Insurance Portability and Accountability Act, 1996 (HIPAA). Personal health information is protected by 128-bit encryption. Unauthorized entry is punishable by law and will be prosecuted to the fullest extent. No advertising is allowed on this site." and a copyright notice: "Copyright © 2012".

The Project dropdown widget; use it to select the appropriate project for the data

Demographics

Every submission will require some amount of demographic information to be provided about the participant or test. The exact information required is dependent on the specific Project the data is being uploaded for. However, regardless of Project, you will always be required to specify:

- The Technician that performed the test
- The date of birth of the participant

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The Upload Interface showing the minimum required demographic information

If an entry is required or the entered data is in error, the interface will notify you of the error so you can properly correct it. **Note that you will not be able to upload data until all identified errors are corrected.**

Fields can have default values that are pre-entered; if the default is appropriate for your submission you can leave the value. Fields might also have associated help text to guide how you fill the field. If help text has been specified for a particular field, it will appear under the field description and input.

The Upload Interface showing how default values, error messages and help text appear

Specifying the Technician

The Technician field is to be filled with the name of the technician that performed the test, not of the user uploading the submission.

If you are a Technician, then this information will be set to your user and it cannot be changed. **You should not upload data for tests that you did not perform.** If there is data that needs to be uploaded but the testing technician is unavailable, please talk to your Site Coordinator.

If you are a Site Coordinator then you can upload test data for your Technicians. From the 'Technician' dropdown menu, select the name of the Technician that performed the test. If the testing Technician is not listed, you can manually enter their name by selecting 'Other...' from the dropdown.

Selecting Data

Test data can be selected for upload by clicking on the 'Add Tests' link at the bottom of the upload interface. Clicking that link will open a new window for the upload tool; you will select the test data from that window.

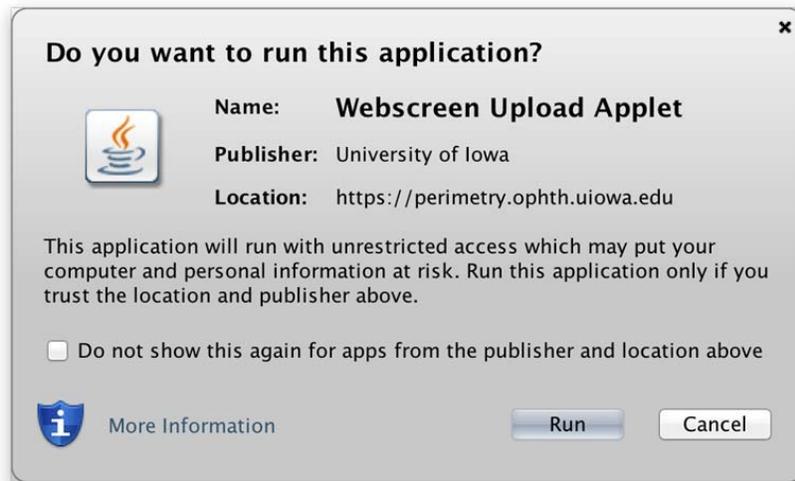
The screenshot shows a web application interface for 'Submission Upload'. At the top, there is a navigation bar with tabs for 'HOME', 'UPLOAD', 'SUBMISSIONS', 'GRADING', 'MY ACCOUNT', and 'ADMINISTRATIVE', along with a 'LOGOUT DEVADMIN' link. The main content area contains a form with the following fields:

- Project:** A dropdown menu with 'VFRCtesting' selected.
- Site:** A dropdown menu with 'Administrative' selected.
- Technician:** A dropdown menu with 'VFRC Testing' selected.
- Patient Date of Birth:** A date input field with '06/04/1982' entered.
- Visit:** A text input field with 'Baseline' entered, with a note below it: 'Automatically generated field from MigrationScript2'.
- Unscheduled:** A radio button field with 'No' selected, with a note below it: 'Automatically generated field from MigrationScript2'.
- Comments to the Reading Center:** A text area containing the text 'This is a test upload'.

At the bottom of the form, there is a red-bordered button labeled 'Add Tests' and a smaller 'Upload' button. A help icon (?) is also visible. At the very bottom of the page, there is a small disclaimer: 'This website conforms to the United States Health Insurance Portability and Accountability Act, 1996 (HIPAA). Personal health information is protected by 128-bit encryption. Unauthorized entry is punishable by law and will be prosecuted to the fullest extent. No advertising is allowed on this site. Copyright © 2012'.

Clicking the 'Add Tests' link will open the Upload Tool

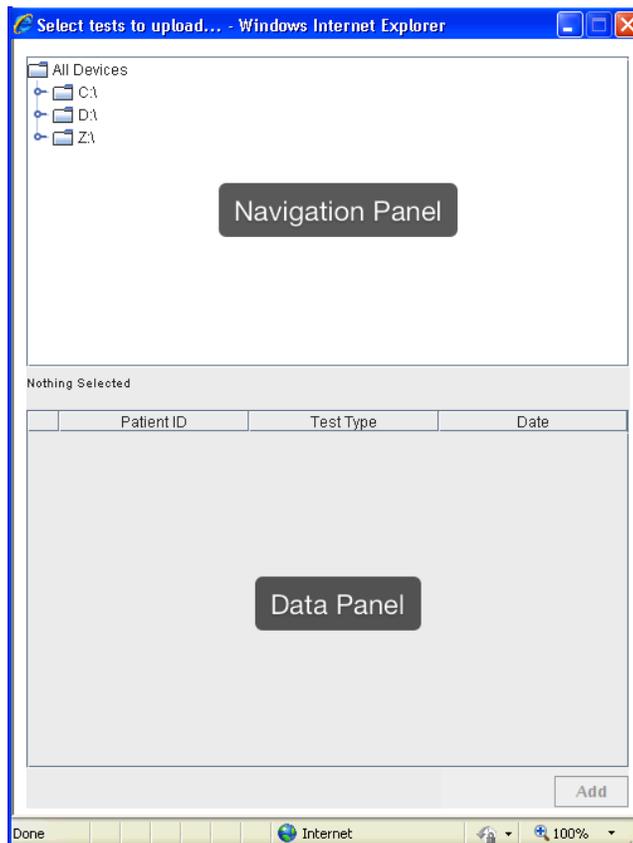
Note: When clicking on the 'Add Tests' link, you might be asked to accept a Security Certificate to allow the Upload Tool to run. You must click the 'Run' button for the Upload Tool to open. Please note that some sites might have more strict IT policies that can require further configuration to ensure the Upload Tool can be run; please contact the VFRC if you need assistance with this.



Security Certificate to allow the Upload Tool to run, click “Run” to accept

Upload Tool

The Upload Tool allows you to view and select test data to upload to the VFRC. The tool consists of two main panels: The Navigation Panel at the top of the window and the Data Panel at the bottom.



The Upload Tool, the top is the Navigation Panel with the Data Panel at the bottom

The **Navigation Panel** shows all the devices and folders that are accessible on your computer. Use this panel to navigate to the location of the test data you would like to upload. Click the triangle to the left of an item to expand it and see the contents of that item. Clicking on any item in the list will populate the Data Panel with any available test data that can be uploaded to the Project. If no test data is present in the selected item, the Data Panel will be empty. If your test data is spread among multiple locations, you can select multiple items in the Navigation Panel by holding down the control button and clicking the various items.

The **Data Panel** shows any test data that can be uploaded to the Project that is present in the location selected in the Navigation Panel. Available tests will be listed in the table, showing the Participant ID, Test Type and Test Date.

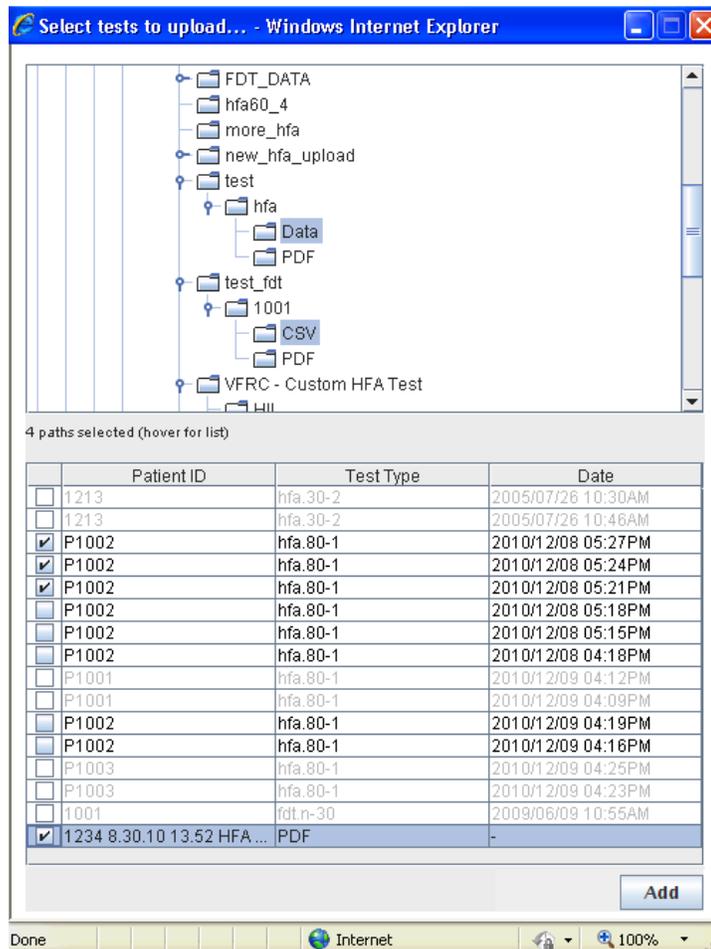
Selecting Test Data

After selecting the proper locations in the Navigation Panel, you can select the test data to upload from the Data Panel by either clicking the desired row in the table or the checkbox for that row. Any tests that are checked in the Data Panel will be marked for upload when the 'Upload' button is pressed.

It is important to note that a submission can **only contain data from one participant and for one test type**. As soon as you select a test for a certain Participant ID and test type, tests for other participants and types will be disabled and cannot be selected.

When selecting PDF data to upload, please note that the Participant ID will contain the name of the PDF document you selected, not the actual Participant ID from the perimeter. Also, the date that is listed will correspond to the date that the PDF document was created (or downloaded from the perimeter), **not** the date that the test was performed.

After you have selected all of the desired test data, click the 'Add' button in the lower right to send the data to the VFRC.



The Upload Tool with test data marked for upload. Note only tests for one Participant ID are available

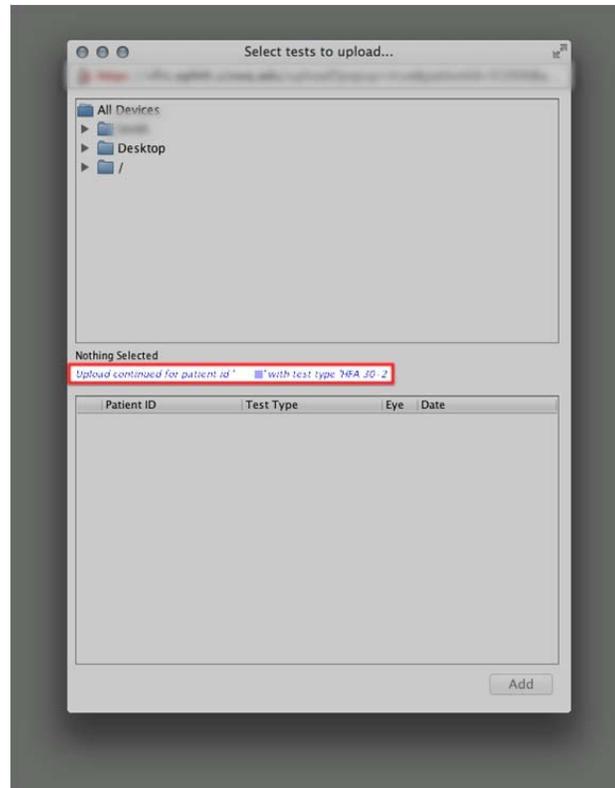
Continuing An Upload

Additional test data can be added to an upload through two methods: the 'Add Files' link and the 'Add Tests' button.

'Add Files'

The 'Add Files' link will allow you to add additional data to a submission for the Participant ID and Test Type specified. Follow the same process for selecting test data and again click the 'Upload' button in the upload tool when you are ready to send the data to the VFRC. However, remember a submission can only contain test data for a single participant. As such, only tests for that Participant ID and test type will be selectable if you are continuing an upload. If you need to upload data for a new participant you will have to start a new upload by clicking on the 'Upload' tab after you have submitted the current visual fields.

The 'Add Files' link provides you a way to add test data to the submission if you forgot to select it the first time the Upload Applet was opened. Adding data this way will constrain the Upload Applet to allow you to only select data for the same Participant ID and Test Type.



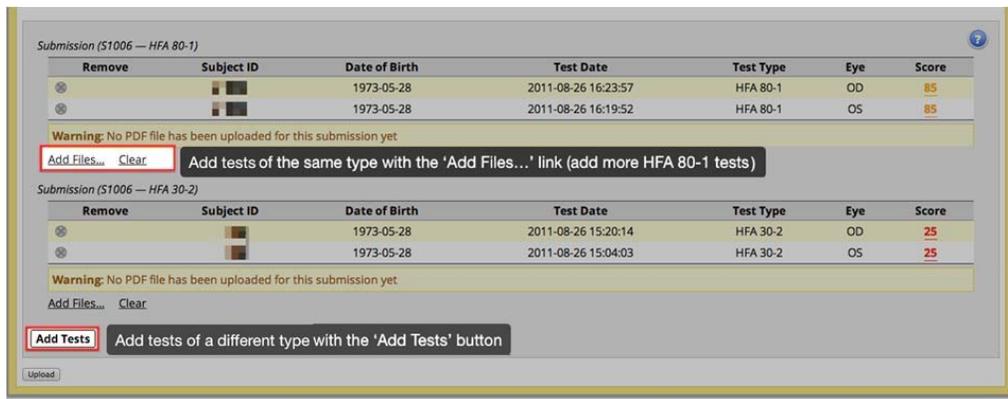
A continued upload showing Participant ID and Test Type, disabling tests for other participants and types

‘Add Tests’

The ‘Add Tests’ button will allow you to specify data for the same Participant ID, however any test type can be selected. This is a convenience method to allow you to specify all the data for a participant, regardless of test type, in a single upload. It is most useful if during a single patient visit, multiple types of tests are performed. The benefit of this method is that the demographic information needs to be filled in only once, but all data is uploaded to the system.

The ‘Add Tests’ button provides you with a convenient way to upload all data for a single participant, regardless of test type. Adding data this way will constrain the Upload Applet to allow you to only select data for the same Participant ID.

Please note that this method will result in the creation of multiple submissions in the system, one for each test type present in the upload session.



In this screenshot, additional HFA 80-1 tests for the Participant ID can be added using the ‘Add Files...’ link. The ‘Add Tests’ button can be used to add tests of a different type for the same P ID (for example, FDT 24-2 tests could be added with this method).

Reviewing Data

Before uploading your submission to the VFRC, you can review the demographics and selected test data. The table at the bottom of the upload interface will list all the test data files that you have selected to include in this submission. The table lists:

- Participant ID
- Date of Birth
- Test Date
- Test Type
- Eye Tested
- Score

Score

The score for test data can inform you of any potential problems with your selected test data; the higher the score, the fewer the number of problems identified. To see a list of the identified problems, hover over the numeric score listed in the ‘Score’ column. The score is only available for visual field test data.

Remove	Subject ID	Date of Birth	Test Date	Test Type	Eye	Score
	12123 7.26.05 10.30	N/A	04/12/2012 - 05:08 PM	HFA 30-2	OD	N/A
	P1002	12/15/1962	12/08/2010 - 05:18 PM	HFA 30-2	OD	72
	P1002	12/16/1956	12/09/2010 - 04:19 PM	HFA 30-2	OD	72
	P1002	12/16/1956	12/09/2010 - 04:16 PM	HFA 30-2	OD	72

Detailed list of problems identified in the specified test.

Removing Test Data

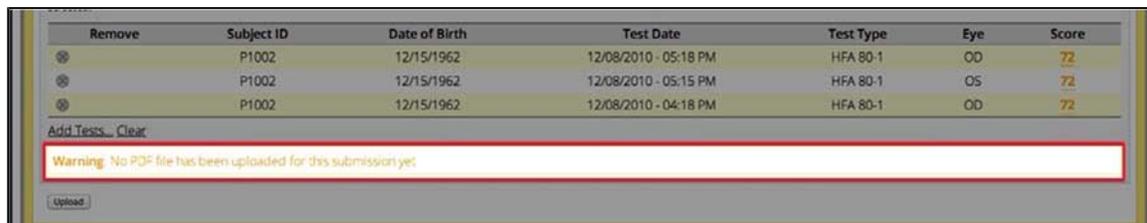
If some test data has been included in error, you can remove the errant data by clicking the ‘Remove’ icon to the left of the row you would like to remove. If you would like to remove all data, you can click the ‘Clear’ link at the bottom of the page. This will remove all test data but leave the demographic information in place.

Remove	Subject ID	Date of Birth	Test Date	Test Type	Eye	Score
	1213 7.26.05 10.30 HFA 30-2 OD.pdf	N/A	04/12/2012 - 05:08 PM	PDF	N/A	N/A
	P1002	12/15/1962	12/08/2010 - 05:18 PM	HFA 80-1	OD	72
	P1002	12/16/1956	12/09/2010 - 04:19 PM	HFA 80-1	OS	72
	P1002	12/16/1956	12/09/2010 - 04:16 PM	HFA 80-1	OD	72

Test data can be removed from the submission by clicking the 'Remove' icon

Missing PDF Data

Submissions should include the corresponding PDF data for each visual field test. If no PDF data has been selected for upload, the upload interface will warn you of the missing data. You may proceed with your upload if no PDF data is required but the message will still remain as a reminder. If you need to add the PDF data, click the 'Add Tests...' link to continue your upload and find the data.



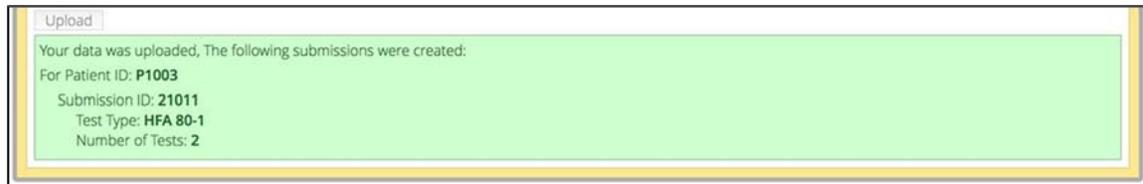
Warning of missing PDF data

Submitting

After you have reviewed the selected test data and demographic information, you can submit the data to the VFRC by pressing the 'Upload' button at the bottom of the upload interface. Once the 'Upload' button is pressed, the submission cannot be stopped, please ensure that the correct data and information has been specified before you submit.

If your test data was successfully uploaded and submitted to the VFRC you will get a listing of the Submission IDs that were created corresponding to the data you selected for upload. You can retrieve more information about these Submission IDs from the 'Submissions' tab (described in the next section). After your data is successfully uploaded, the upload interface will reset so you can upload more data if desired.

If any error occurred while trying to submit your data, you will be informed of the error. If the error relates to any demographic information, you will be asked to correct that information before the upload can proceed. You will not be able to upload any data to the VFRC until all demographic information is correctly specified. If you need help or are unfamiliar with any errors, please contact the VFRC.

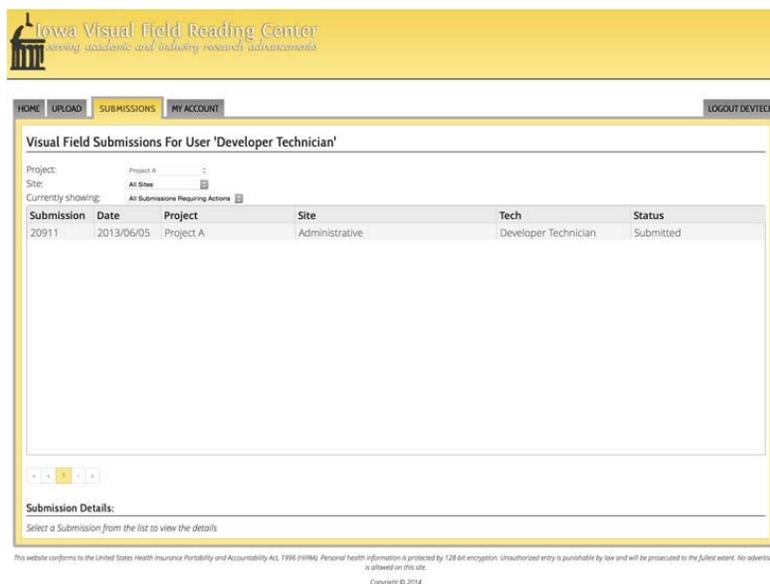


Clicking the 'Upload' tab will take you to the interface to upload test data

Submissions Tab

The 'Submissions' tab can be used to retrieve additional details about a submission, verify the status of a submission, resolve any required actions and to review the comments on a closed submission. You will also receive emails as the submission makes its way through the system. If you receive an email and would like to follow up or need to perform an action, you can login to the system and visit the 'Submissions' tab.

The 'Submissions' Tab



View Details of a Submission

Additional details about a submission can be obtained from the "Submission Details" section of the page. This area is populated after you select a submission from the table. This table can be sorted by clicking on the header columns of the table. To select a submission, scroll to the desired submission in the table and click on its row; the background color of the selected row will turn blue. After selecting a submission, you will see the details after they have been retrieved from the system, which might cause a short delay.

The "Submission Details" will show the participant demographics, the status of each test that is in the selected submission and also any additional values that were collected during submission upload.

Submission Details:	
Upload Information	Submission Information
Submission ID: 20911	Unscheduled: No
Project: Project A	Visit: Baseline
Testing Site: Administrative	Name: Test
Technician: Developer Technician	Eye Condition: Good
Uploaded By: Developer Technician	Gender: Male
Upload Date: 2013-06-05 16:26:49.0	
Status: Submitted	
Participant Information	
Participant Name: NAME	
Participant ID: PID_001	
Date of Birth: 1983-08-20	
Tests	
<input type="checkbox"/> HFA 30-2 (OD) performed on 2013/04/09 at 11:10:27 This test has not been evaluated yet	
<input type="checkbox"/> HFA 30-2 (OS) performed on 2013/04/09 at 11:18:11 This test has not been evaluated yet	
<input checked="" type="checkbox"/> This submission is missing data (Please submit missing data)	
The following comments were provided: <i>This is a test to see if different actions can be resolved with a single upload.</i>	
<input checked="" type="checkbox"/> Required Action: Please submit the missing test data.	

The “Submissions Details” section: upload details can be viewed in the upper left of this screenshot, with the participant information below. Any additional submission information that was specified during upload will appear in the upper right of this screenshot. The bottom of the submission details will display status information for all tests in the submission

Verify Status of a Submission

After completing a submission, the status of the submission will be set to “*submitted*” while it is reviewed by the VFRC. After the submission has been reviewed, that status will be changed based on the review.

Each test of a submission can be evaluated individually so the status for each test can vary within the same submission. If any errors exist for the submission as a whole (e.g. data missing from the submission) or individual tests (e.g. QC issues), you can resolve these issues by clicking on the appropriate action from the test status information.

Please note that resolving some actions will result in a completely new submission while resolving other actions can result in appending new data to the existing submission. Clicking on the resolution link will load the “Upload” interface to allow you to submit the new data. If the resolution is to append to the current submission, any patient demographics on the “Upload” Interface will be filled with the submissions previously entered values and disabled. However, you can add new comments for the new data.

It is important to resolve any required actions through the resolution link found on the Submissions tab; doing so will alert the system that the action has been performed.

Submission Details:	
Upload Information	Submission Information
Submission ID: 20911	Unscheduled: No
Project: Project A	Visit: Baseline
Testing Site: Administrative	Name: Test
Technician: Developer Technician	Eye Condition: Good
Uploaded By: Developer Technician	Gender: Male
Upload Date: 2013-06-05 16:26:49.0	
Status: Submitted	
Participant Information	
Participant Name: NAME	
Participant ID: PID_001	
Date of Birth: 1983-08-20	
Tests	
HFA 30-2 (OD) performed on 2013/04/09 at 11:10:27	
This test has not been evaluated yet	
HFA 30-2 (OS) performed on 2013/04/09 at 11:18:11	
This test has not been evaluated yet	
! This submission is missing data (Please submit missing data)	
The following comments were provided: This is a test to see if different actions can be resolved with a single upload.	
Required Action: Please submit the missing test data.	

This submission is missing data, notice the resolution link in the orange box. Clicking this link would open the Upload Applet to append the missing data to this submission,

Review Comments on a Submission

After a submission is reviewed by the VFRC it may have comments with more information. Because each test in a submission is evaluated individually, comments for each test will be displayed in the test summary.

Submission Details:	
Upload Information	Submission Information
Submission ID: 20911	Unscheduled: No
Project: Project A	Visit: Baseline
Testing Site: Administrative	Name: Test
Technician: Developer Technician	Eye Condition: Good
Uploaded By: Developer Technician	Gender: Male
Upload Date: 2013-06-05 16:26:49.0	
Status: Submitted	
Participant Information	
Participant Name: NAME	
Participant ID: PID_001	
Date of Birth: 1983-08-20	
Tests	
HFA 30-2 (OD) performed on 2013/04/09 at 11:10:27	
This test is closed and has been evaluated as valid (Valid. No further action needed). The following comments were provided: "This test passed all QC tests, nothing more is needed"	

A Closed Submission with Comments

A. APPENDIX

a.) Transmitting Interim Visual Fields

Visual field tests performed since the last OHTS visit will be retrieved for the following participants:

1. Those who developed VF POAG in OHTS Phase 1 or 2.
2. Those who were ocular hypertensive at their last OHTS visit and have newly developed VF POAG in OHTS Phase 3.
3. Those who are unable/unwilling to return to the Clinical Center.

Prior to Assessment 1, please upload the interim visual fields and corresponding pdf copies to the VFRC website at www.perimetry.com. If your site is seeing patients who were seen at non-OHTS sites for interim visual fields, you will need to contact the non-OHTS sites to receive a copy of the visual fields. Prior to upload, please make sure to de-identify all of the visual field tests by correcting the patient ID and patient name fields to follow study protocol. The patient ID and Name fields should adhere to study protocol, consisting of the 2 character alphanumeric code “Site ID” (i.e. A1 or W1,) that was assigned by the OHTS Coordinating Center and 5 numeric character “Participant ID” (i.e. 01234).

We should never see the patient’s name on the Interim visual fields uploaded to the VFRC website.

To de-identify the data:

The VFRC recommends saving the data to your floppy disk or thumb drive prior to changing participant information. This ensures that you only need to change the patient ID and Name once.

1. From the “Main Menu,” choose “File Functions.”

2. Select “Change Patient Data.”

3. When prompted, select “All Tests.”

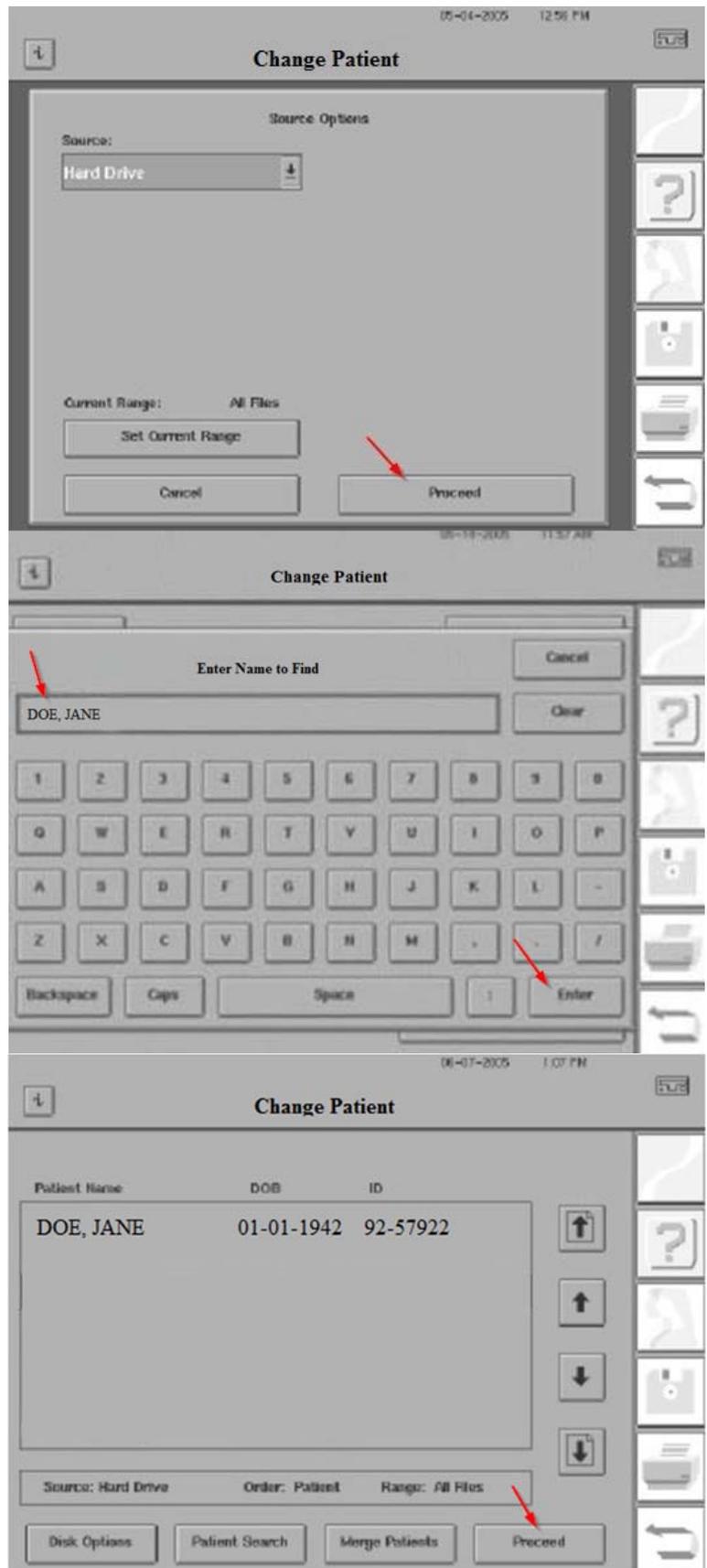


11-4 Visual Field Reading Center

7. Under “Source,” select “Hard Drive” or “Floppy” (depending on where your data resides and then click “Proceed.”

8. Enter the name of the patient to locate the files and then select “Enter.”

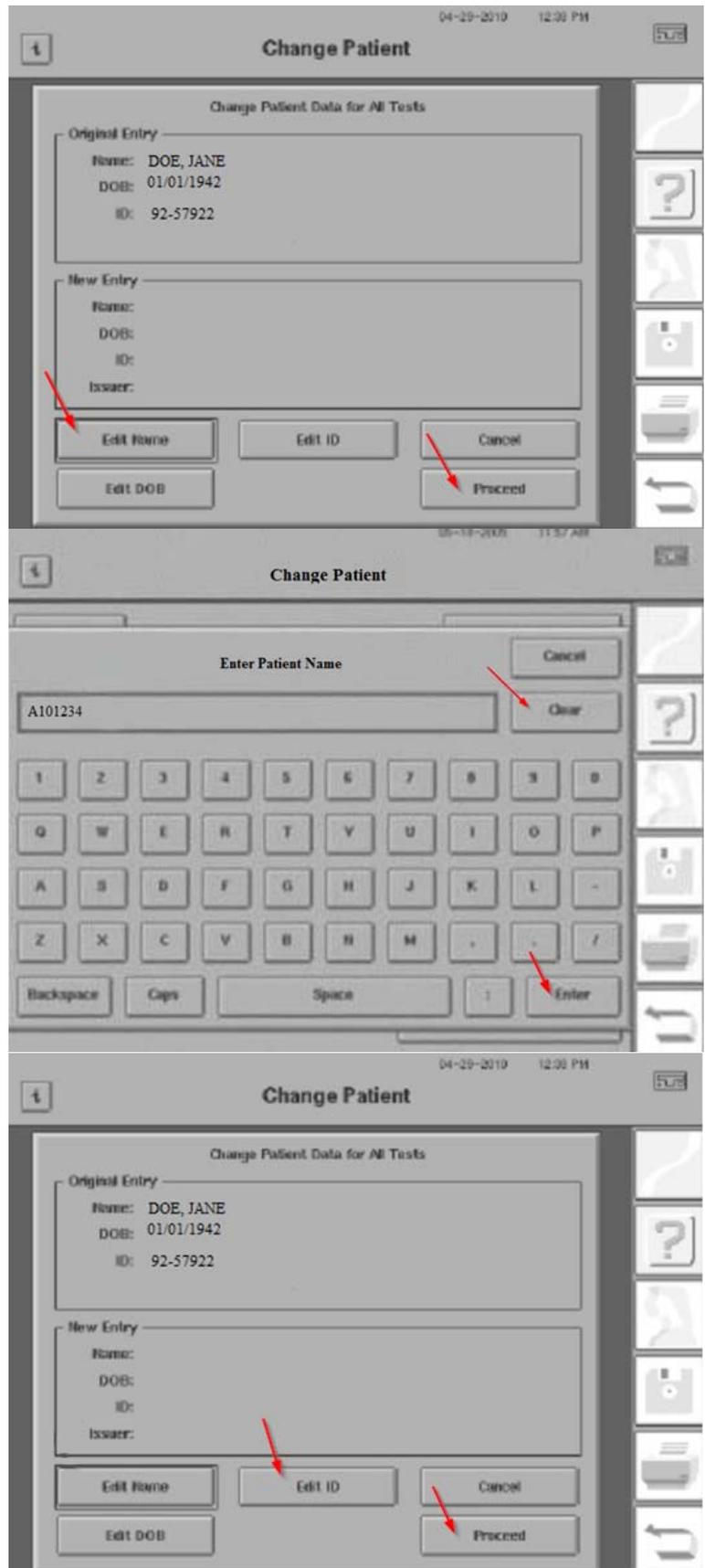
9. Select the patient and then select “Proceed.”



7. Select “Edit Name” and then select “Proceed.”

8. Select “Clear” and enter the Site ID and Participant ID (i.e., A101234). Select “Enter.”

9. Select “Edit ID” and then select “Proceed.”



11-6 Visual Field Reading Center

10. Select “Clear” and, once again, enter the Site ID and Participant ID (i.e., A101234). Select “Enter.”

11. Verify that the patient Name and patient ID are the same and then select “Proceed” twice to return to the “File Functions” menu.

The image displays two screenshots of the 'Change Patient' software interface. The top screenshot shows the 'Enter Patient ID' screen. A text box contains the patient ID 'A101234'. To the right of the text box are 'Cancel' and 'Clear' buttons. A red arrow points to the 'Clear' button. Below the text box is a numeric keypad and a full QWERTY keyboard. A red arrow points to the 'Enter' key. The bottom screenshot shows a table with columns 'Patient Name', 'DOB', and 'ID'. All three columns contain the value 'A101234'. To the right of the table are four navigation buttons: up, down, and two arrows. Below the table are three status indicators: 'Source: Hard Drive', 'Order: Patient', and 'Range: All Files'. At the bottom are four buttons: 'Disk Options', 'Patient Search', 'Merge Patients', and 'Proceed'. A red arrow points to the 'Proceed' button.

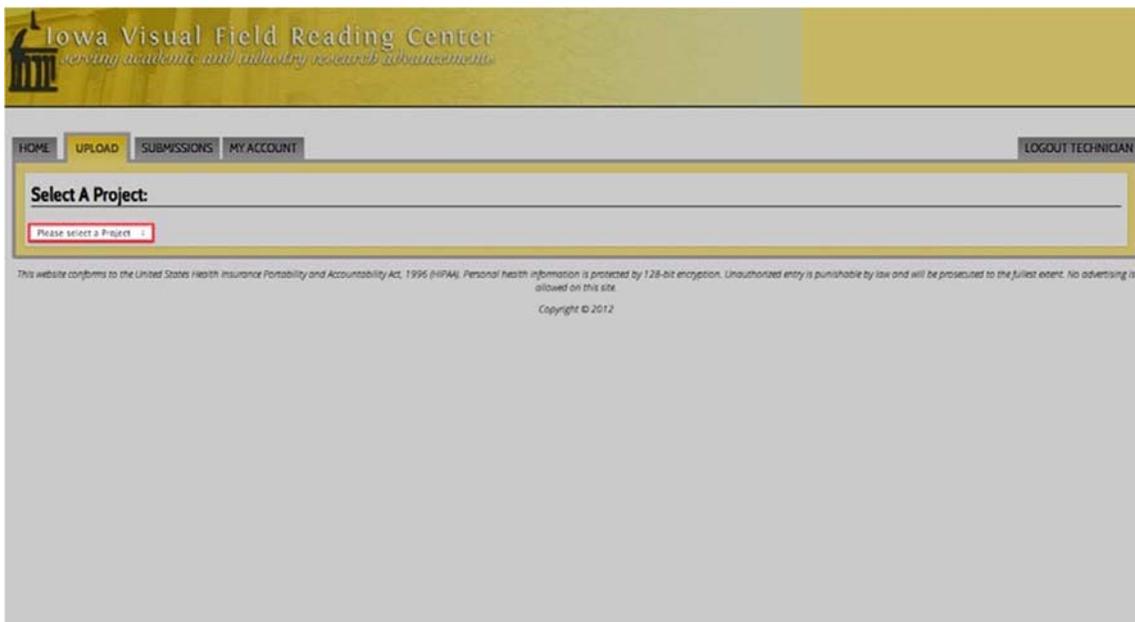
Once you have saved the HFA data, you will save the visual field images as described in section 7.

You will upload the Interim visual fields following the same procedure as uploading study data. You can upload multiple visits in the same submission, as long as they are the same type of test (for example, all HFA 30-2 in one submission or all HFA 24-2 in one submission). You can complete this by following the steps below:

Begin by logging into your account at www.perimetry.com. Once you are logged in, select the “Upload” tab, as pictured below:



You will then be asked to select the project, using the dropdown menu pictured below. Please select OHTS 3.



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Once you have selected the OHTS 3 project, you will be asked to provide information, as pictured below:

Submission Upload

Project:

Site:

Technician:

Patient Date of Birth:

Visit:

- Assessment 1
- Assessment 2
- Assessment 3
- Interim Visual Fields
- Certification
- Re-Certification

Retest: Yes (Only select this option if this is a repeat due to QC issues, such as trial lens rim artifact, excessive false positives, and/or fixation losses)

Dilation:

- NO dilation
- Cycloplegic
- Phenylephrine
- N/A

Comments to the Reading Center:

You will select the site and technician from a dropdown menu. You will also enter the patient date of birth, select the Interim Visual Fields visit, and select N/A for the dilation code.

Submission Upload

Project:

Site:

Technician:

Patient Date of Birth:

Visit:

- Assessment 1
- Assessment 2
- Assessment 3
- Interim Visual Fields
- Certification
- Re-Certification

Retest: Yes (Only select this option if this is a repeat due to QC issues, such as trial lens rim artifact, excessive false positives, and/or fixation losses)

Dilation:

- NO dilation
- Cycloplegic
- Phenylephrine
- N/A

Comments to the Reading Center:

Once you have entered the requested information, you will then click on the “Add Tests” button to select the Interim test data.

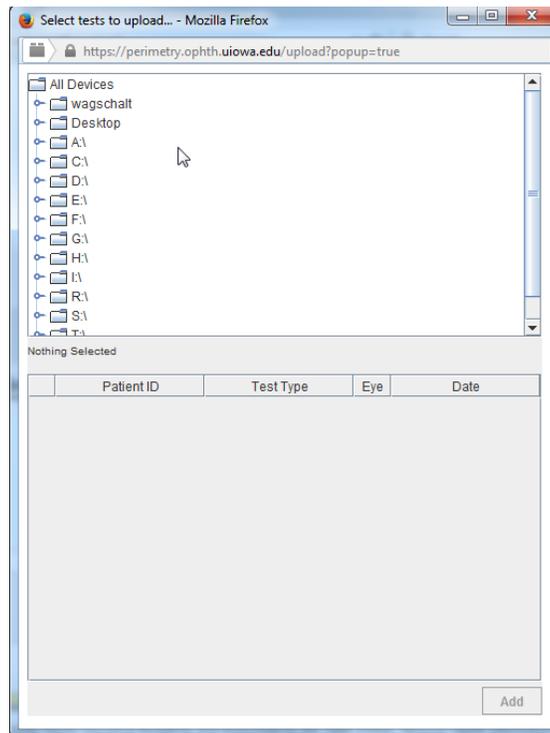
Interim Visual Fields
 Certification
 Re-Certification

Retest: Yes (Only select this option if this is a repeat due to QC issues, such as trial lens rim artifact, excessive false positives, and/or fixation losses)

Dilation:
 NO dilation
 Cycloplegic
 Phenylephrine
 N/A

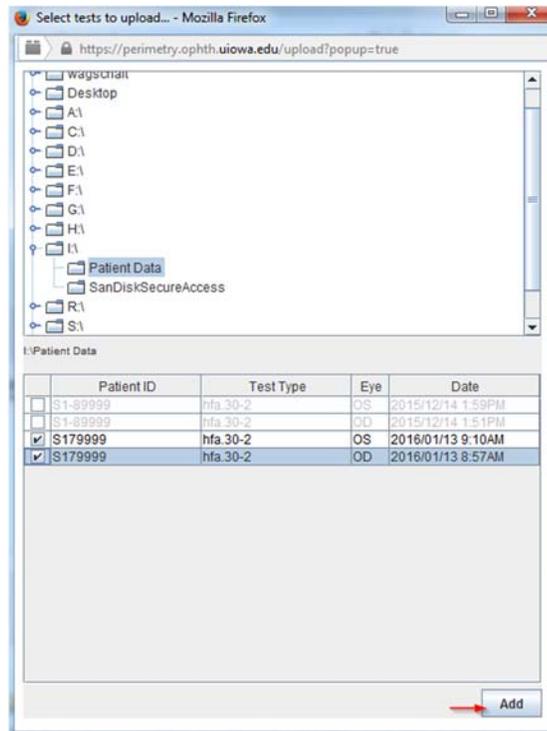
Comments to the Reading Center:

Clicking the “Add Tests” button will open the navigation tool below:

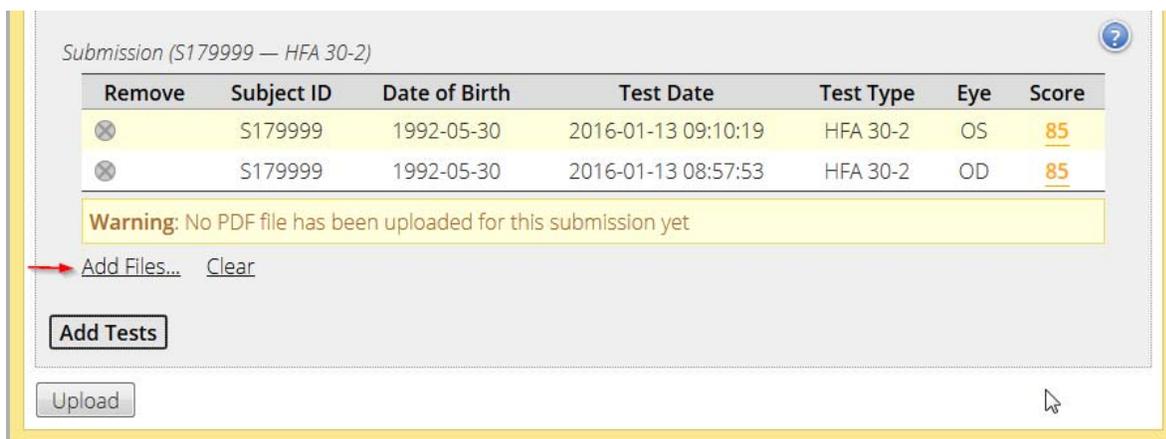


11-10 Visual Field Reading Center

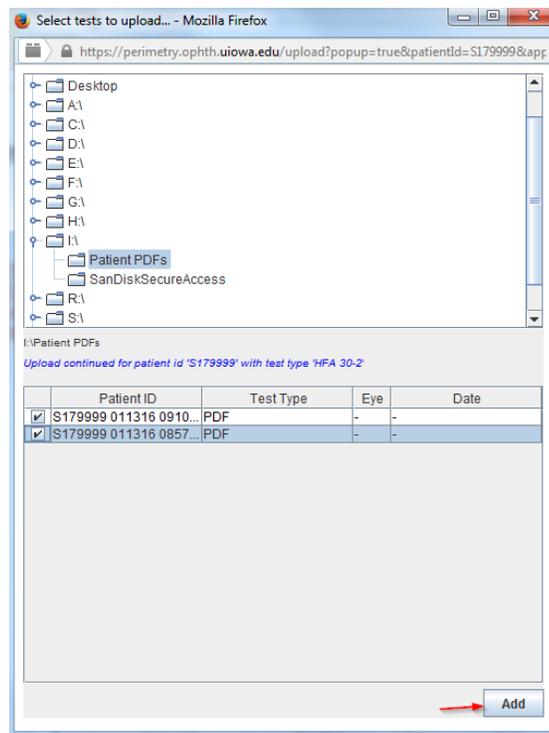
You will then navigate to the data. In this example, we are uploading using the SanDisk USB flash drive provided for the study (for raw data only) and navigated to the data by clicking on the flash drive (in this example, I:\), selecting the Patient Data folder, and then by selecting the raw data files. Finally, select the “Add” button. Do not use any other flash drive for this!



Once you select the “Add” button, you will be redirected back to the upload screen. Notice that the selected data is now attached to the upload screen. You will also see the warning indicating that the submission is missing PDF files. To attach the corresponding PDF visual field printouts, select the “Add files...” button.



Clicking on “Add Files...” will open the navigation tool. In this example, we ejected the raw data only USB flash drive and replaced it with the PDF only USB flash drive. We are uploading using the SanDisk USB flash drive provided for the study (for PDF files only) and navigated to the data by clicking on the flash drive (in this example, I:\), selecting the Patient Data folder, and then by selecting the PDF files corresponding to this submission. Then, click the “Add” button again. Do not use any other flash drive for this!



Once you select the “Add” button, you will once again be redirected back to the upload screen. Notice that the PDFs are now attached to the upload screen and the warning regarding missing PDFs is now gone. The final step is to click on the “Upload” button. Once you do so, your submission for Interim visual fields is complete.

11-12 Visual Field Reading Center

Submission (S179999 — HFA 30-2) ?

Remove	Subject ID	Date of Birth	Test Date	Test Type	Eye	Score
<input type="checkbox"/>	S179999 011316 0857 HFA 30-2 OD.pdf	N/A	02/08/2016 - 3:02 PM	PDF	N/A	N/A
<input type="checkbox"/>	S179999 011316 0910 HFA 30-2 OS.pdf	N/A	02/08/2016 - 3:02 PM	PDF	N/A	N/A
<input type="checkbox"/>	S179999	1992-05-30	2016-01-13 09:10:19	HFA 30-2	OS	<u>90</u>
<input type="checkbox"/>	S179999	1992-05-30	2016-01-13 08:57:53	HFA 30-2	OD	<u>90</u>

Add Files... Clear

In some instances, these participants have been tested at clinical sites that were not OHTS Clinical Centers. For these cases, the OHTS Clinical Center where the participant was last examined must obtain copies of interim visual field results for all visits occurring after the last OHTS visit. This can be accomplished by having the non-OHTS Clinical Center send a diskette containing the visual fields to the OHTS Clinical Center. In this manner, the OHTS Clinical Center can upload de-identified visual field tests to the VFRC and send pdf copies of the visual field printout to the VFRC.

Both the electronic and printed copies of the visual field results are needed by the VFRC. If a diskette copy of the visual fields cannot be obtained, then the printed visual field output should be sent to the VFRC. Only OHTS Clinical Centers can transmit visual field results electronically to the VFRC. To upload the de-identified visual field tests to the VFRC, please create a submission for each test date including the raw data and the corresponding PDF of the printed visual field output.

If you are unable to upload the electronic and printed copies of the visual field results to the VFRC website, you can instead mail the electronic and printed copies of the visual field results to the VFRC. You will also need to fill out the “OHTS 3 Visual Field Information” form (example below), including a copy in the shipment. You can access an electronic copy of this form under the “Resources” tab of the VFRC website.

Iowa Visual Field Reading Center
centering diagnosis, improving research, advancing care

Department of Ophthalmology & Visual Science
 2501 Crosspark Road
 B148 - MTF
 Coralville, IA 52241-8802
www.uiowa.edu
vfrc.uiowa.edu
 (319) 467-4540 Tel
 (319) 336-8724 Fax

OHTS 3 Visual Field Information

Patient ID: Z101234
 Test Date: 12/02/2016
 OD Test Time: 10:38 AM
 OS Test Time: 10:49 AM
 Site: The University of Iowa
 Technician: Tana Wagschal
 Patient Date of Birth: 05/05/1925

Visit: Assessment 1
 Assessment 2
 Assessment 3
 Interim Visual Fields
 Certification
 Re- Certification

Retest: Yes (Due to Quality Control)

Dilation: No Dilation
 Cycloplegic
 Phenylephrine
 N/A

If you are mailing diskettes, please make sure to label the diskettes and to include a printed copy of the visual field printout in the shipment. If you use the USB/flash drives, please make sure to include both the USB/flash drive that contains only the electronic data as well as the USB/flash drive that contains the corresponding pdf copies of the visual field printout. The electronic and printed copies of the visual field results can be sent to the following address:

**Visual Field Reading Center
 University of Iowa
 2501 Crosspark Road
 B148-MTF
 Coralville, IA 52241**

The VFRC will return USB/flash drives to the site within two weeks of the date of shipment receipt.

b.) Instructions for Forum and Axxess systems

Forum and Axxess systems change the way you are able to download data files. If your site uses Forum or Axxess, please contact the VFRC to troubleshoot the best method for your site to download and submit data to the VFRC. You can contact us via email at vfrc@uiowa.edu or at 319-467-4539.

12. Optic Disc Reading Center (ODRC)

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Appendix

Photographer Certification Checklist
ODRC Data Forms
How to Convert TIFF Files into JPEG Files
OHTS ODRC Transmittal Log

ODRC Reproducibility Report Slides versus Digital Images

12.1 Optic Disc Photography Purpose

Optic disc (nerve) stereoscopic photography will be used to evaluate optic disc outcomes in OHTS Phase 3. Optic disc color stereo photography was performed at the baseline visit in OHTS 1 and annually thereafter in OHTS Phases 1 and 2. Photographers will be certified to ensure high quality images for evaluation by the Optic Disc Reading Center (ODRC).

The ODRC personnel will be masked to diagnosis, to the temporal sequence of the photos and to the assessment of the other grader.

The ODRC performs the following tasks:

1. Certify clinical center photographers
2. Monitor quality of photographs and take corrective action when needed
3. Perform masked assessment to determine optic disc change (The Endpoint Committee will determine if this is a glaucomatous change from baseline, which will be referred to as POAG conversion; or glaucomatous change in an eye with prior glaucoma conversion established in OHTS 1 or 2 by the Endpoint Committee, which will be referred to as POAG progression)
4. Perform quality control procedures to assess reproducibility of ODRC readings
5. Prepare quarterly performance reports to clinical centers and Coordinating Center (CC), and semi-annual reports to Executive/Steering Committee
6. Assist in the writing of major outcome manuscripts
7. Document and archive study data for public sharing

In the following protocol, “photographs” means either digitized stereoscopic or digital stereoscopic photographs. The ODRC digitized the 35 mm slides that were taken in OHTS 1 and 2. The photographs to be taken in OHTS 3 will be digital. The ODRC will view these photographs as digital images on computer monitors.

12.2 Optic Disc Photography Protocol

12.2.1 Certification of Photographers

At least one experienced photographer at each clinical center will be certified to take optic disc photographs for OHTS 3. They will be responsible for archiving, labeling and submitting optic disc photographs for analysis by the ODRC.

Stereoscopic optic disc photographs for OHTS 3 must be taken by certified OHTS photographers. The process of certifying photographers at the clinical centers is outlined below:

- Clinical Coordinator notifies ODRC Assistant Director that a photographer requires certification
- Photographer takes two pairs of stereo photographs of each eye, of two patients who are not part of OHTS 3: Patient 1: right eye - two stereo pairs; left eye - two

stereo pairs and Patient 2: right eye - two stereo pairs; left eye - two stereo pairs

- ODRC Photographer Consultant determines per photography checklist if labeling and technical quality of photographs are adequate (See Appendix). If the photographs are acceptable, the photographer's initials will be used as their certification code number. If the photographs are not acceptable, the reason is discussed with the photographer and additional sets of photographs are requested. The review process continues until the photographs submitted are acceptable and the photographer is certified. Once quality standards are acceptable, the ODRC will notify the Coordinating Center of the photographer's name, initials, clinical center, and date of certification. ODRC will also contact the photographer and notify him/her of receiving certification.
- ODRC contacts the Coordinating Center with the new photographer certification information. Certification code consists of a three character name code: the first, middle and last initial; for example name, John A. Doe, certification would be JAD. Use the letter "X" is used in the absence of a middle initial, JXD.
- Photographer certification may be rescinded if the ODRC determines that the photographer's performance is unacceptable and does not improve after consultation and review by the ODRC Photographer Consultant
- Photographer will need to be re-certified if the camera designated for OHTS 3 stops working and has to be replaced by a different one

12.2.2 When to take Optic Disc Photographs

- Stereoscopic optic disc photographs will be taken at the OHTS 3 follow-up visit
- Retakes:
When technical quality is determined to be poor or unacceptable, retake photographs are requested by the ODRC. Repeat photographs must be taken within 3 months of the ODRC request and must be received at the ODRC within 15 days of the date of the photographs.

If the clinician, upon review of the printed image of disc photographs, determines that repeat photographs are unlikely to improve photographic quality, the Clinical Center clinician should write a note explaining why retakes would not be worthwhile.

12.2.3 Acceptable Photographic Methods

Each Clinical Center will designate one camera for OHTS 3. If a clinical center has a sequential and a simultaneous camera, the simultaneous one will be used.

Prior to submitting any photographs for OHTS 3, the study photographer will report make, model and serial number of fundus camera designated for the study activities to the ODRC and notify the ODRC if another camera is used for any reason.

12.2.4 Setting up the Camera for Photography

Eyepiece settings: 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 counterclockwise as far as possible. Next, look into the eyepiece with both eyes open, looking beyond the cross-hairs. With smooth motions, turn the eyepiece clockwise until the cross-hairs are sharp. Stop, note the setting, and repeat the procedure twice more to determine the average reading. Use this reticule setting for each session.

Magnification: When taking stereo photographs, the highest magnification available should be used.

Flash settings: 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.

12.2.5 Preparing the Participant for Photography

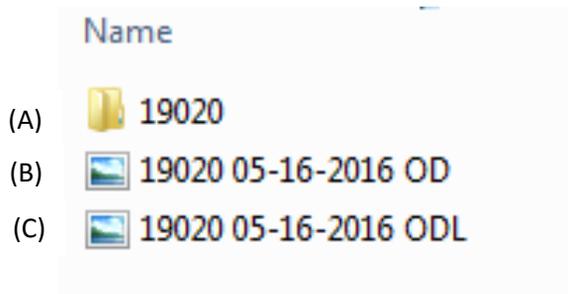
The standard pharmacologic pupil dilation regimen is tropicamide 1% and phenylephrine 2.5%, one drop each, instilled at least 20 minutes prior to photography. The drops can be repeated up to three times total if necessary. Participants are to be instructed to remain with eyes closed at least 20 minutes prior to photography to minimize corneal epithelial changes and to maintain a clear view. If the pupils have been previously dilated for other procedures, further dilating eye drops may not be necessary as long as adequate dilation is obtained and protocol imaging can be performed.

12.2.6 Photography Instructions

- Describe the procedure to the participant
- Clean the headrest and chinrest before each participant and clean the lens with isopropyl alcohol disposable wipes
- Both participant and photographer should be seated comfortably at the camera
- Enter participant's data in to the fundus camera
- Two best quality possible stereo pairs are required for each eye.
- Photograph the right eye first, then the left eye
- Instruct the participant to follow the fixation light until the optic nerve is centered on the cross-hairs
- When using a sequential fundus camera, tilt the joystick right to the 3 o'clock position just outside the retinal pigment epithelium peripapillary crescent, if present, and take the first right stereo photograph, focusing at the junction of the RPE and the neuroretinal rim. After taking this photograph, tilt the joystick left to the 9 o'clock position outside the peripapillary crescent, if present, focusing at the junction of the RPE and the neuroretinal rim
- Repeat this technique to obtain two good stereo pairs of the right eye
- It is possible to position the optic disc accurately by having the participant monitor the internal red LED directly

12.2.7 Naming Photograph Files

The digital photograph files should be named with the participant's study ID, date of photography, and OD for right eye or OS for left eye. For photographs captured with a sequential fundus camera, file name should also reflect whether photograph is left or right of the stereo pair. The letters "L" or "R" should be added to left or right photograph of the stereo pair, respectively. All photo files from each participant should be in a digital folder named with participant's study ID. See examples below:



- A. Folder with photograph files
- B. File of photograph captured with simultaneous camera
- C. File of photograph captured with sequential camera

Name, date of birth, date of photography or any identifiable information must be deleted from the digital image before being submitted to the ODRC. The ODRC will be responsible for masking digital file names to the readers.

12.3 Tracking and Storage of Disc Photographs

12.3.1 Logging in Photographs

The Clinical Center photographer should maintain an "OHTS Disc Photography Logbook" for study participants. 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 photographs.

1. Digital file naming data: the participant's study ID, date photographs were taken, and OD or OS. (The photographs will be relabeled with a tracking number at the ODRC to mask the readers.) The date will be entered as MM-DD-YY, 2 digits for month, 2 digits for day, and 2 digits for year.
2. Factors that affect photograph quality include pupil size, flash settings, media clarity and the presence of photophobia. If the quality of the photographs is not acceptable and a decision needs to be made on whether and how to retake the photographs these factors should be considered.

12.3.2 Storage of Optic Disc Photograph Files

All digital images should be archived at the Clinical Center on DVD or computer hard drive as back-up.

12.4 Using WUStL Box to Send Optic Disc Photos to Coordinating Center

Clinical Centers must submit 2 best quality possible stereoscopic photographs for each study participant. Digital files to be uploaded to WUStL box should be in JPEG format. Please see Appendix for instructions on how to convert TIFF files into JPEG files. All digital photograph files for each participant are to be in a folder named with participant's study ID as described in 12.2.7. All optic disc photograph transfer to WUStL must be accompanied by OHTS Optic Disc Reading Center Transmittal Log (See Appendix).

Clinical Centers can transfer Optic Disc Photos to the Coordinating Center in two ways:

1. Password-protected flash drive (section 12.4.2)
2. Uploading data electronically using WUStL Box (described here)

12.4.1 Setting up a WUStL Box account

1. Coordinating Center will create an account for each Clinical Center that uses WUStL Box. This needs to be done only once, and will allow access to the Reading Center folders.
2. Each clinic will confirm acceptance of the Box account by responding to an email inviting them to collaborate on Box. See example email below:

Clark Laseter, Karen has invited you to collaborate on Box Inbox x 

 **Clark Laseter, Karen** <noreply@box.com> 5:14 PM (0 minutes ago) ☆  
to me ▾



Clark Laseter, Karen has invited you to collaborate on a folder:

"Hello, I want to share my folder, "OHTS", on Box." – Clark Laseter, Karen

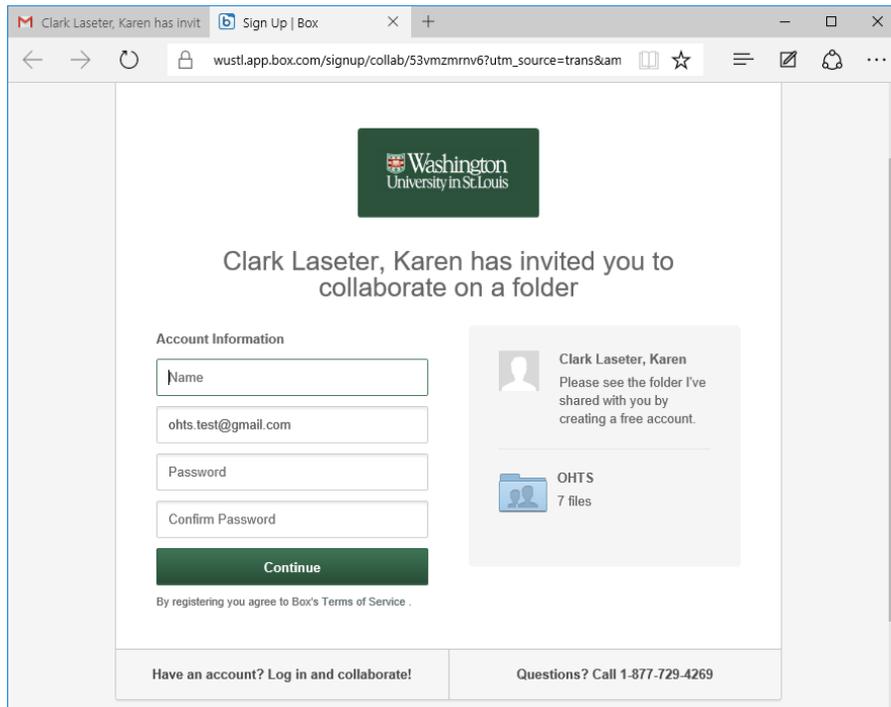


OHTS
Collaboration Folder

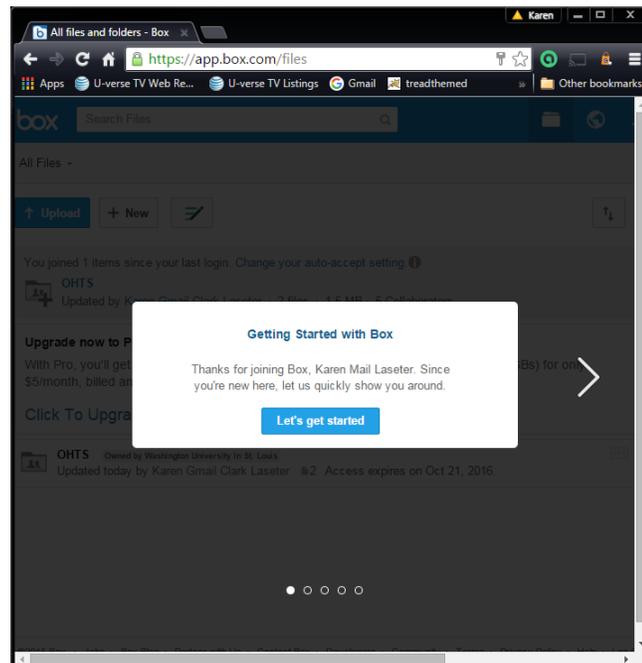
Accept Invite

Get our app to view this on mobile

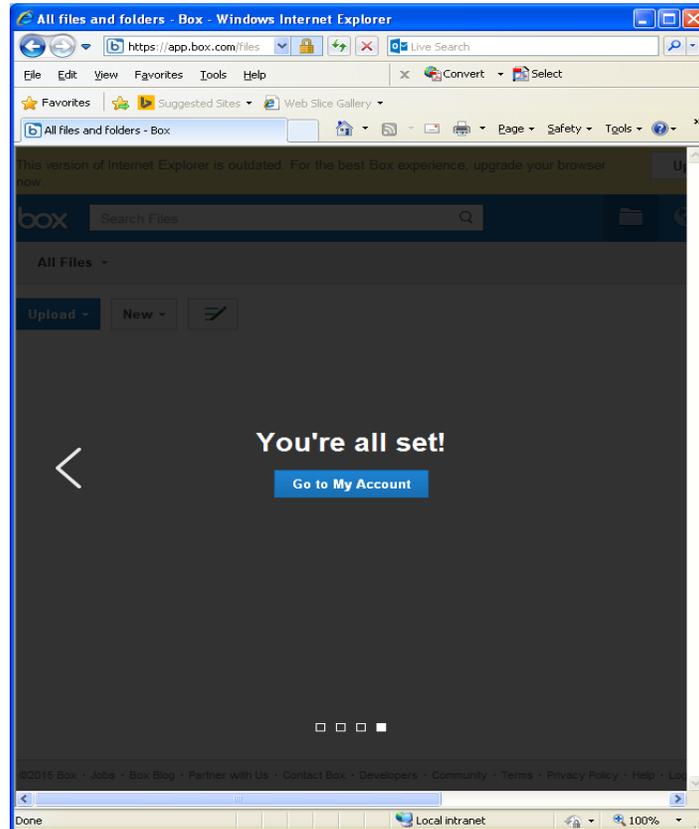
3. Click on **Accept Invite**. It will take you to the Washington University Box System (Clark Laseter, Karen)



4. Your email address will be pre-filled. Enter your name and create a password. Once logged in, it will offer you a brief walk-through of the features:

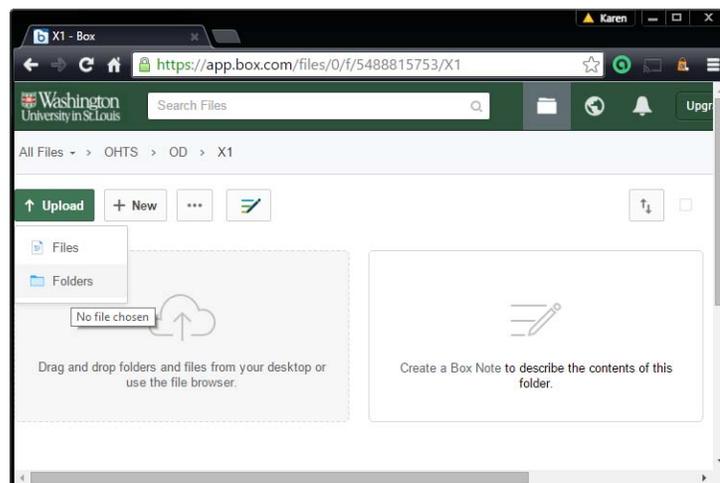


5. Scroll through 3 more screens by clicking on the right arrows. On the 4th screen, choose **Go to My Account**

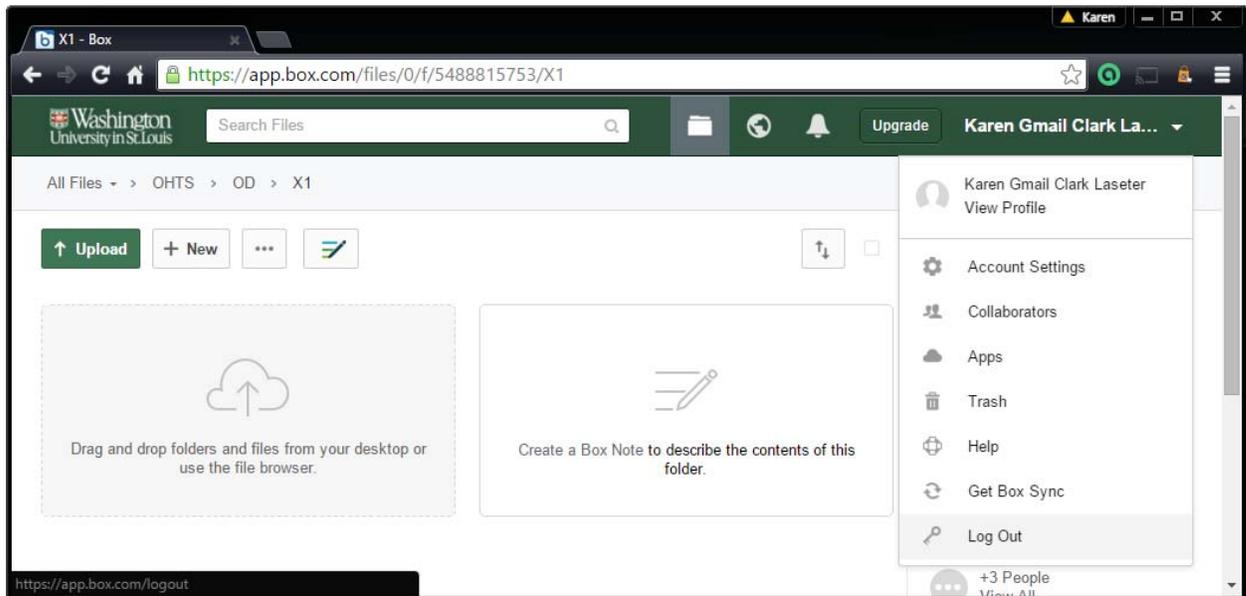


12.4.1.1 Accessing WUSTL Box Drives (You may want to bookmark this page.)

1. You will see your main OD folder. **Click on the Upload tab** to upload folders.



- When finished uploading files, log out of Box by clicking on your name in the upper right corner, and choose Logout.



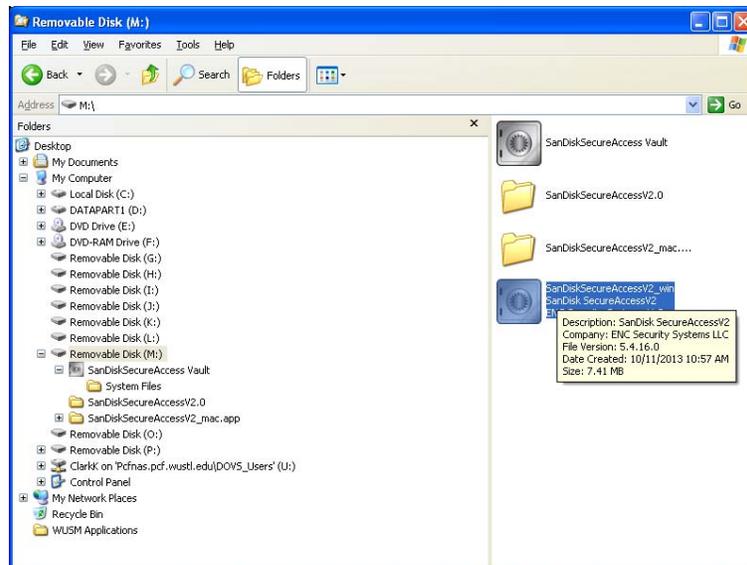
12.4.2 Using Encrypted Flash Drive to Send Optic Disc Photos to Coordinating Center

If a Clinical Center is unable to use the WUSTL Box system to upload photos, the optional method is using a password-protected flash drive for this purpose. The Coordinating Center will send you a password-protected flash drive. The Coordinating Center will send you the password for the flash drive separately.

These instructions apply to Windows users. Mac users should contact to Coordinating Center to request Mac-appropriate flash drives.

12.4.2.1 Loading data onto USB flash drive

- Extend the retracted drive. Insert the flash drive into a USB port. If you have a USB 3.0 port, use this, as it will provide the fastest transfer speeds. If the drive does not automatically open, go to **My Computer (below)** to find the drive, and click on the flash drive. See example below.



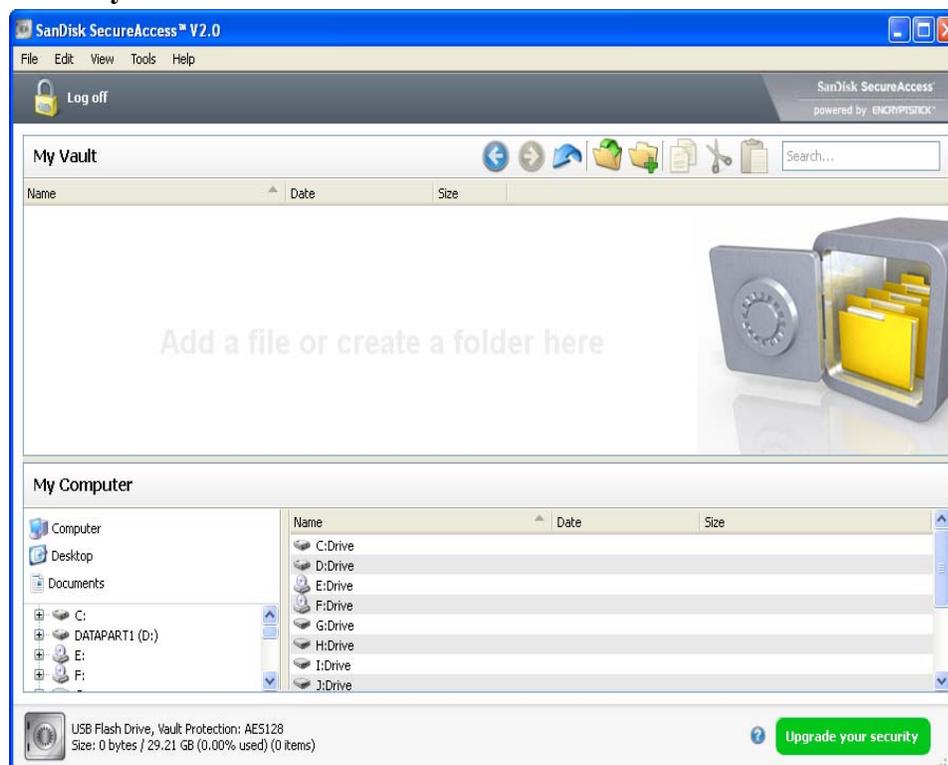
2. Click on the SanDisk SecureAccessV2-win (as highlighted above).
3. Enter the password to log in (provided via email):



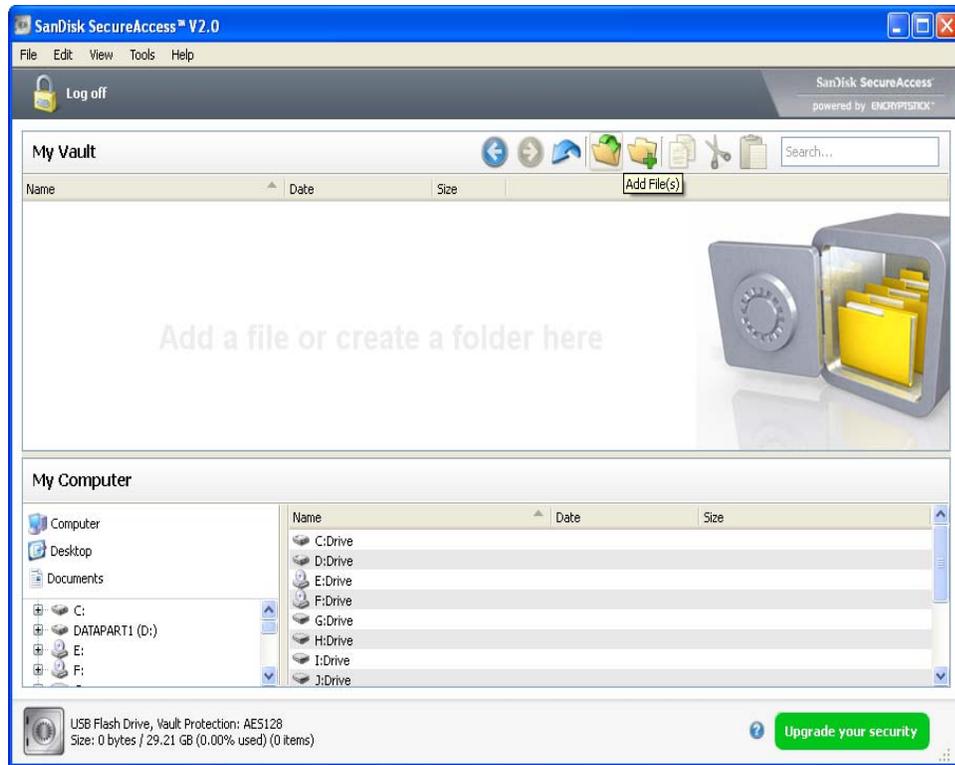
Introductory screen is shown:



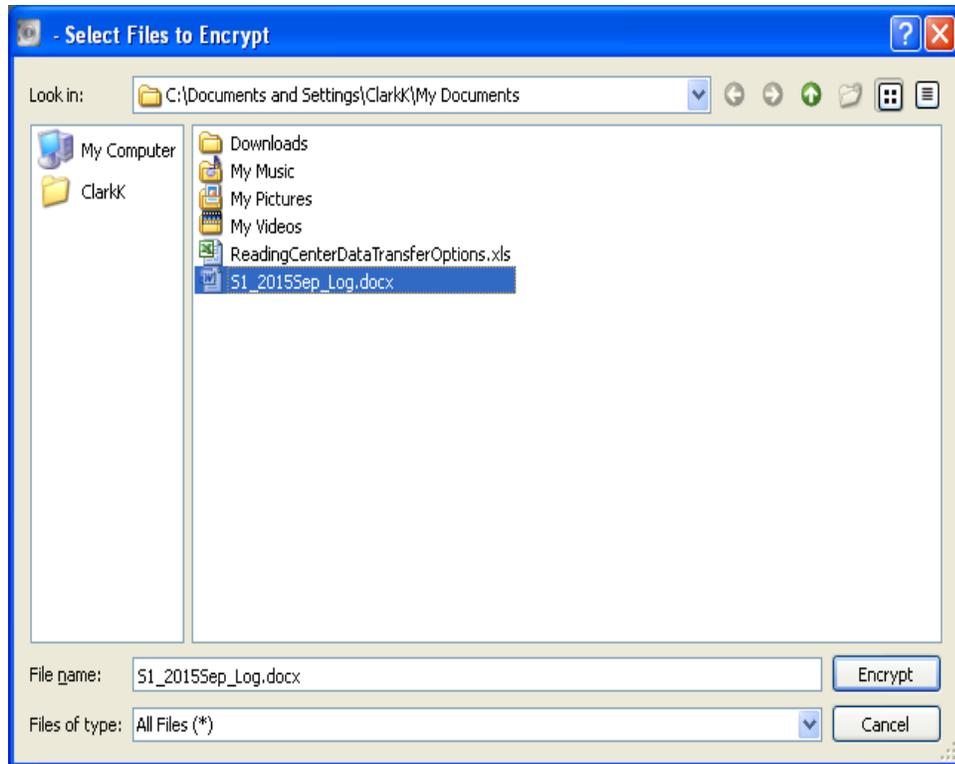
4. Click the green Next button
5. You will see **My Vault** as shown below.



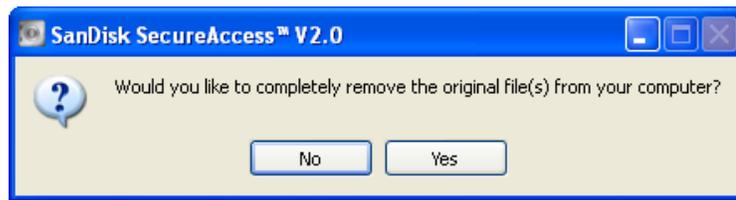
6. You may need to navigate to the OD subdirectory. Select files to be copied to drive by pressing the icon (in “My Vault”) with the green arrow in the folder, or select an entire folder to be copied by pressing the folder with a green plus sign.



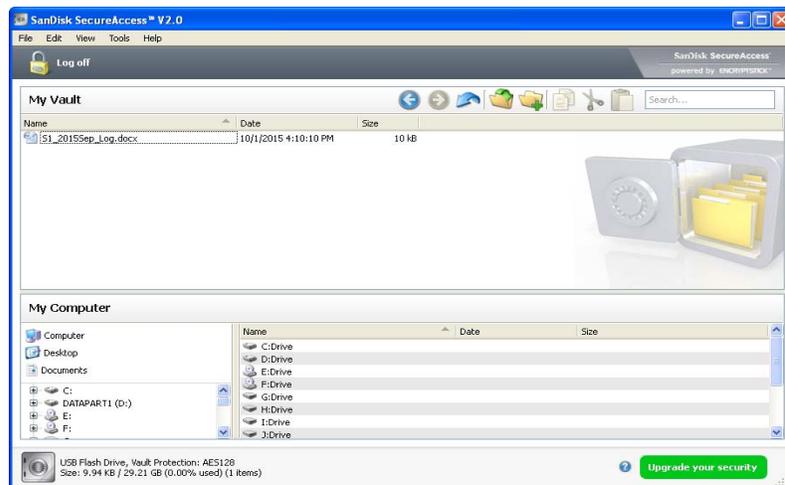
Identify the file(s) or folder(s) you want to transfer to the vault and select **Encrypt**



7. You are given an option to remove the original file from your computer. Select “No”



8. Confirm that the file is in your vault



9. When done transferring files/folders, select **Log off** in upper left corner.
10. You can now remove the drive from your computer.

If you have any questions or problems with the data transfer, contact Karen at Karen@wubios.wustl.edu, or (314) 362-2349. If you have any questions about Reading Center-specific issues (what files to transfer, etc.) please contact the ODRC: Eleonore Savatovsky at esavatovsky@med.miami.edu

12.5 Communications with OHTS Clinical Centers and Coordinating Center

12.5.1 Communication with Clinical Centers

The ODRC will send an immediate electronic receipt confirmation for photograph files submitted. Within 7 days of receipt of photographs, the ODRC will notify the clinical centers of the need for retake, suspicion of optic disc change, disc or retinal hemorrhage, as well as any protocol violations or edits.

12.5.2 Transmission of Data from the ODRC to Coordinating Center

The ODRC will send relevant photograph files and grading forms to the Coordinating Center by WUSTL Box.

Daily:

- Photographs and grading forms demonstrating suspected disc changes
- Photographs and grading forms demonstrating confirmed disc changes

Monthly:

- Data logs including: participant ID, photographer ID, date photograph was taken, date photographs were received at ODRC, reader ID, date photographs were read, Senior Reader ID and date photographs were adjudicated (if applicable), retake reason and date requested (if applicable)

Ad hoc basis:

- Any problem with a clinical center with regard to labeling, image quality, retakes, or timeliness of receipt of images

If the ODRC determines that a participant shows optic disc change, then all photographs of both eyes of this patient will be forwarded to the OHTS Coordinating Center for review by the OHTS Endpoint Committee. This will include all photographs from OHTS 1, 2, and 3.

12.6 Optic Disc Reading Center (ODRC) Background and Objective

Optic disc color stereo photography was performed at the baseline visit in OHTS 1 and annually thereafter in OHTS 1 and 2. During OHTS 1 and 2, the ODRC read optic disc photographs (35 mm slides) to evaluate if glaucomatous optic disc damage had occurred (POAG conversion) and demonstrated its ability to do so in a reproducible fashion.^{1,2} Additionally, the ODRC assessed disc photographs for other important covariates such as disc hemorrhages and peripapillary atrophy.³ In OHTS 3, digital optic disc photographs will be taken. The ODRC will evaluate if optic disc damage has developed in those eyes without prior optic disc damage (change from baseline), and to assess if damage has progressed in those eyes with established glaucomatous optic disc damage in OHTS 1 or OHTS 2 (change from conversion).

In order to assess agreement of ODRC's original determinations of optic disc change from slides to their determination from digital photographs, ODRC readers independently compared baseline and follow-up digital stereoscopic disc photographs from 70 eyes selected by the OHTS Coordinating Center. The agreement measured by kappa demonstrated that the reading of the digital images is very good. (See Appendix for ODRC Reproducibility Report).

12.6.1 Personnel

Principal Investigator/Director and Senior Reader

Richard K. Parrish III, M.D.
E-mail: rparrish@med.miami.edu

Assistant Director/Primary Reader	Eleonore Savatovsky, Ph.D. E-mail: esavatovsky@med.miami.edu
Primary Reader	TBA
Statisticians	William Feuer, M.S. E-mail: wfeuer@med.miami.edu
Photographer Consultant	TBA

Telephone#: 305-243-5488

Fax#: 305-243-5487

Surface and Express Mail Address:

University of Miami Miller School of Medicine
Bascom Palmer Eye Institute
Optic Disc Reading Center
Dominion Tower
1400 NW 10th Avenue – Suite 510B
Miami, FL 33136

12.6.2 Responsibilities of ODRC

- Train and certify Optic Disc Readers at the ODRC
- Develop protocol for performing optic disc photography at the clinical centers and for evaluation of photographs at the ODRC
- Certify study photographers at the clinical centers
- Receive, process, and archive all photographs and associated data
- Assess photographic quality and notify clinical centers in a timely manner when photographs must be repeated due to poor quality
- Document optic disc features and characteristics such as cup/disc (C/D ratio), disc hemorrhage
- Determine if optic disc characteristics in eyes previously normal have changed from baseline in a fashion consistent with conversion to glaucoma
- Determines if optic disc characteristics in eyes with previously established optic disc damage have changed in a fashion consistent with progression of glaucoma
- Enter and manage optic disc related data
- Transmit data to the Coordinating Center and the clinical centers in a timely fashion

- Generate reports for the Executive/Steering Committee
- Provide statistical analyses requested by the Coordinating Center

12.7 ODRC Procedures

12.7.1 Reader Pre-requisite

Candidate readers must demonstrate stereopsis at a level of 40 seconds of arc with a standard stereo acuity test.

12.7.2 Training and Certification of Optic Disc Readers

Drs. Parrish and Savatovsky are both experienced optic disc readers for the ODRC who have graded optic disc photographs for prior clinical trials. A third reader will be hired and trained as described below.

The Optic Disc Reading Center developed training and test sets for reader certification for detecting optic disc change during OHTS 1 and 2. The ODRC has photographs from the Collaborative Initial Glaucoma Treatment Study (CIGTS), which show progression, i.e., progression of glaucomatous disc damage in an eye that already had damage. Certification occurs at four levels.

Part I. Recognition of optic disc characteristics (e.g., giant drusen of the disc)

Training: A teaching set contains at least one example of optic disc characteristics: poor and unacceptable stereo and clarity, focal pallor and diffuse pallor, non-glaucomatous atrophy, optic disc coloboma, congenital pit, disc drusen, notch in the rim, and disc hemorrhage.

Testing: The test set includes at least one example of each optic disc characteristic. Special attention is paid to localized thinning of the neuroretinal rim. Competent readers should have no trouble detecting obvious entities such as optic disc drusen. The most important test is to verify that the prospective reader recognizes a thinned neuroretinal rim. Two test sets are available so that if the prospective reader fails the first test (100% correct identification expected) the second set is used after further training. If the prospective reader passes on the first attempt, the second set is reviewed for additional experience.

Part II. Quantifying the cup/disc ratio

Training: The Director/Senior Reader of the ODRC reads photographs with the trainee simultaneously. Grading the photos side by side with an experienced reader has been demonstrated to be an effective method of training new readers.

Testing: When the Senior Reader believes the trainee is sufficiently competent at reading disc photos, the trainee will review the photographs independently. The trainee's results will not be used for study purposes, but will be compared with the readings of the Senior Reader. On 50 consecutive sets, the vertical C/D ratio must be within 0.1 of the Senior Reader. For example, the candidate may designate 0.3 in one eye and 0.5 in the other. This would be an

acceptable match with 0.4 and 0.6 reading of the Senior Reader, but would not be a match with 0.4 and 0.7 readings. If the candidate fails to correctly grade 50 consecutive correct readings, the count for 50 consecutive correct readings begins again and continues until 50 consecutive correct responses are given.

Part III. Judgment of Change in a Normal Disc

Training: The trainee will grade stereo pairs side by side with a Senior Reader until is deemed ready to be tested to detect changes in the appearance of a normal optic disc.

Testing: As in Part I, successful match with the reading of a Senior Reader in 50 consecutive stereo pairs of disc photographs with at least 3 demonstrating disc change are required for certification of judging change in a normal disc. One false positive reading in the set of 50 is permitted. All true positive cases must be correctly identified.

The trainee is certified as a reader to judge change in a normal disc after successfully completing parts I, II and III.

Part IV. Judgment of Change in a Glaucomatous Disc

Training: The trainee will grade stereo pairs side by side with a Senior Reader until the trainee is deemed ready to be tested.

Testing: As in Part I, successful match with the reading of a Senior Reader in 50 consecutive stereo pairs of disc photographs (same set of 50 as above), with at least 3 demonstrating change in a glaucomatous disc, are required for certification of judging progression. One false positive reading of change in the set of 50 is permitted. All true positive cases must be correctly identified.

The trainee is certified as a reader to judge change in a glaucomatous disc after successfully completing parts I, II, III, and IV.

12.7.3 Logging in Photographs from Clinical Centers

- Upon receipt of photographs in a file sent by WUStL Box, the ODRC reader compares digital contents with the transmittal log file which lists intended contents. The ODRC contacts the clinical center when there are inconsistencies.
- The ODRC reader assigns a unique tracking number (two alpha and three numeric characters provided by the Statistical Coordinating Center) to the photograph for the right eye and another unique tracking number for the left eye. This masks the readers to the information such as clinic, date of the photographs, visit.
- The reader logs in the photographs received in the "Daily Photo Receipt Log Sheet" and enters into a computer log.
- The biostatisticians will queue the appropriate digital photographs for the ODRC to assess and compare. For eyes without previous optic disc conversion and for eyes

with conversion by visual field alone, the photographs will be the baseline from OHTS 1 and the follow-up OHTS 3 photograph. For those eyes which showed optic disc conversion in OHTS 1 or 2, the “baseline” photograph will be the first one which showed optic disc conversion in OHTS 1 or 2, and the follow-up OHTS 3 photograph. On presentation all photographs are masked with respect to the visit on which they were taken; the readers are not aware of which photos were taken at the initial OHTS 1 baseline, OHTS 1 or 2 conversion, or OHTS 3 follow up.

12.7.4 Creation of Digital Stereoscopic Optic Disc File

As described earlier, all photographs from OHTS 1 and 2 have been previously digitized. The readers at the ODRC will crop and combine digital or digitized optic disc photographs originally captured with a sequential fundus camera into stereoscopic images using Adobe Photoshop Elements 12. Digital or digitized photographs originally captured with a simultaneous fundus camera do not require post-image capture manipulation.

12.7.5 Storage of Optic Disc Photographs

Digital photographic files will be stored on a password-protected server which will be backed up daily by University of Miami Information Technology.

12.7.6 Evaluation of Stereo and Clarity

- Only technically acceptable photographs will be evaluated for change. Photographs will be displayed simultaneously and in random order on two 11” X 17” computer monitors and viewed stereoscopically using a hand-held stereoscope (Screen-VU, Portland, OR). The stereoscope allows the reader to achieve stereoscopic vision by fusing the pair of images into a single three-dimensional image
- Each ODRC reader will independently assess stereo and clarity on a five-point scale: excellent, good, fair, poor, unacceptable. If there is disagreement of greater than one point on clarity or stereo, or between "poor" and "unacceptable," the readers will come to a consensus. If they cannot, the Senior Reader will adjudicate
- If one reader grades an "unacceptable," retake photos will automatically be requested. The reader does no further grading of a stereo pair judged "unacceptable"
- A final grade of "poor" for clarity or stereo demands retake; however, the reader completes the grading form for change
- If retakes are needed, the ODRC contacts the clinical center to request that photographs be retaken within one week and discusses the reason for additional photographs

If readers disagree on technical quality, they will review the images and come to a consensus.

We expect the experienced photographers from the clinical centers to provide good quality images. The Principal Investigator should send a note to the ODRC if he believes that image

quality is poor due to patient dependent factors such as media opacities or inability to cooperate and there is no hope for improvement by a retake.

12.7.7 Disc Change Assessment

Custom developed software will arrange photographs from “baseline” and follow-up on side-by-side computer screens in alphabetic order by tracking number, thus masking which is the “baseline” and which is the follow-up photograph. For eyes where glaucomatous optic disc damage was determined by the Endpoint Committee in OHTS 1 or OHTS 2, the “baseline” photograph will be the photograph from the first visit at which conversion was detected.

Each primary reader will determine independently if the two stereo pairs are different and identify which photograph is “baseline” and which is follow-up. The reading is positive for optic disc change only if the temporal order is judged correctly.

If it is judged that the “baseline” photograph shows “more damage” than the follow-up, this finding is noted, however, it will not be called progression. It will be documented in the database as “reversal of cupping”.

Optic nerve change is defined for OHTS 3, as in OHTS 1 and 2, 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 or development of a notch is also evidence of change. The development of an optic nerve hemorrhage or a visible nerve fiber layer defect is not an endpoint for optic nerve change.

To minimize false positives and to assure uniform reading, the Senior Reader will adjudicate any set in which one or both of the readers report change. When the ODRC has decided there is suspected change, the ODRC Assistant Director will e-mail the clinical center Coordinator within one working day to request confirmation photographs.

12.7.8 Confirmatory Change Photographs

ODRC Assistant Director will notify the clinical center Coordinator and Principal Investigator by e-mail to schedule the participant for a confirmatory photograph after the ODRC determines optic disc change from study entry has occurred. Confirmatory photographs must be taken as soon as possible (within 3 months of the ODRC request).

The masked reading of confirmatory photographs is conducted in an identical fashion to all other photographs, and is not identified as "confirmatory", i.e., the readers are masked that previous photographs were judged to show optic disc change.

If the ODRC determines that the confirmatory photographs show optic disc change, the biostatisticians will inform the ODRC Assistant Director who will notify the Coordinating Center, which in turn notifies the Endpoint Committee. The ODRC then prepares a digital file of all the photographs in the participant file and sends them by WUSTL Box to the Coordinating Center.

If the confirmatory photographs graded by the two readers do not show disc change, then the Clinical Coordinator and Principal Investigator at the clinical center are notified that change has not been confirmed.

12.8 Quality Control Procedures

- I. Quality control procedures seek to ensure that disc change from baseline is reproducible over time. This process involves inserting masked photographs into the stream of current study photographs given to the readers for evaluation. The biostatistician will insert the quality control photographs and they will appear no different than other photographs to be read.
- II. All usual ODRC procedures are followed for each pair of test photographs until a determination of change or no change from baseline has been made.
 - Three sets of photographs will be used for Quality Control purposes. The readers compare stereo follow-up images and baseline images
 - Set 1 consists of 50 normal stereo optic nerve photographs, which were randomly selected from the photographs of participants who have not demonstrated optic disc conversion as confirmed by the Endpoint Committee in OHTS 1 or OHTS 2. Quality control readings of Set 1, the normal photographs without change are considered in agreement with the original determination if both readers score them as no change; or if a consensus is needed, the consensus is no change. The readings are considered not in agreement with the original determination if they are scored as change, even though no confirmation photo was obtained. The relevant 35mm slides from OHTS1 and 2 will need to be scanned and combined to create a digital stereoscopic optic disc file
 - Set 2 will consist of 72 stereo photographic pairs (36 annual and 36 confirmation photographs) which the OHTS Endpoint Committee determined showed optic disc conversion due to primary open angle glaucoma. Readings of conversion photographs are considered in agreement with the original determination if both readers read them as showing disc change. The confirmation photographs must also be judged as showing change from baseline. Any other outcome is considered not in agreement. The relevant 35mm slides from OHTS1 and 2 will need to be scanned and combined to create a digital stereoscopic optic disc file
 - Set 3 will consist of 40 stereo photographic pairs from the Collaborative Initial Glaucoma Treatment Study (CIGTS): 20 pairs, which the ODRC determined had glaucomatous optic disc changes at baseline and no optic disc progression at five years; and 20 pairs which the ODRC determined had optic disc change at baseline and which the ODRC and CIGTS Endpoint Committee decided showed optic disc progression at the five-year follow-up visit. Readings of progression photographs are considered in agreement with the original determination if both readers read them as showing change. The ODRC used

the same protocol for CIGTS as they used for OHTS 1 and 2 with the exception that there are no confirmation photographs. The relevant 35 mm slides from CIGTS will need to be scanned and combined to create a digital stereoscopic optic disc file

- All Quality Control photographs are masked to appear as ordinary study photographs. The readers are unaware that these photographs are part of Quality Control Sets
- Agreement between the original study readings and the quality control readings of these photographs will be tabulated and reported to the Coordinating Center. Agreement of the total grading process for the ODRC is also quantified with the kappa statistic

12.9 Data Management

12.9.1 Data Entry

Data will independently be entered to computer files from the paper forms by the two readers (See Appendix). Paper forms completed by the Senior Reader data will be entered to computer files by one of the primary readers. The ODRC will also keep a paper and a computer log including participant ID number, eye, date photograph was taken, date of receipt of each photograph at the ODRC, and date readers read photographs, date of consensus.

12.9.2 Report Generation

The ODRC will produce semi-annual reports for Steering Committee meetings. These reports include the following information:

- I. Summary of Reading Center Activity
 1. Certification
 - a. Number of photographers certified by month
 - b. Number of photographers per site and equipment
 2. Number of units/participants:
 - a. Logged in by month, total to date
 - b. Under review
 - c. Completed review

(The balance of the report is based on photographs that have been reviewed)

- II. Technical Quality/Performance at Clinic
 1. Number and percentage (n, %) failing technical criteria for clarity or stereo and requiring retake photographs
 2. Tabulation by clinic/photographer with regard to ranking of photographs for clarity, stereo, percentage retake required, and protocol violations

III. Technical Quality at Optic Disc Reading Center

1. Intergrader Agreement

IV. Timeliness

1. Number of days from date of photographs to receipt at ODRC
 2. Number of days from receipt at ODRC center to completion of the evaluation process
 3. Number of days from date of photographs to transmission of data to Coordinating Center
-

12.10 References

- 1 Feuer WJ, Parrish RK 2nd, Schiffman JC, Anderson DR, Budenz DL, Wells MC, Hess DJ, Kass MA, Gordon MO. The Ocular Hypertension Treatment Study: reproducibility of cup/disk ratio measurements over time at an optic disc reading center. *Am J Ophthalmol.* 2002 Jan; 133(1):19-28. PMID: 11755836
- 2 Parrish RK 2nd, Schiffman JC, Feuer WJ, Anderson DR, Budenz DL, Wells-Albornoz MC, Vandenbroucke R, Kass MA, Gordon MO; Ocular Hypertension Treatment Study Group. Test-retest reproducibility of optic disk deterioration detected from stereophotographs by masked graders. *Am J Ophthalmol.* 2005 Oct; 140(4):762-4. PMID: 16226544
- 3 Budenz DL, Anderson DR, Feuer WJ, Beiser JA, Schiffman J, Parrish RK 2nd, Piltz-Seymour JR, Gordon MO, Kass MA; Ocular Hypertension Treatment Study Group. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. *Ophthalmology.* 2006 Dec; 113(12):2137-43. Epub 2006 Sep 25. PMID: 16996592

Rev. Jul 29, 2015

OHTS Optic Disc Reading Center Photographer Certification Checklist

CLINIC: __ __

Photographer's Name: _____

E-mail: _____ **Phone #:** _____

Camera make/model: _____ **Serial #:** _____

PATIENT #1

Right Eye

	Labeling	Technical Quality
Set 1	(Yes__No__)	(Yes__No__)
Set 2	(Yes__No__)	(Yes__No__)

Left Eye

	Labeling	Technical Quality
Set 1	(Yes__No__)	(Yes__No__)
Set 1	(Yes__No__)	(Yes__No__)

PATIENT #2

Right Eye

	Labeling	Technical Quality
Set 1	(Yes__No__)	(Yes__No__)
Set 2	(Yes__No__)	(Yes__No__)

Left Eye

	Labeling	Technical Quality
Set 1	(Yes__No__)	(Yes__No__)
Set 1	(Yes__No__)	(Yes__No__)

Certified (Yes__ No__)

If Yes, Date: ___ - ___ - ___

Certification Number: _____

If not certified, ODRC will contact Photographer

Comments:

OPTIC DISC READING CENTER QUALITY & FOLLOW-UP FORM

	TRACKING #					TRACKING #				
	—	—	—	—	—	—	—	—	—	—
EYE			R	L				R	L	
CLARITY			E	G	F P U			E	G	F P U
STEREO			E	G	F P U			E	G	F P U
Is RETAKE wanted?			Y	N				Y	N	

GLAUCOMATOUS DISC HEMORRHAGE (if yes in either photo) #___ Loc ___	Y	N	___	___	___	#___ Loc ___	Y	N	___	___	___
RETINAL HEMORRHAGE	Y	N				Y	N				
NON-GLAUCOMATOUS ATROPHY	Y	N				Y	N				
INCREASE IN CRESCENT	Y	N				Y	N				
INCREASE IN CONSTRICTION	Y	N				Y	N				
VERTICAL C/D RATIO	___	.	___	___		___	.	___	___		
HORIZONTAL C/D RATIO	___	.	___	___		___	.	___	___		
SUSPICIOUS FOR GLAUCOMATOUS DAMAGE	Y	N				Y	N				

PROGRESSION CRITERIA:

NEW THINNING OF DISC RIM (if Y or P)	Y	P	Q	N	Y	P	Q	N
			Focal				Diffuse	
	Max	___	___	___	Range	___	___	___
NOTCH IN RIM (Location if Y or P)	Y	P	Q	N	Y	P	Q	N
INCREASED LOCAL PALLOR	Y	P	Q	N	Y	P	Q	N
INCREASED DIFFUSE PALLOR	Y	P	Q	N	Y	P	Q	N
CHANGE IN C/D RATIO	Y	P	Q	N	Y	P	Q	N
OTHER (If yes, specify _____)	Y	P	Q	N	Y	P	Q	N

<u>DISC DAMAGE HAS OCCURRED</u>	<u>Y</u>	<u>P</u>	<u>Q</u>	<u>N</u>
If yes, these photos are	<u>Base</u>	<u>Foll</u>	<u>Base</u>	<u>Foll</u>

ENDPOINT CONFIRMATION PHOTOS? Y N

COMMENTS:

Date photos read ___ - ___ - ___ Reader ID ___ - ___ - ___

OHTS 3 FOLL.002 9/30/15

OPTIC DISC READING CENTER ADJUDICATION FORM

	TRACKING #		TRACKING #	
EYE	R	L	R	L
GLAUCOMATOUS DISC HEMORRHAGE (if yes in either photo) #___ Loc ___	Y	N	Y	N
RETINAL HEMORRHAGE	Y	N	Y	N
NON-GLAUCOMATOUS ATROPHY	Y	N	Y	N
INCREASE IN CRESCENT	Y	N	Y	N
INCREASE IN CONSTRICTION	Y	N	Y	N
VERTICAL C/D RATIO	___	. ___	___	. ___
HORIZONTAL C/D RATIO	___	. ___	___	. ___
SUSPICIOUS FOR GLAUCOMATOUS DAMAGE	Y	N	Y	N

PROGRESSION CRITERIA:

NEW THINNING OF DISC RIM (if Y or P)	Y	P	Q	N		Y	P	Q	N
			Focal			Diffuse			
			Max	___		Range	___	___	
NOTCH IN RIM (Location if Y or P)	Y	P	Q	N	___	Y	P	Q	N
INCREASED LOCAL PALLOR	Y	P	Q	N		Y	P	Q	N
INCREASED DIFFUSE PALLOR	Y	P	Q	N		Y	P	Q	N
CHANGE IN C/D RATIO	Y	P	Q	N		Y	P	Q	N
OTHER (If yes, specify _____)	Y	P	Q	N		Y	P	Q	N

<u>DISC DAMAGE HAS OCCURRED</u>	<u>Y</u>	<u>P</u>	<u>Q</u>	<u>N</u>	
If yes, these photos are	<u>Base</u>	<u>Foll</u>			<u>Base</u> <u>Foll</u>

COMMENTS:

Date photos adjudicated ___ - ___ - ___

Senior Reader ID ___ - ___ - ___

How to Convert TIFF Files into JPEG Files Using Paint

1. Locate the TIFF file you want to convert into JPEG in your computer.
2. Right click the file and on the pop-up menu point to Open With.
3. Select by clicking on Paint, opening a Paint window.
4. Click File then click on Save As. On the pop-up menu select JPEG picture.
5. Name the file and click Save.

13 Optical Coherence Tomography Reading Center (OCTRC)

Chapter 13 OCTRC Version Change Log			
New Version	Effective Date	Section	Description of Change
4.0	8/24/2016		No changes to this chapter
3.0	4/1/2016		No changes to this chapter of OHTS MOP
2.1	11/10/2015	13.10	Added directions for Forum users for Cirrus.
2.0	11/5/2015	13.4, 13.13	Added Spectralis scan types RNFL Circle and P.Pole and removed GMPE scan types ONH-RC, P.PoleH and P.PoleV. Changed Spectralis software version requirements to 5.4 or higher.
		13.12, 13.13	Updated USB data transfer directions and shipping directions. USB drives are to be sent to Wash. University.

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13.1 Overview

The Optical Coherence Tomography Reading Center (OCTRC) is located within the UCSD Hamilton Glaucoma Center in the Department of Ophthalmology at the University of California, San Diego. The OCTRC is responsible for certification of OCT technicians, processing and reviewing the quality of spectral domain optical coherence tomography (SDOCT) scans for the Ocular Hypertension Treatment Study (OHTS): 20-Year Follow-up. This manual contains specific information regarding Spectralis and Cirrus spectral domain SDOCT image acquisition and processing for the OHTS 20-Year Follow-up Study.

Certified SDOCT operators should be familiar with all aspects of the *Spectralis Operating Instructions Manual* provided with the Spectralis Instrument by Heidelberg Engineering or the *Cirrus User Manual* provided with the Cirrus Instrument by Carl Zeiss Meditec, Inc. The *OCTRC Manual of Procedures* should be used in conjunction with the *Spectralis Operating Instructions Manual* and *Operation Software Release Updates* or the *Cirrus User Manual* and *Operation Software Release Updates*, but should not replace them.

13.2 OCTRC Personnel

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13.2.1 Roles of OCTRC Personnel

Dr. Linda Zangwill serves as Director of the OCT Reading Center (OCTRC), which will process and review spectral domain optical coherence tomography retinal nerve fiber layer and ganglion cell layer images. Specifically, she will oversee protocol development, training of OCTRC staff for quality assessment and for providing PDFs of printouts to Endpoint Committee review, certification of Clinical Center staff, and analysis and interpretation of results and manuscript preparation.

Keri Dirkes, the OCTRC supervisor, will oversee all operations of the OCTRC. Specifically, she will oversee database development, protocol development, certification of OCTRC staff, certification of imaging operators from the 33 Clinical Centers, image processing and standardized review of Cirrus and Spectralis SDOCT scans. Ms. Dirkes will also be responsible for working with instrument manufacturers to ensure appropriate study-specific software set-ups with the 33 Clinical Centers and for troubleshooting technical issues with Clinical Centers and instrument manufacturers. She will also oversee communication with study Clinical Centers and the Coordinating Center (CC).

Suzanne Vega will assist Ms. Dirkes in the implementation of the SDOCT protocol. Specifically, she will assist in the certification of imaging operators, image processing and review of the SDOCT scans, communication with study Clinical Centers and the CC. In addition, she will serve as a reviewer for the SDOCT scans.

Maria Hunsicker will also assist Ms. Dirkes with the certification of imaging operators, image processing and review of the SDOCT scans and communication with study Clinical Centers. In addition, she will serve as a reviewer for the SDOCT scans.

13.3 General Participant Preparation

13.3.1 Participant ID Format

The OHTS participant ID consists of a 5 digit OHTS ID i.e.19001.

13.3.2 Participant Visits

Participants will have 2 types of OCT scans acquired on both eyes on either the Spectralis or Cirrus instrument at a single OHTS visit to provide RNFL thickness measurements and macular or ganglion cell complex measurements. Technicians should test a participant even if he/she may appear “unable” to perform reliably due to dementia, muscular skeletal problems, poor vision or poor fixation, etc... In addition, all scans should be submitted to the OCTRC with an explanation for poor quality in the comment section of the transmittal log.

13.4 Spectralis Imaging Procedures

The Spectralis OCT is a spectral-domain optical coherence tomography system that allows high-speed, high-resolution cross-sectional imaging of the retina. This section is based on the *Spectralis User Manual 5.4 (October 2011)* that is relevant to image acquisition, archiving, backing-up, data exporting and transfer, and the *Spectralis 5.4 Release Notes*.

For the OHTS Study, imaging will be performed with a non-dilated pupil, unless:

- The pupils are smaller than 2.5 mm, or
- The pupils have been dilated for another test, or
- The OCT image quality is low, or
- If in the opinion of the investigator, dilation is required

13.4.1 Quality Criteria for Spectralis Images

- Quality number > 15 and ART Mode > 50 (for RNFL circle scans only)
- Scan centered on the optic disc (for RNFL circle scan) or centered on the fovea (for macula scan)
- Vessels well aligned
- Scan is well centered on screen
- Uniform illumination with the focus sharp and clear
- Few to no artifacts present
- All scans are to be acquired by an OHTS certified technician

13.4.2 Spectralis Software

The Spectralis OCT is a spectral-domain optical coherence tomography system that allows high-speed, high-resolution cross-sectional imaging of the retina.

All participating Clinical Centers should be using Spectralis software 5.4 or higher. Please contact the OCTRC prior to performing any software upgrades.

13.4.3 Spectralis Instrument Parameters Specific for OHTS

Default settings are used for the RFNL Circle Scan and P.Pole scan types.

Table 13.1: Instrument Parameters

RNFL Circle Field	Parameter Settings
Resolution	High-speed
Scan Angle	30°
Circle Diameter	3.6mm
OCT ART Mode	100

P. Pole Field	Parameter Settings
Resolution	High-speed
Scan Angle	30°
# of B-Scans	61
OCT Pattern Size	30° x 25°
IR ART Mode	9

13.4.4 Entering Spectralis Participant Data

13.4.4.1 Creating a Spectralis Visit for an Existing Patient

For the OHTS study we will be collecting all OHTS participants' previous Spectralis scans acquired as part of regular clinical care, in addition to the scans acquired at the OHTS study visit. To ensure all patient scans are under one patient record it is important to search for OHTS participants in your site's Spectralis instrument using the participants name, MRN or ID specific to your clinical practices. De-identifying the patient (adding OHTS ID) will take place when exporting scans for transfer to the OCTRC.

Once you have located the participant on the Spectralis instrument, the scans for the OHTS visit should be acquired, see section "Acquiring Spectralis Images". If the participant has never had Spectralis scans acquired on your site's Spectralis instrument, follow steps below for creating a new database entry with new participant data.

13.4.4.2 Creating a New Database Entry with New Participant Data

If an OHTS participant does NOT have previous Spectralis scans acquired as part of their regular clinic visit, it is necessary to create a new database entry by entering the data for a new participant. If there are previous scan visits available, see section "Creating a Spectralis Visit for an Existing Patient" above.

- To create a new participant, click on the **New Patient** symbol  in the tool bar or select **Record** in the main tool bar and choose **New Patient**. A dialog box will appear. Participant data must be entered according to the standard protocol. Fill in the patient information (see '**Patient Data**' Table below). Then select **OK**.

Table 13.2: Patient Data

Last:	Enter OHTS ID (5 digit ID), Example 19123
First:	Enter Site ID , Example S1
Title:	<i>Leave blank</i>
Date of Birth:	mm/dd/yyyy
Sex:	Choose Male or Female from dropdown
Patient ID:	Enter OHTS ID (5 digit ID), Example 19123
Ancestry:	<i>Leave blank</i>

- After creating a new patient record, another dialog box will appear to set up a new examination. The box is titled “Examination Data.” Fill in the information for this screen (see ‘**Examination Data**’ Table below). Select **OK**.

Table 13.3: Examination Data

Device type:	Choose Spectralis HRA + OCT from the pull down
Operator:	Enter your 3 initials ^a
Study:	<i>Leave blank</i>

^aOperator initials: 3 are required. If there is no middle name, use an ‘X’.

- After entering the examination data, a new dialog box titled “Eye Data” will appear. Enter parameters for the appropriate eye (see ‘**Eye Information Data Entry**’ Table below). Then select **OK**.

Table 13.4: Eye Information Data Entry

C-Curve [mm]:	<i>Leave default 7.7</i>
Refraction [dpt]:	<i>Leave blank</i>
Cylinder [dpt]:	<i>Leave blank</i>
Axis [deg]:	<i>Leave blank</i>
Pupil size [mm]:	<i>Leave blank</i>
IOP [mmHg]:	<i>Leave blank</i>
VFieldMean:	<i>Leave blank</i>
VFieldVar:	<i>Leave blank</i>
Corrective Lens:	<i>Leave default None</i>

*If a k-curve is available it should be used instead of the default. Also if previous Spectralis scans are available, the k-curve from these scans may be used.

13.5 Acquiring Spectralis Images

Acquire two good quality RNFL Circle scans and two good quality P.Pole Scans per eye. The OCTRC will accept up to four RNFL Circle scans per eye and up to four P.Pole scans per eye. See ‘**Required Spectralis Scans**’ Table below. **The scan pattern default presets should be used to acquire all scans.**

Table 13.5: Required Spectralis Scans

Scan Type	Resolution	ART Mode	# of Scans Required per Eye	Max # of Scans OCTRC Can Accept per Eye
RNFL Circle Scan	High-speed	100	2	4
P. Pole Scan	High-speed	9	2	4

13.5.1 Situating the Participant

1. Confirm the participant is not wearing contacts and/or glasses.
2. Add rewetting drops. You may also add additional rewetting drops during imaging as needed. Do not use gel type drops.
3. Ask the participant to position their head and chin firmly against the headrest and chin rest. Have the participant look into the laser-scanning camera and then have them focus on the fixation target, the brightest blue light.
4. The OD/OS buttons show the eye currently being examined with the Spectralis. The eye examined is automatically detected and displayed. Start with the right eye.

13.5.2 Acquiring RNFL Circle Scans

1. On the left side of the camera, move switch to “R” for both study scan types.
2. Press the **yellow start button** on the control panel box and then press the **IR+OCT** button.
3. On the computer screen, in the OCT section, click on the **RNFL Scan** icon . The **default settings, high-speed and ART Mode of 100**, will be used for this study.
4. Confirm the blue fixation light is lit on the control panel. Ask the subject to look at the internal fixation target (brightest blue light).
5. Locate the optic nerve head and center the optic disc by moving the camera head manually. You can also click the mouse on the circle scan pattern to grab it and center it on the optic nerve. Use the focus knob to adjust the focus of the optic nerve. The brightness may have to be adjusted by turning the **Filter Wheel (black round button)** on the control panel.
6. Wait for the red circle scan pattern centered on the ONH of the IR image to turn **blue** on left side of screen.
7. Slowly move the camera toward the subject’s eye until the **OCT scan** appears in the middle of the right screen on the computer. Confirm the subject’s forehead stays pressed to the headrest.
8. Once the optic disc is in focus and the RNFL scan is in the middle of the screen on the right, press the **Filter Wheel (black round button)** on the control panel. This will start the eye tracker.
9. Wait for “ART 100 Frame” blue bar to get as close to 100 as possible. Monitor the live OCT scan box in the lower right of the screen and make sure the scan is not too high or low and the blue quality bar is as far to the right as possible.
10. Tell the subject to hold still and not blink and press **Acquire**.
11. If all still looks good, press **Acquire** again.
12. Press **Save Images** at the top left of the screen.
13. After acquiring two scans, repeat the above steps for the left eye.

14. Press **Save Images** at the top left of the screen and exit the screen by pressing the **red X** on the right side of the screen.

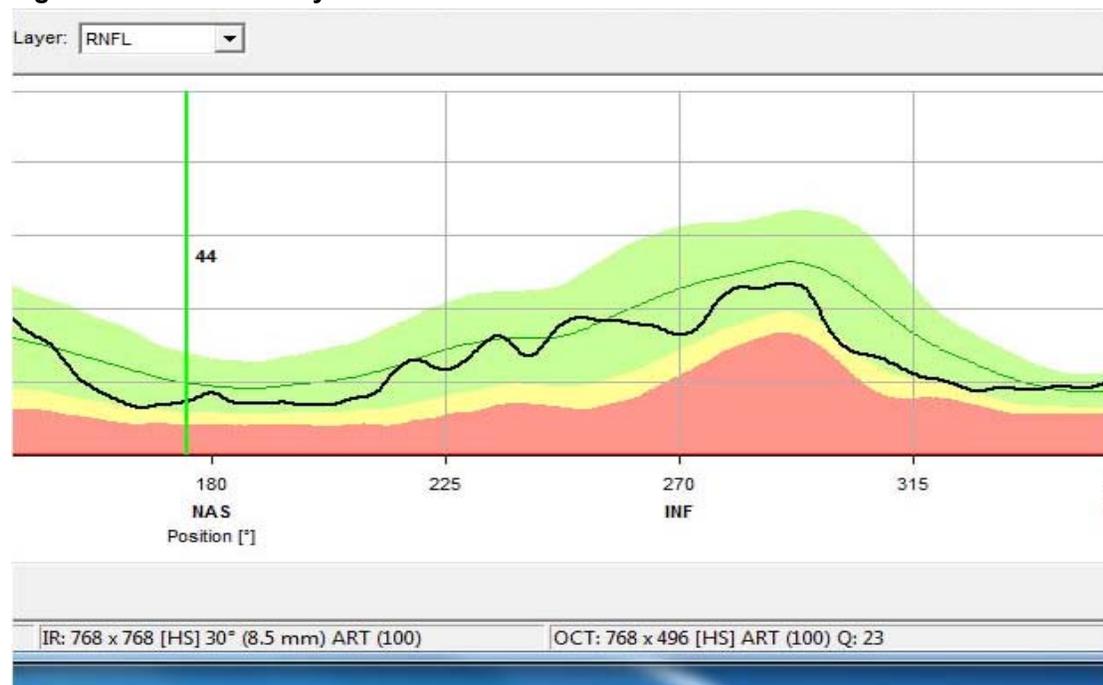
Reviewing Acquired RNFL Scans

15. Double click on each scan icon and choose **Thickness Profile** tab to review. The scan quality information is located on the lower right side of the image. See ‘**Scan Quality Info**’ **Figure 1**. A good quality image should have the following:

- Bottom right corner next to “OCT:” in **Figure 1**, “HS” indicates image was taken in high-speed mode.
- Bottom right corner next to “OCT:” in **Figure 1**, the **number next to “ART”** indicates **ART Mode**. The ART Mode should be 50 or higher.
- Bottom right corner next to “OCT:” in **Figure 1**, the **number next to “Q”** indicates the **quality score**. The quality score should be 15 or higher.
- Confirm circle scan is centered on the optic disc.
- Confirm IR image has uniform illumination with the focus sharp and clear
- Confirm there are few to no artifacts present.

16. If the Quality number (≤ 15) or ART Mode (< 50) is low, the image should be re-taken. If, after several attempts, it is not possible to get higher, still send the images to the OCTRC. The OCTRC will decide if they can be used for analysis.

Figure 13.1: Scan Quality Info



13.5.3 Acquiring P.Pole Scans

1. On the left side of the camera, move switch to “**R**” for both study scan types.
2. After taking the RNFL Circle scans, single click on the same subject on the right side of the screen and click the **Continue Examination** icon . Click **Yes** when asked if you are sure you want to re-examine patient.
3. Press the **yellow start button** on the control panel box and then press the **IR+OCT button**.
4. On the computer screen, in the OCT section, click on the **P. Pole** icon . The **default settings, high-speed and ART Mode of 9**, will be used for this study. Note that the scan pattern is slightly tilted.
5. Confirm the blue fixation light is lit on the control panel. Ask the subject to look at the internal fixation target (brightest blue light). FoDi alignment is dependent upon good fixation for this scan type.
6. Focus the scan on the macula. Use the appropriate knobs on the camera mount to move the laser scanning camera left, right, up or down so that the visible laser enters the eye through the center of the pupil.
7. Wait for the red scan pattern to turn **blue** on the IR image on left side of screen.
8. Slowly move the camera toward the subject’s eye until the **OCT scan** appears in the middle of the right screen on the computer. Confirm the subject’s forehead stays pressed to the headrest.
9. Press the **Filter Wheel (black round button)** on the control panel. This will start the eye tracker.
10. Press **Acquire**. During live acquisition, the OCT scan that is displayed is the center most scan in the scan pattern. When actual scanning takes place after pressing the **Acquire** button, scan acquisition begins with the bottom scan. For this reason, try and lower the OCT scan that is used during live acquisition so that when this shift occurs, the first few scans are not cut off.
11. Monitor the live OCT scan box in the lower right of the screen and make sure that the scan is not too high or too low and that the blue quality bar is as far to the right as possible. Make adjustments to the camera as needed.
12. Press **Save Images** at the top left of the screen and exit the screen by pressing the **red X** on the right side of the screen.
13. To take another P. Pole scan, click the **Continue Examination** icon . Click **Yes** when asked if you are sure you want to re-examine the patient. Follow the above steps to take the second P. Pole scan.
14. When the second scan has been taken, press **Save Images** at the top left of the screen and exit the screen by pressing the **red X** on the right side of the screen.
15. After acquiring two scans, repeat the above steps for the left eye.

Reviewing Acquired P. Pole Scans

16. Once scans are finished for both eyes, double click on each scan icon and choose **Thickness Profile** tab to review. The scan quality information is located on the lower right side of the image. See ‘**Scan Quality Info**’ **Figure 1**. A good quality image should have the following:

- Bottom right corner next to “OCT:” in **Figure 1**, “HS” indicates image was taken in high-speed mode.
 - Bottom right corner next to “OCT:” in **Figure 1**, the **number next to “Q”** indicates **quality score**. Quality score should be 15 or higher.
 - Confirm scan is centered on the macula.
 - Confirm there is uniform illumination with the focus sharp and clear.
 - Click the play icon  to show movie, which will show all b-scans for the image. Confirm there are few to no artifacts present, the scan is not inverted or clipped at the top or bottom, and it is centered horizontally and vertically.
17. If the Quality score is low (≤ 15) or the scan is poor quality for another reason, the image should be re-taken. If after several attempts it is not possible to get a better image, send the available images to the OCTRC. The OCTRC will decide if they can be used for analysis.

13.6 Exporting Spectralis Images

On a monthly basis, send all OHTS Spectralis scans (previously acquired and scans from the OHTS visit) to the OCTRC. If you have more than one Spectralis instrument, check to see if any OHTS patients seen in the last month have previously acquired scans taken as part of regular clinical care and send them to the OCTRC.

13.6.1 De-identifying Spectralis Scans by Adding OHTS ID

All Spectralis scans previously acquired as part of regular clinical care and the scans acquired at the OHTS visit are transferred to the OCTRC. Prior to exporting the scans, all patient names and/or MRNs must be replaced with the OHTS ID. If scans acquired previously, as part of regular care, are available on another instrument in your clinic, they should also be de-identified.

NOTE: after the scans have been exported, the OHTS ID and Site ID can be changed back to the patient’s name and/or MRN.

The OHTS ID must be entered according to standard protocol format.

1. Search for the participant in the Spectralis instrument using the participant’s name, MRN or ID specific to your clinic practices.
2. Double click on the participant and click the box labeled **Patient** at the top of the screen. A “Patient Data” box will appear.
3. Replace name or MRN with **OHTS ID** in “Last” name and “Patient ID” fields. Replace first name with **Site ID** in “First” name field (see ‘**Spectralis Patient Data Fields to Be De-Identified**’ Table below).

Table 13.6: Spectralis Patient Data Fields to Be De-Identified

Last:	Enter OHTS ID (5 digit ID), Example 19123
First:	Enter Site ID , Example S1
Patient ID:	Enter OHTS ID (5 digit ID), Example 19123

4. Click **OK**
5. Repeat these steps for all OHTS patients seen that month. Once all patient names and/or MRNs have been replaced with OHTS IDs, begin the exporting process below.
6. Repeat the above steps on any additional Spectralis instruments containing the OHTS patients, who were seen in the last month, that have previously acquired scans taken as part of regular clinical care.

13.6.2 Batch Exporting Monthly Spectralis Images to Send to OCTRC

On a monthly basis, send all OHTS Spectralis scans acquired during the OHTS visit and previous scans taken as part of regular clinical care. The steps for batch exporting are as follows:

1. Create a new folder on the desktop by right-clicking on the desktop, choosing **New**, and **Folder**. Name the folder using your site ID # (i.e. S1), year and month of the list of images being exported (i.e. 2015Sep) and include “Spectralis” (i.e., S1_2015Sep_Spectralis).
2. Use the filter option to pick the participants that have an OHTS ID. Choose **Database** from the main menu and select **Filter** or click the **Filter icon** .
3. In the **Last** field enter the first to numbers of the OHTS ID (e.g. 19). Do **NOT** check the box, “Show only examinations within the patients that match to this filter”. Only participants with OHTS IDs should be displayed.
4. Click on the circle next to each of the OHTS participants on the left side of the screen that were seen during the previous month to load them to the right side. Only load OHTS participants who were seen in the previous month to the right side of the screen (not non OHTS clinic patients, any patients with names or OHTS patients already transferred to the OCTRC).
5. Once all appropriate participants are loaded, right click on any participant on the right side of the screen. **Select HRA/Spectralis Batch**, then **Export E2E**.
6. An “Export Options” dialog box will appear. Under **Export folder**, click the browse button and choose the appropriate desktop folder created in Step 1. Select **OK**.
7. Do **NOT** check the “Anonymize data” box.
8. Under location, enter your institution, e.g. UCSD. Click **OK**. (Exporting monthly images may take an hour or more).
9. Send all exported images, including previous images taken as part of regular clinical care, to the OCTRC. See section “Transferring OCT Scans to OCTRC” for scan transfer directions.
10. All data transfers must be accompanied by a transmittal log. See section “Transmittal Log” for details.

13.7 Spectralis Archiving and Backing Up

Archiving and backing up should take place at least once a week. All images that are acquired and saved with the Spectralis are initially stored in files on the hard drive of the computer. Since the hard drive has limited storage capacity, these image files must be archived at regular intervals to an additional connected hard drive. Below are the steps for archiving to a dual hard drive.

1. In the main database window, unload any participants that are loaded to the right side of the screen (participants should only be listed on the left of the screen).
2. From the **Database** menu, select **Archive Images**.
3. You will then be asked to select the appropriate hard drive (or network location) from the pull-down menu.
4. The database is automatically backed-up when images are archived to the dual hard drive. It is not necessary to back up the database separately.
5. If participants were selected and not unloaded prior to the archive session, a message will appear asking whether to archive the selected participants only (which are located on the right side of the screen). If **Yes** is selected, only those selected participants will be archived. If **No** is selected, the Heidelberg Eye Explorer software will scan the entire database and archive any exams which have not yet been archived.

13.8 Cirrus imaging procedures

For the OHTS Study, imaging will be performed with a non-dilated pupil, unless:

- The pupils are smaller than 2.5 mm, or
- The pupils have been dilated for another test, or
- The OCT image quality is low, or
- If in the opinion of the investigator, dilation is required

13.8.1 Cirrus Software

The Cirrus HD-OCT is a spectral domain optical coherence tomography system that allows high-speed, high-resolution, cross-sectional imaging of anterior and posterior ocular structures. This section is based on parts of the *Cirrus 6.0.2 User Manual (2012)* that are relevant to image acquisition, archiving, backing-up, data exporting and transfer, and the *Cirrus Addendum Software Version 6.5*.

All participating Clinical Centers should be using the Cirrus software 6.0 or higher. Please contact the OCTRC prior to performing any software upgrades.

13.8.2 Cirrus Scans Specific for OHTS

For OHTS, acquire two good quality **Optic Disc 200x200** scans for each eye, and two good quality **Macular Cube 512x128** scans for each eye. The OCTRC will accept up to four scans per eye for each scan type (see ‘**Required Cirrus Scans**’ Table below).

Table 13.7: Required Cirrus Scans

Scan Type	# of Scans Required per Eye	Max # of Scans OCTRC Can Accept per Eye
Optic Disc Cube 200x200	2	4
Macular Cube 512x128	2	4

13.8.3 Quality Criteria for Cirrus Images

- Signal strength of 7 or higher

- Scan centered on the optic disc for the Optic Disc Cube scan or on the fovea for the Macular Cube scan
- Vessels well aligned
- Uniform illumination with the focus sharp and clear
- Few to no artifacts present
- Scan is well centered on screen
- All Scans are to be acquired by an OHTS certified technician

13.8.4 Entering Cirrus Participant Data

13.8.4.1 *Creating a Cirrus Visit for an Existing Patient*

For the OHTS study we will be collecting all OHTS participants previous Cirrus scans acquired as part of regular clinical care, in addition to the scans acquired at the OHTS study visit.

To ensure all patient scans are under one patient record, it is important to search for OHTS participants in your site’s Cirrus instrument using the participants name, MRN or ID specific to your clinical practices. De-identifying the patient (adding OHTS ID) will take place monthly when exporting scans for transfer to the OCTRC.

Once you have located the participant on the Cirrus instrument, acquire the scans for the OHTS visit (see section “Acquiring Cirrus Images”). If the participant has never had Cirrus scans acquired on your site’s Cirrus instrument, follow the steps below for creating a new database entry with new participant data.

13.8.4.2 *Creating a New Database Entry with New Participant Data*

If an OHTS participant does NOT have previous Cirrus scans acquired as part of their regular clinic visit, it is necessary to create a new database entry by entering the data for a new participant. If there are previous visits available, see section “Creating a Cirrus Visit for an Existing Patient” above.

1. To create a new participant, click the **Add New Patient** tab. For this study, participant data must be entered according to the standard protocol (see ‘**Patient Data**’ Table below).

Table 13.8: Patient Data

Last Name:	Enter OHTS ID (5 digit ID), Example 19123
First Name:	Enter Site ID , Example S1
Middle Name:	<i>Leave blank</i>
Date of Birth:	mm/dd/yyyy
Gender:	Choose Male or Female from drop down
Patient ID:	Enter OHTS ID (5 digit ID), Example 19123

2. Click **More** to enter additional participant information such as “Categories” or “Comments”. Although it is not required, if your Cirrus instrument is also used to acquire im-

ages for non-OHTS participants, you may find it useful to utilize the Category field to tag and identify your OHTS participants.

3. Once all the participant information is entered, click **Save**.

13.9 Acquiring Cirrus Images

13.9.1 Situating the Participant

1. Dim the lights in the room.
2. Add rewetting drops. You may also add additional rewetting drops during imaging as needed. Do not use gel type drops.
3. With the participant selected, click the **Acquire** button to initiate a new exam.
4. Select scan type. Start with Optic Disc Cube 200x200.
5. Obtain both scan types for the right eye, then the left eye.

13.9.1.1 Acquiring Optic Disc Cube 200x200 Scan

1. Begin with the right eye. Position subject's chin in the left chinrest to image the right eye.
2. Choose **Optic Disc Cube 200x200** scan type. Position the subject firmly against the chinrest and forehead rest.
3. Have the subject focus on the internal fixation target (green starburst).
4. Use the chinrest arrow buttons in the live iris view at the top left of the screen to adjust the chinrest so that the red target is aligned to the center of the pupil. If necessary, click the center of the pupil using the mouse to auto center pupil.
5. Use the **Auto Focus** button and arrow buttons in the live fundus view at the bottom left of the screen to adjust the image focus. The **Optimize** button may also be used to bring the image into focus, but **Auto Focus** is preferred.
6. Center the optic disc on the screen in the live fundus view by holding down the **Shift** key while scrolling with the mouse. You can also click to drag the scan pattern to adjust scan pattern placement over the optic disc.
7. Check the scan displays on the right side of the screen to ensure the scans are well centered and not inverted. To adjust the centering of the scan, scroll with the mouse while holding down the **Shift** key. The **Enhance** and **Center** buttons can be used to auto adjust the scans if necessary.
8. When the image view is centered and in focus, and the OCT scans are well centered and strong, instruct the subject to blink and then hold still.
9. Press the **Capture** button. The scan begins when the button is clicked.
10. Review the scan to check for good quality. A good quality image should have the following:
 - Signal strength of 7 or higher
 - Optic disc on lower left of screen is centered and has vessels and disc well aligned (no shifting of vessels or disc)
 - OCT scans on right of screen not cut off and well-centered vertically and horizontally
 - Uniform illumination with the focus sharp and clear
 - Few to no artifacts present
11. If the scan is good quality, click **Save**.

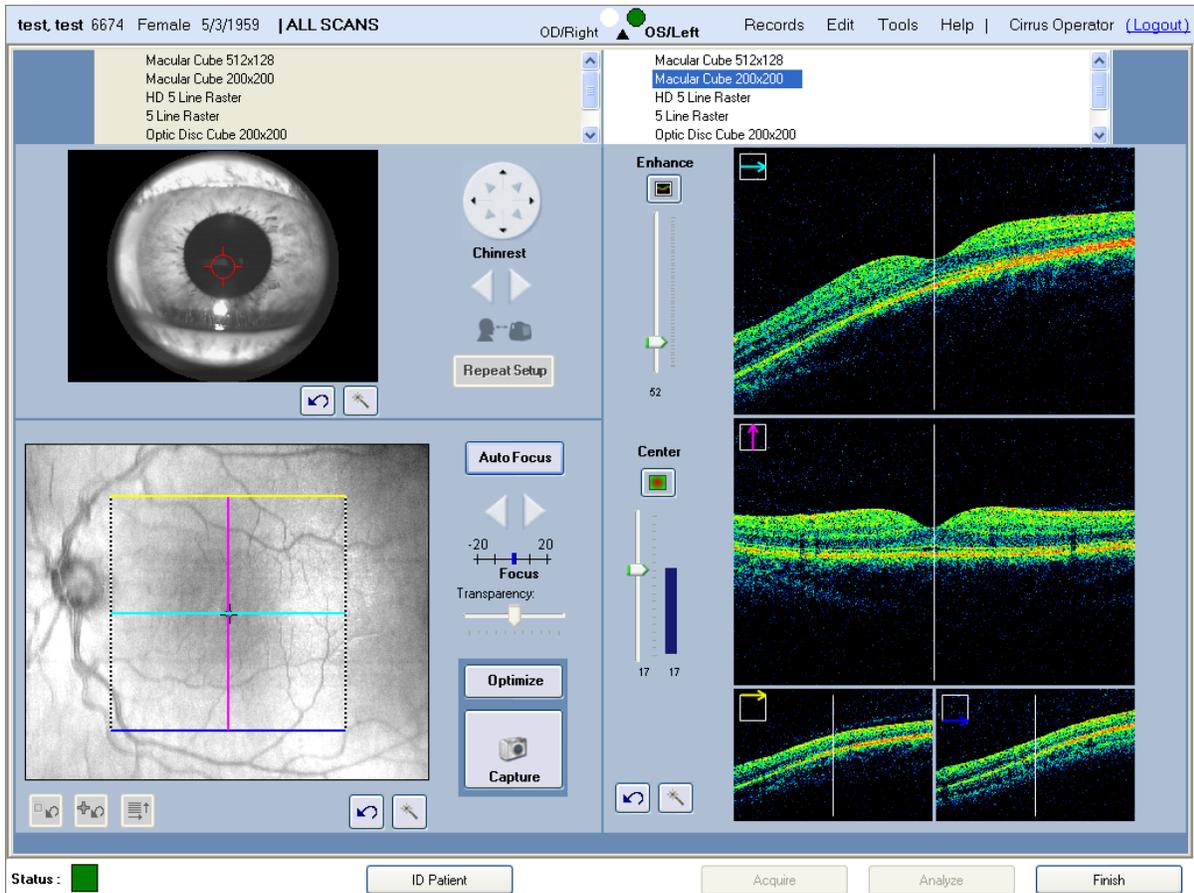
12. Repeat the above steps for the second Optic Disc Cube 200x200 scan.

13.9.1.2 Acquiring Macular Cube 512x128 Scan

1. Still imaging the right eye, choose **Macular Cube 512x128** scan type.
2. Position the subject firmly against the chinrest and forehead rest.
3. Have the subject focus on the internal fixation target (green starburst).
4. Use the mouse and/or chinrest arrow buttons in the live iris view at the top left of the screen to adjust the chinrest so that the red target is aligned to the center of the pupil. If necessary, click the center of the pupil using the mouse to auto center pupil (see '**Acquire Screen**' **Figure** below for an example of the acquire screen).
5. Use the **Auto Focus** button and arrow buttons in the live fundus view at the bottom left of the screen to adjust the image focus. The **Optimize** button may also be used to bring the image into focus, but **Auto Focus** is preferred.
6. Click to drag the scan pattern in the live fundus view to adjust scan pattern placement over the foveal pit.
7. While viewing the scan displays on the right side of the screen, center the scans by holding down the **Shift** key while scrolling with the mouse. Use the **Enhance** and **Center** buttons to auto adjust the scans if necessary.
8. When the image view is centered and in focus, and the scans are well centered and strong, instruct the subject to blink and then hold still.
9. Press the **Capture** button. The scan begins when the button is clicked.
10. Review the scan to check for good quality. A good quality image should have the following:
 - Signal strength of 7 or higher
 - Fovea on lower left of screen is centered and has vessels well aligned
 - OCT scans on right of screen are not cut off and are well-centered vertically and horizontally
 - Uniform illumination with the focus sharp and clear
 - Few to no artifacts present
11. If the scan is good quality, click **Save**.
12. Repeat the above steps for the second Macular Cube 512x128 scan.
13. After scans for both scan types of the right eye are saved, repeat above steps to acquire scans for the left eye.
14. Once both eyes are taken, click **Finish** to return to the **Patient** screen.
15. If both scans acquired are poor quality, the operator may take a third scan if they believe they can get a higher quality scan. This is at the discretion of the operator.

Even if after several attempts it is not possible to get a higher score or good quality scan, still send the images to the OCTRC. The OCTRC will decide if the images can be used for analysis.

Figure 13.2: Acquire Screen



13.10 Exporting Cirrus Images

On a monthly basis, send all OHTS Cirrus scans (previously acquired and scans from the OHTS visit) to the OCTRC. If you have more than one Cirrus instrument, check to see if any OHTS patients seen in the last month have previously acquired scans taken as part of regular clinical care and send them to the OCTRC.

13.10.1 De-identifying Cirrus Scans by Adding OHTS ID

All Cirrus scans previously acquired as part of regular clinical care and the scans acquired at the OHTS visit are transferred to the OCTRC. Prior to exporting the scans, all patient names and/or MRNs must be replaced with the OHTS ID. If scans acquired previously, as part of regular care, are available on another Cirrus instrument in your clinic, they should also be de-identified.

13.10.1.1 De-identifying Cirrus Scans in FORUM

If your Cirrus instrument(s) are connected to a Forum archive, you must replace the patients name with the OHTS ID in Forum before exporting your scans from the Cirrus instrument. Images **MUST** be exported from a Cirrus instrument (not Forum).

1. To de-identify a patient on Forum, in the main menu, go to **Patient** and **Patient Administration**.
2. Look up patient and then click to highlight patient record. Click on **Edit Patient** and replace “Last Name” and “Patient ID” with OHTS ID and “First Name” with site ID. Click **Save**.
3. See directions in section below “Batch Exporting Monthly Cirrus Images to Send to OCTRC” for exporting scans from your Cirrus instrument.
4. Repeat these steps for all OHTS patients seen that month. Once all patient names and or MRNs have been replaced with OHTS IDs in Forum, begin the exporting process below from your Cirrus instrument.
5. After the scans have been exported from the Cirrus instrument, the OHTS ID can be changed back to the patient’s name and/or MRN in Forum.

13.10.1.2 De-identifying Cirrus Scans in Cirrus Instrument

The OHTS ID must be entered according to standard protocol format.

1. In the “Last Name” or “Patient ID” box in your Cirrus instrument, search for the participant using the participant’s name, MRN or ID specific to your clinic practices. Click **Search**.
2. Highlight the participant and click **Edit** in the top right menu and choose **Patient Record**. A patient data box will appear.
3. Replace name or MRN with **OHTS ID** in “Last Name” and “Patient ID” fields. Replace first name with **Site ID** in “First Name” field (see ‘**Cirrus Patient Data Fields to Be De-Identified**’ Table below).

Table 13.9: Cirrus Patient Data Fields to Be De-Identified

Last Name:	Enter OHTS ID (5 digit ID), Example 19123
First Name:	Site ID , Example S1
Patient ID:	Enter OHTS ID (5 digit ID), Example 19123

4. Click **OK**
5. Repeat these steps for all OHTS patients seen that month. Once all patient names and or MRNs have been replaced with OHTS IDs, begin the exporting process below.
6. Repeat the above steps on any additional Cirrus instruments containing the OHTS patients, who were seen in the last month, that have previously acquired scans taken as part of regular clinical care.
7. After the scans have been exported from the Cirrus instrument, the OHTS ID can be changed back to the patient's name and/or MRN.

13.10.2 Exporting Cirrus Images to Send to OCTRC

On a monthly basis, send all OHTS Cirrus scans acquired during the OHTS visit and previous scans acquired as part of regular clinical care. If you have more than one Cirrus instrument, you may have to export from both instruments to capture all scans taken as part of regular clinical care. If you have Forum, then you can retrieve all data from one patient to a single Cirrus instrument. The steps for batch exporting are as follows:

13.10.2.1 Retrieving Patient Scans from Forum to Cirrus Instrument

If your site uses Forum, you must retrieve your de-identified patients/scans from Forum to your Cirrus instrument BEFORE exporting.

1. In the Cirrus instrument go to **Records** and choose **DICOM Retrieve**.
2. Enter OHTS ID in "Patient Last Name" and click **Search**. Highlight patient in list and click **Retrieve**.
3. Repeat steps for ALL patients seen in the previous month.
4. Follow steps below to export your scans.

13.10.2.2 Batch Exporting Monthly Cirrus Images

1. Create a new folder on the **D drive** (data should not be exported to the C drive, which is reserved for operating system and application files). Name the folder using your site ID # (i.e. S1), year and month of the list of images being exported (i.e. 2015Sep) and include "Cirrus" (i.e., S1_2015Sep_Cirrus).
2. In the **Main Patient** screen, Go to **Records** on the upper right and choose **Export Exams**.
3. Under the **Path** field, click **Browse** and select the **folder** on the D drive created in Step 1 for the export destination and click **OK** (do NOT check Export to Zip Format).
4. Under "Search for Patient Exams to Export", find the desired participants by entering your site's 2-digit site number in the **Last Name** (see 'Export Options Box' Figure below).

5. Click **Search**. The “Results” list displays all participants matching the search criteria. Choose all OHTS patients who came in for that month (hold down the shift key to choose multiple patients).
6. Click **Export**. Export progress is displayed at the bottom of the window.
7. When the export is complete, a dialog box with an export success message will appear. Click **OK**. If any problems occurred during the export, a **Summary Log** will appear to inform you.
8. Send all exported images, including previous images taken as part of regular clinical care, to the OCTRC. See section “Transferring OCT scans to OCTRC” for scan transfer directions.
9. A transmittal log must accompany all data transfers. See section “Transmittal Log” for details.

Figure 13.3: Cirrus Export

Export Options

Export To

Label 128437436347099-E-20150825105431

Path C:\Users\kdirkes\Desktop\S1_2015Sep_Cirrus

Export to Zip Format

Omit Patient Identifiers

Omit Patient Name

Omit Patient Name and day of birth

Omit Patient Name, day and month of birth
(Omits entire date of birth for patients over 80 yrs old)

Search for Patient Exams to Export

Last Name 19 Patient ID Category

Exam Date

All Last 90 Days Last 60 Days Last 30 Days Last 7 Days Interval From 8/25/2015 Through 8/25/2015

[Advanced Search](#)

Results

Patient Export Exam Export

Last Name	First Name	Birth Date	Patient ID	Local Exams
19123	S1	9/1/1990	19123	2
19124	S1	1/31/1942	19124	39

IMPORTANT: The Cirrus does not override previously exported data. Multiple exports can be saved to the same folder location and only those exams not already exported will be added.

13.11 Cirrus Archiving and Backing Up

All images that are acquired and saved with the Cirrus are initially stored on the instrument hard drive. Since the hard drive has limited storage capacity, these image files must be archived at regular intervals to an additional connected hard drive or network file server. **It is recommended that archiving be done daily. Archiving should take place at least once a week.**

IMPORTANT: Never save data to the C drive, which is reserved for operating system and application files. For archiving and backing up, use either D: or E: hard drive partitions.

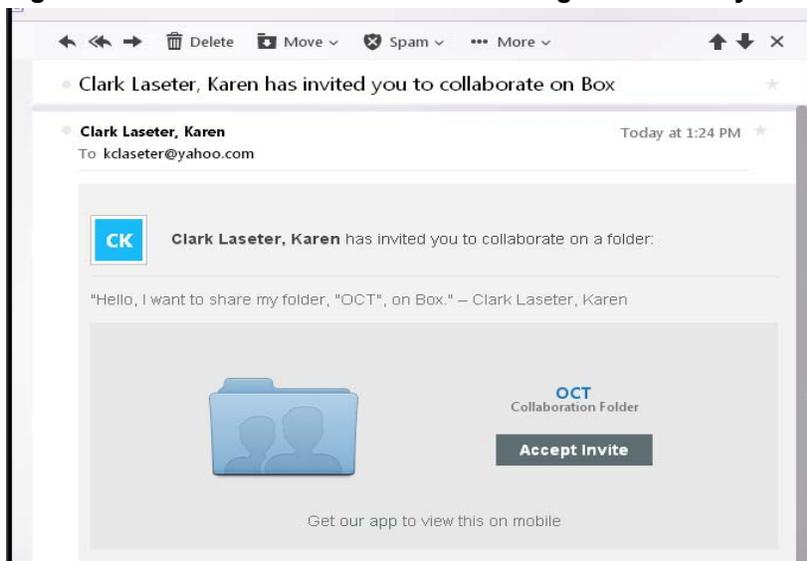
13.12 Transferring OCT Scans to OCTRC

13.12.1 Transferring Scans Via Secure Washington University Box System

The **preferred** method of data transfer (OCT scans and accompanying transmittal log) to the OCTRC is electronically via the secure Washington University Box System.

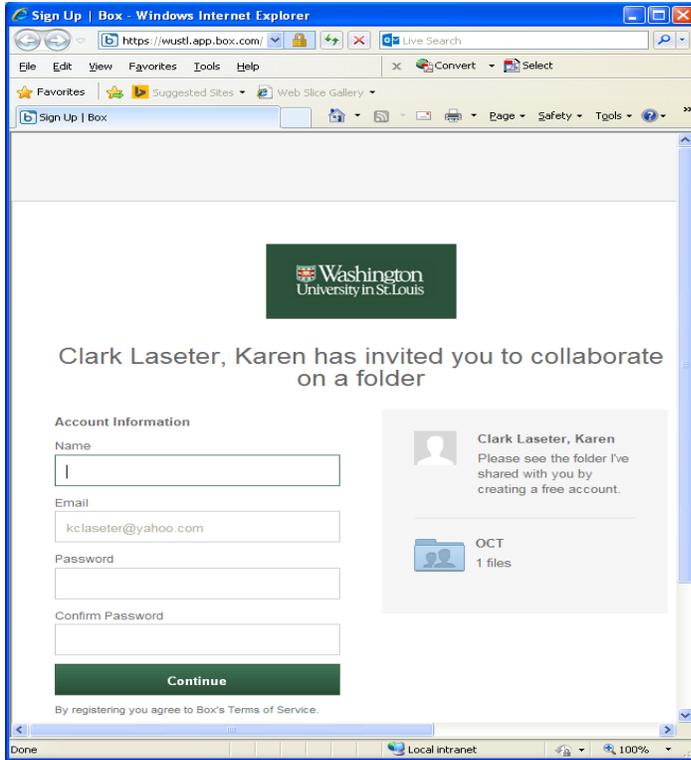
1. Create an account for each staff member that will be uploading scans (this only needs to be done one time). Each person will be sent an email inviting him or her to “collaborate on Box” (see **figure** below).

Figure 13.4: Email Invite to Create a Washington University Box System Account



2. Click “Accept Invite” button. It will take you to the Washington University Box System. Add your name and create a password and click the “Continue” button. Your email should be pre-filled (see **figure** below).

Figure 13.5: Creating a Washington University Box System Account



3. It will go through some features of the drop box. Then click “Go to My Account”.
4. Click the OCT folder.
5. Click the green “Upload” button at the upper left and choose “Folders”.
6. Choose the folder created by your site with the previous month’s scans (and any additional data collected from previous clinical care) and click “Upload” at the bottom right of the screen.
7. A message will appear letting you know your upload is complete and you will be able to see your folder listed in the drop box.
8. Once your upload is complete, click your name on the upper right and choose “Log Out”.
9. Before leaving the website, bookmark the site if possible for easy access to the drop box.
10. Once files have been dropped, send an email to the following OCTRC staff members to notify them data is available for pick up.

Keri Dirkes kdirkes@ucsd.edu
Maria Hunsicker mhunsicker@ucsd.edu
Suzanne Vega smvega@ucsd.edu

13.12.2 Transferring Scans Via Encrypted USB Drive

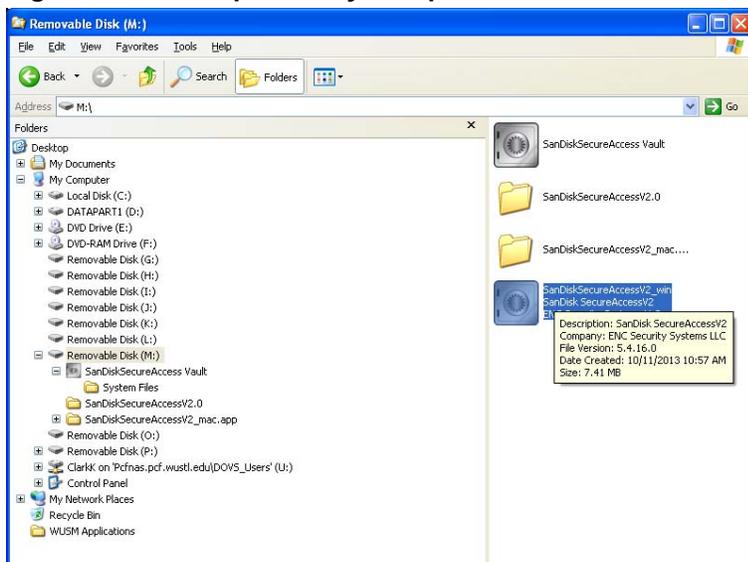
If data transfer using the Washington University Box System is not possible, the scans may also be transferred to an encrypted, password protected USB drive. The OHTS Coordinating Center will provide the USB drive and password. Contact Karen Clark Laseter with any questions at Karen@wubios.wustl.edu.

These instructions apply to Windows users. Mac users should contact Coordinating Center to request Mac-appropriate flash drives.

13.12.2.1 Loading data onto USB flash drive

1. Extend the retracted drive. Insert the flash drive into your OCT instrument. If you have a USB 3.0 port, use this, as it will provide the fastest transfer speeds. If the drive does not automatically open, go to **My Computer (below)** to find the drive, and click on the flash drive. See example below.

Figure 13.6: Example of “My Computer”



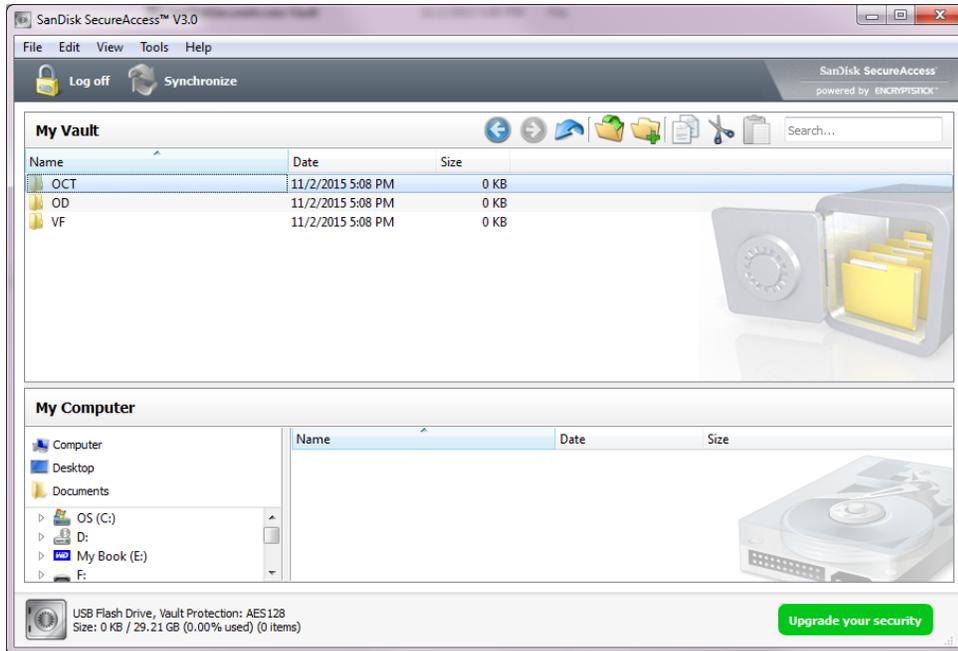
2. Click on the SanDisk SecureAccessV2-win (as highlighted above).
3. Enter the password to login (provided via email) and select **Login**.

Figure 13.7: Secure Access Screen



4. Click the green **Next** button.
5. You will see **My Vault** as shown below.

Figure 13.8: My Vault



6. Double click the **OCT** folder.
7. Select folders to be copied to drive by pressing the icon (in “My Vault”) with the green plus sign in the folder. It will prompt for a new folder name.
8. Enter your Site_YearMonthofExport_OCTMachine (e.g. S1_2015Sep_Cirrus).
9. Double click on the newly created folder.
10. Choose the OCT folder that contains the OCT exported scans for the month (e.g. S1_2015Sep_Cirrus) and choose the transmittal log file, transfer to the vault and select **Encrypt**.
11. You are given an option to remove the original file from your computer. Select “No”.
12. Confirm that the files are in your vault (OCT folder with scans and transmittal log).
13. When done transferring files/folders, select **Log off** in upper left corner.
14. You may now remove the USB drive from your computer.

If you have any questions or problems with the data transfer process, contact Karen at karen@wubios.wustl.edu or (314) 362-2349. For questions regarding data acquisition or exporting scans, please contact Keri Dirkes at kdirkes@ucsd.edu or Suzanne Vega at smvega@ucsd.edu.

13.12.2.2 Shipping USB Drive

1. Once copying data to the drive is complete, ship USB drives to Washington University at the address below via 2 day FedEx. Do NOT use regular parcel post to ship external media.

Vision Research Coordinating Center

724 S. Euclid Avenue Ste 1125

Saint Louis, MO 63110

Attn: Sam Pistorius

(314) 747-7691

2. Send an email to the following OCTRC staff members to notify them the USB drive has been shipped.

Keri Dirkes kdirkes@ucsd.edu

Maria Hunsicker mhunsicker@ucsd.edu

Suzanne Vega smvega@ucsd.edu

To save on shipping costs, we highly recommend using the Washington University Box System to transfer OCT files, whenever possible.

13.12.3 Transmittal Log

All OCT data transfers must have an accompanying electronic transmittal log (see ‘**Sample OCTRC Transmittal Log**’ Figure below). The transmittal log contains the ID of all OHTS patients who are being transferred, the OHTS visit date, and a place for the technician to communicate to the OCTRC any issues they may have encountered while imaging the patient. The log also has a place to indicate for each patient if the data transfer includes previous scans taken as part of regular clinical care. The log can be completed by hand or electronically. If completing by hand, the completed form must be scanned and sent with OCT scans as an electronic file. Name the file using your site ID # (i.e. S1), year and month of the list of patients exported (i.e. 2015Sep) and “Log” (Transmittal Log). For example: S1_2015Sep_Log.

Contact the OCTRC if you need an electronic copy of the Transmittal Log.

Figure 13.6: Sample OCTRC Transmittal Log

OHTS OCT Reading Center Transmittal Log

Directions: A transmittal log is to accompany all monthly OCT scan transfers to the OCTRC. Complete the form below and save file OR print, complete, and scan log to send electronically.

OHTS ID	OHTS OCT Visit Date	Scans Acquired Prior to the OHTS Visit Included in the transfer?	Technician Comments
<i>5 digit OHTS ID</i> <i>Example: 19123</i>	<i>MM/DD/YYYY</i>	<i>Enter Yes or No</i>	

13.13 Clinical Center Certification Procedures

Each Clinical Center should have two imaging technicians certified for OHTS imaging. It is the responsibility of the Investigator at each Clinical Center to ensure that the appropriate personnel are adequately trained and experienced using the Spectralis or Cirrus instrument. The coordinators and/or directors at the OCTRC supervise the certification of technicians.

To become certified for OHTS Spectralis or Cirrus imaging, a technician must demonstrate an understanding of the correct procedures for all aspects of image acquisition and processing to include:

- Adjusting the comfort features for the participant, such as the chin rest and chair
- Adjusting the laser target and monitoring fixation during imaging
- Entering participant data
- Operating the Spectralis or Cirrus instrument; choosing the appropriate focus parameters and obtaining an image
- Saving and archiving images
- Exporting images for transfer to the OCTRC
- Completing transmittal logs

After the candidate for certification has studied the *OHTS Manual of Procedures* and the *Spectralis or Cirrus Operation Manuals* the following steps must be completed in order to perform Spectralis and Cirrus imaging for the study.

1. The technician or Clinical Center Coordinator should contact the OCTRC directly to schedule an appointment for a certification telephone session. Also be sure to let them know which instrument your site is using for the OHTS study.
2. On the day of the appointment, the technician will call the OCTRC to initiate the telephone session.

3. After a satisfactory telephone session, the technician must acquire on each of two non-study volunteers using mock OHTS IDs following OHTS study ID format. NEVER SEND SCANS WITH NAMES TO THE OCTRC.
 - Spectralis; 2 RNFL Circle scans, and 2 P.Pole scans of each eye
or
 - Cirrus; 2 Optic Disc Cube 200x200 and 2 Macular Cube 512x128 scans of each eye
4. Complete transmittal log
5. Export and upload scans and transmittal log to Wash U. box system or send scans via encrypted USB drive to Wash U.
6. Send an email to the following OCTRC staff members to notify them the scans have been uploaded or shipped.

Keri Dirkes kdirkes@ucsd.edu

Maria Hunsicker mhunsicker@ucsd.edu

Suzanne Vega smvega@ucsd.edu

Certification will be awarded if the images are of satisfactory quality. All certified technicians must maintain their certification by obtaining OHTS Spectralis or Cirrus images on a regular basis. If there is a lapse of longer than 6 months without taking images, the operator must go through a re-certification process.

IMPORTANT: The telephone “test” asks the technician to walk through a series of mock images, (i.e. explain any issues and how to improve the scan). Before the telephone interview, make sure your Clinical Center has these certification PDF files (containing Spectralis or Cirrus example scans) and the scans can be viewed on a computer. If the Clinical Center does not have these image files, contact the OCTRC.

13.14 OCTRC Image Review

13.14.1 Training and Certification Procedures for Graders at the OCTRC

Details of the training and certification procedures for the OCTRC graders are outlined in the “Reading Center Coordinator Training Standard Operating Procedures”. In brief, the grader first reviews all relevant manuals of procedures, and quality control standard operating procedures for specific instruments. The OCTRC supervisor or other designated staff provides one-on-one training on the specific study protocols that first includes observation of the quality review, segmentation editing and identification of referral to endpoint committee. The grader then completes all aspects of the review under supervision. Finally, the grader independently completes all aspects of the review and the work is reviewed for accuracy and completeness by the supervisory staff. Certification of the OCTRC grader is obtained after successful completion of each of these stages as determined by the OCTRC supervisor.

13.14.2 Image Quality Control Assessment

The OCTRC Center is responsible for reviewing for quality the OCT scans and confirming the segmentation accuracy between the retinal layers acquired. The reading center will import the scans into their review system and will perform the scan review to ascertain if the scans meet

study protocol data entry, scan setting and quality standards and are evaluable for analysis including outcome determination. Each image will be reviewed for quality according to standard protocols by trained, experienced graders as outlined in the OCTRC Standard Operating Procedures. If the scans are evaluable for analysis, the grader will review the designated segmentation layers and correct segmentation algorithm failures when possible. The grader will also edit scans to improve designation of the center of the fovea of the macula scan, and centering of the measurement circle on the optic nerve head scan.

The OCTRC will generate quarterly performance reports to Clinical Centers summarizing quality and timeliness of OCT data including but not limited to:

1. Monthly export images/data received by 7th day of following month
2. Of scans reviewed by OCTRC, scans are good quality (goal>85%)

The OCTRC will generate semi-annual performance reports to the Executive/Steering Committee and Coordinating Center.

13.15 RNFL Scans Reviewed by the Endpoint Committee

The OCTRC uploads requested RNFL and Macula OCT report printouts (PDFs) to the Washington University Box System for Endpoint Committee review. A PDF for each eye is sent, regardless of the quality. The OCTRC will indicate in the PDF file name if the scan was deemed poor quality.

The Endpoint Committee uses the original OHTS definition and processes to determine whether confirmed conversion or progression is due to optic disc deterioration and/or visual field changes detected by the reading center(s) is due to POAG or not. After a consensus decision has been reached using the photographs and visual fields, the Endpoint Committee re-reviews the same eye with the addition of OCT RNFL data and makes a second determination using the “updated” definition of POAG conversion or progression. The Coordinating Center notifies the Clinical Center Investigator, Clinical Center Coordinator and the OCTRC of the Endpoint Committee decisions.

14 Clinical Center Procedures

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14.1 Overview of OHTS Clinical Center Certification Procedures

It is important that all procedures in OHTS be standardized and that all study personnel understand the protocol to the degree necessary to fulfill their responsibilities. Only data from study certified personnel will be accepted for the following tests and measures: 1) IOP; 2) Visual fields; 3) Stereoscopic optic disc photography; 4) OCT Imaging; 5) ETDRS visual acuity; 6) Pelli-Robson Contrast Sensitivity; and 7) Blood pressure. Test and Measures that require study certification are outlined in sections 5.1.1 and 7.2.

A fully staffed Clinical Center includes a Clinical Investigator (back-up Investigator), a Clinical Center Coordinator (back-up Coordinator), a photographer (back-up photographer), imaging technician (back-up imaging technician) and a visual field technician (back-up visual field technician). Each Clinical Center has a back-up for each position, although one person can serve more than one function and can back-up more than one position. **Back-up personnel must be certified to perform their functions.** Certification code is recorded on the case report form for study examinations and measures requiring certification. Only study data collected by study certified personnel in good standing are accepted for inclusion in analyses.

All Clinical Center personnel must complete training programs in research ethics, in maintaining the safety of human subjects in clinical research and in complying with HIPAA regulations prior to OHTS certification. Training may be provided by the Clinical Center's approved training program or by the NIH website (www.phrp.nihtraining.com). Certificates documenting the successful completion of research ethics, patient safety programs and HIPAA compliance must be submitted to the Coordinating Center by all members of the Investigative Group prior to OHTS certification.

14.2 Certification for all members of the OHTS Group

All members of the OHTS will be supplied a copy of the Manual of Procedures (MOP) which is also available at <https://vrcc.wustl.edu>. At least one person must be certified for each of the functions below. One person can be certified for more than one function.

Functions requiring OHTS certification	Certification Procedure	MOP Section
Clinical Center Investigator Clinical Center Coordinator	OHTS Phase 3 Protocol knowledge Satisfied by attendance at FIG meeting or Certification by Coordinating Center	7.16
Visual field testing	Testing & certification by VFRC	5.10, 11.8
Optic disc photography	Testing & certification by ODRC	5.11, 12.2.1
OCT	Testing & certification by OCTRC	5.12, 13.7

Functions requiring OHTS certification	Certification Procedure	MOP Section
IOP, ETDRS, Pelli-Robson contrast sensitivity	Grandfathered if previously OHTS certified	
IOP	Certification by Coordinating Center	5.6.1, 7.13
ETDRS	Certification by Coordinating Center	5.3, 7.10
Pelli-Robson contrast sensitivity	Certification by Coordinating Center	5.4.1, 7.11
Ophthalmoscopy, gonioscopy, SLE	<ul style="list-style-type: none"> • OHTS Phase 3 Protocol knowledge • Satisfied by attendance at FIG meeting or • Certification by Coordinating Center 	5.8, 7.3
Blood Pressure	Certification by Coordinating Center	5.9.1, 7.16
REDCap data entry	Certification by Coordinating Center	5.15, 7.17

The Coordinating Center will maintain a log of certifications in human subjects training and OHTS certification/de-certification of all personnel.

14.3 Responsibilities of Clinical Center Investigator

The OHTS Clinical Center Investigator and any back-up Investigator(s) is the treating physician who is responsible for the overall conduct of the OHTS at her/his study site and any satellite Clinical Center. The Clinical Center Investigator is responsible for enrolling, treating and following OHTS participants.

14.4 Certification of Clinical Center Investigators

Clinical Center Investigators and back-up Investigators can be certified for knowledge of the OHTS Phase 3 Protocol by attendance at the Full Investigative Group meeting or by demonstrating knowledge of the protocol by satisfactorily completing a brief summary of OHTS Phase 3 Protocol Review for Certification. The completed summary is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center.

New Clinical Center Investigators are furnished with a copy of the Manual of Procedures (MOP) which is also available at <https://vrcc.wustl.edu>. Clinical Center Investigators must demonstrate knowledge of the study protocol by satisfactorily completing a brief summary of OHTS Phase 3 Protocol Review for Certification. The completed summary is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center. The study protocol is described in Chapter 2 Study Design of OHTS Phase 3.

14.4.1 Specific Requirements for Clinical Center Investigator Certification

The certification process entails fulfillment of several criteria to demonstrate knowledge and proficiency in study procedures by satisfactorily completing a brief summary and faxing it to the Coordinating Center (314-362-0231) or scanning the summary and emailing to the Coordinating Center.

To be certified, the OHTS Clinical Center Investigators must:

- Review specific sections of the OHTS Manual of Procedures.
- Complete the brief summary of the OHTS Phase 3 Study General Knowledge Assessment.

Upon successful completion of these certification requirements, a certification code for the Clinical Center Investigator (back-up Investigator) will be issued by the Coordinating Center. No data will be accepted from non-certified personnel for OHTS tests and measures requiring study certification.

14.5 Responsibilities of the Clinical Center Coordinator

Clinical Center Coordinators are responsible for supervising activities related to the OHTS and integrating these with clinic operations. Coordinators are responsible for tracing participants, managing participant visits, retrieving OCT scans and visual field tests and overseeing collection of data from visits, insuring completion of tests and measures of high quality and the timely transmission of data to OHTS resource centers. The Clinical Center Coordinator insures adherence to the timetable for data transmission to resource centers as follows:

Data from Tests	Days from test date to transmission to Resource Centers	Days to Resource Center feedback to Clinics
Visual Fields	14 days Transmit data to VFRC	VFRC 7 days
Optic Disc Photographs	14 days Transmit data to OHTS Coordinating Center	ODRC 7 days
OCT scans	Monthly uploads Transmit data to OHTS Coordinating Center	OCTRC, not applicable, limited feedback on image quality
Case report forms entered in REDCap	7 days from test date	Coordinating Center Immediate auto editing

Clinic Coordinators collaborate with the Coordinating Center in the resolution of unit cost payments. Clinical Center Coordinators must be knowledgeable about appropriate procedures for data correction and alert study personnel of problems.

14.5.1 Qualifications for the Clinical Center Coordinator

Because the Clinical Center Coordinator plays a pivotal leadership role in coordinating the responsibilities of the Clinical Center, it is important that this individual be selected carefully, thoroughly trained in the OHTS protocol and recognized as the local OHTS Study “expert” in the Clinical Center. It is essential that the Clinical Center Investigator allocates sufficient time to the Clinical Center Coordinator to allow for the myriad of activities required. The Clinical Center Coordinator has extensive contact with OHTS participants; therefore this individual must have excellent “people skills”. The rapport that frequently develops between a participant and the Clinical Center Coordinator is extremely important to assure the continued cooperation of a participant throughout the course of a Study. Thus it is mandatory that the Clinical Center Coordinator be a mature, responsible person with a thorough understanding of the OHTS protocol, design and rationale. In addition, the Clinical Center Coordinator must have excellent organizational skills and attention to detail.

14.5.2 Specific Responsibilities of the Clinical Center Coordinator

The responsibilities of the Clinical Center Coordinator include, but are not limited to, the following:

- To coordinate Clinical Center activities related to the OHTS.
- To have a thorough understanding of the OHTS study protocol and methods and to serve as the “go to” expert on matters of the OHTS protocol at the Clinical Center.
- To ensure timely submissions and renewals of the Clinical Center’s IRB.
- To maintain complete and current contact and employment information on each participant enrolled for the duration of the OHTS.
- To locate, contact, schedule and consent participants.
- To schedule and coordinate participant transportation, tests, measures and examinations.
- To retrieve OCT scans and visual field tests since the participants’ last OHTS visit from OHTS and non-OHTS sites, de-identify the records and transmit them to the Coordinating Center for coding and data entry.
- To provide the primary interface between the Clinical Center, Coordinating Center and the Reading Centers by being the primary recipient of incoming mail from the US Postal Service, express carriers such as Federal Express, voice mail and e-mail.

14-6 Clinical Center Procedures

- To ensure accurate and timely data entry of OHTS case report forms into the REDCap system.
- To promptly respond to data system edit queries and notices from Resource Centers regarding tests, measures or documents provided for OHTS participants.
- To notify the Coordinating Center concerning personnel changes that affect local OHTS operations.
- To inform the Clinical Center Investigator of any problems with Clinical Center management and to suggest ways to resolve them.
- To assist Clinical Center personnel with OHTS certification.
- To assure that the Clinical Center Investigator spends sufficient time with each OHTS participant during follow-up examinations to satisfy the participant and to reassure the participant of the importance of continuing examinations and contact.

To maintain required study documentation, including:

- Complete PDF set of current versions of OHTS case report forms in the event that REDCap data entry is not available.
- Patient Regulatory Binder, containing OHTS identifiers (OHTS Participant ID number), patient name, consent dates as well as the signed consent forms and the participant information sheet of each participant in OHTS identification number order.

14.5.3 Certification of Clinical Center Coordinators

Clinical Center Coordinators can be certified for OHTS Phase 3 Protocol knowledge by attendance at the Full Investigative Group meeting (FIG) or by demonstrating knowledge of the protocol by satisfactorily completing a brief summary of the OHTS Phase 3 Protocol Review for Certification. The completed summary is faxed to the Coordinating Center (314-362-0231) or scanned and emailed to one of the Central Coordinators at the Coordinating Center.

OHTS Phase 3 Protocol Review is a summary of the OHTS Phase 3 protocol. The summary covers knowledge of required tests and measures, retesting for poor quality and for suspected conversion/progression. The summary may include participant-based examples so that the Clinical Center Coordinators can think through the protocol in participant-oriented terms. The study protocol is described in Chapter 2, “Study Design of OHTS Phase 3”.

Clinical Center Coordinators and their back-ups will be required to satisfactorily complete OHTS data-entry training and demonstrate proficiency with the OHTS Data Management System – REDCap.

A certification code will be issued by the Coordinating Center after the knowledge assessments have been completed and data entry proficiency has been demonstrated.

The Clinical Center Investigator will be advised of any problems with the performance of the Clinical Center Coordinator.

14.6 Organization of OHTS Records at the Clinical Center

To supplement information in the Manual of Procedures and to communicate new procedures and policy expeditiously between updates to the Manual, numbered OHTS protocol memoranda are sent from the Coordinating Center or Chair's Office. One copy of each memorandum should be filed in numeric order in the regulatory binder set up specifically for this purpose.

14.7 Clinical Center Workspace

The physical facilities of the Clinical Center must include waiting rooms, examination rooms, visual field rooms, Optical Coherence Tomography imaging rooms and photography rooms, all of which are accessible to handicapped individuals. An appropriately equipped Clinical Center has, in good working order, ophthalmoscopes, tonometers (including calibration device), ETDRS and Snellen Eye Charts, Pelli-Robson Contrast Sensitivity Charts, OMRON blood pressure monitor (supplied by the Coordinating Center), Extech light meter (401027-foot candle light meter-2000 (supplied by the Coordinating Center) and a fundus camera capable of taking stereoscopic digital disc photos. (If a Clinical Center has a sequential and a simultaneous camera, the simultaneous one will be used.) The make, model and serial number of the fundus camera is provided to the ODRC, spectral domain optical coherence tomography imaging (specifically a Spectralis or a Cirrus instrument) and an OHTS certified Humphrey program 30-2 visual field perimeter (HFA II &/or HFA Iii).

14.8 Optic Disc Photography Certification

Photographers previously certified for OHTS Phases 1 or 2 are required to recertify for OHTS Phase 3.

The stereoscopic optic disc photography certification for photographers is supervised by the Director of the Optic Disc Reading Center (ODRC). This process is detailed in Chapter 12.2.1 Optic Disc Photography. Briefly, photographers and back-up photographers are supplied with the ODRC chapter of the MOP. They read this material and review the protocol with the ODRC Coordinator. The educational material covers photographic technique, proper logging in and storage of photographs, and transmitting photographs to the OHTS Coordinating Center.

The photographer takes two stereo pairs for 2 non-study eyes, of two participants: Participant 1: right eye – two stereo pairs; left eye – two stereo pairs, and Participant 2: right eye – two stereo pairs; left eye – two stereo pairs and submits them to the OHTS Coordinating Center. If these photographs pass quality standards per ODRC protocol, the ODRC certifies the photographer.

Certification may be rescinded if the ODRC determines that the photographer's performance is unacceptable and does not improve after consultation and review by the ODRC. The

stereoscopic optic disc photography protocol is described in detail in Chapter 12 Optic Disc Reading Center.

14.9 Perimetry Certification

The Visual Field Reading Center (VFRC) recommends that each Clinical Center have at least two visual field technicians certified to perform visual fields. Technicians and back-up technicians previously certified for OHTS Phase 1 or 2 are required to recertify for OHTS Phase 3.

Certification of technicians to perform visual field testing is supervised by the Coordinator of the VFRC. This process is detailed in Chapter 11(11.8) Visual Field Reading Center. Briefly, visual field technicians and backups are supplied with the VFRC chapter of the MOP. The technician reads this material and reviews the protocol with the VFRC Coordinator. The technician submits visual fields from two non-study patients to the VFRC. If these visual fields meet quality standards per VFRC protocol, the Coordinator of the VFRC certifies the technician. All certified visual field technicians must maintain their certification by performing OHTS visual field tests on a regular basis. Certification will lapse for any technician who does not perform an OHTS visual field test for a period of six months.

14.10 Optical Coherence Tomography (OCT) Certification

The OCTRC recommends that each Clinical Center have at least two imaging technicians certified for OHTS OCT imaging. It is the responsibility of the Clinical Center Investigator at each Clinical Center to ensure that the appropriate personnel are competent using a Spectralis or Cirrus instrument. Certification of technicians is supervised by the OCT Reading Center. To become certified for OHTS Spectralis or Cirrus imaging, the imaging technician must complete a telephone certification with the OCTRC. After satisfactory telephone session, the technician must submit images on two non-study volunteers as described in the OCT protocol, Chapter 13 (13.7) to the OHTS Coordinating Center. Certification will be awarded if the images are of satisfactory quality.

All certified technicians must maintain their certification by obtaining OHTS Spectralis or Cirrus images on a regular basis. If there is a lapse of longer than 6 months without taking images, the technician must go through a re-certification process.

15. Chairman's Office

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15.0 Introduction

The Study Chair's Office is located in the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine in St. Louis, MO. The staff of the Chair's Office includes:

- **Michael A. Kass, M.D., Study Chair** — Washington University School of Medicine
- **Dale K. Heuer, M.D., Vice-Chair** — Medical College of Wisconsin, Milwaukee, WI
- **Eve J. Higginbotham, M.D., Vice-Chair** — Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
- **Richard K. Parrish, II, M.D., Vice-Chair** — University of Miami School of Medicine, Miami, FL
- **Deborah Dunn, Project Manager** — Washington University School of Medicine

15.1 Study Chair Duties

The Study Chair is responsible for the overall scientific conduct of the trial and for maintaining the study organization as an effective collaborating group. Dr. Kass has been Study Chair of OHTS since 1993. The Chair's duties are listed below.

15.1.1 Design and Protocol Development

The protocol is developed in close collaboration with the Vice-Chairs, Reading Centers and Coordinating Center.

- Develop eligibility criteria.
- Outline examinations, testing and safety procedures.
- Develop procedures for training and certification of study personnel.
- Develop Manual of Procedures (MOP).

15.1.2 Initiate and Perform OHTS 3

- Develop patient education and consent forms.
- Monitor patient recruitment.
- Deal with problems at the Clinical Centers and Reading Centers.
- Inform NEI program office on study progress, outcomes and other important issues.
- Implement protocol modifications and update the MOP.

15.1.3 Study Administration

- Chair the Executive/Steering Committee and the Full Investigator Group.
- Appoint all study committees as need arises and dissolve committees that have completed their charge.

15.1.4 Data Interpretation and Presentation

- Establish all writing committees.
- Insure that information is conveyed to clinicians, participants, news organization and the public.
- Serve as primary spokesperson for public relations.

15.1.5 Closeout and Termination

- Develop a plan for subsequent care of participants.
- Inform personnel of the requirements for storage and retention of study documentation and results to be in compliance with NIH, IRB and HIPPA guidelines.
- Help prepare data for sharing.

15.1.6 Vice-Chairs

Three Vice-Chairs assist the Study Chair with the leadership of the trial. They are prominent, acknowledged leaders of the vision research community. They have all served with OHTS since 1993. Their duties are described below:

- Serve on Executive/Steering Committee and Full Investigator Group.
- Chair committees in Chair's absence.
- Help develop and implement the study protocol.
- Deal with problems in the Reading Centers and Clinical Centers.
- Conduct site visits as necessary.
- Serve as Endpoint Committee.
- Review outcome manuscripts prior to submission.
- Serve on selected writing committees.

15.1.7 Project Manager

The Project Manager assists the Study Chair in many duties related to the trial. Deborah Dunn has served as Project Manager since 1993. Her duties include the following:

- Prepares annual budget for continuation of Chair's grant.
- Monitor expenditures for the Chair, Vice-Chairs and Reading Centers and pays invoices.
- Arranges all meetings of the Executive/Steering Committee and Full Investigative Group.
- Attends meetings and prepares minutes.
- Prepares informational and educational materials related to the study.
- Develops participant continuing education.
- Develops and implements a program for participant retention.
- Assists Chair with public relations.
- Maintain important study documents including minutes of meetings, protocol memoranda and a mail directory.

16. Coordinating Center

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16.1 Introduction

The Coordinating Center (CC) is a joint effort of the Department of Ophthalmology and Visual Sciences and the Division of Biostatistics at Washington University School of Medicine, St. Louis, MO. The Coordinating Center collaborates with the Study Chairman's Office, Executive/Steering Committee and the Full Investigative Group in the design and implementation of the Ocular Hypertension Treatment Study Phase 3.

The Coordinating Center's responsibilities change according to the phase of the study. Responsibilities of the Coordinating Center are therefore listed by phase of the study as follows: 1) protocol development 2) study initiation and participant follow-up 3) study closeout, and 4) study termination.

16.2 Coordinating Center Personnel

Coordinating Center
Department of Ophthalmology and Visual Sciences
660 South Euclid, Box 8203
St. Louis, MO 63110-1093
Office: 314-362-3018
Fax: 314-362-0231
e-mail: VRCC@wustl.edu

Director	Mae Gordon, Ph.D.
Project Manager Central Coordinator	Ellen Fischbach, BS, CCRP
Central Coordinator Back-up Project Manager	Shirley Pistorius, CCRP, COA
Biostatistician	Ling Chen, Ph.D. Phillip Miller, A.B.
Statistical Data Analyst	Julie Beiser Huecker, M.A. Bradley Wilson B.A.
Database Manager Systems Analyst	Leonard Haertter, B.A., CCRP Karen Clark Laseter, M.S.

16.3 Personnel Responsibilities

Director:

Mae O. Gordon, Ph.D.

The Coordinating Center Director has responsibility for providing overall leadership for the ethical and scientific conduct of the study. This includes guidance with regard to study design, implementation, administration and dissemination of results, data archiving and public data sharing. The Director also has overall responsibility for all functions of the Coordinating Center and works closely with the Project Manager to insure successful completion of OHTS Phase 3.

Specific responsibilities include the following:

- To insure that the Coordinating Center provides expertise and infrastructure support to Clinical Centers, Reading Centers and the Chairman's Office in the implementation of the study;
- To serve as a voting member of the OHTS Executive/Steering Committee, the Full Investigative Group with responsibility for developing the agenda for each meeting in consultation with the Study Chairman;
- To lead internal meetings of the Coordinating Center staff and Analysis Team;
- To collaborate with Statistical Data Analysts in the generation of recurrent performance reports including quarterly Clinical Center performance reports, semi-annual Resource Center Performance reports to the Executive/Steering Committee and to the NEI;
- To collaborate with Statistical Data Analysts and Biostatisticians in the analysis of study data for presentations and publications;
- To be responsible for personnel decisions of the Coordinating Center including training staff;
- To be responsible for the Coordinating Center budget;
- To conduct site-visits as needed.

Project Manager/Back-up Central Coordinator: Ellen Fischbach, BS, CCRP

Central Coordinator/Back-up Project Manager: Shirley Pistorius, CCRP, COA

The Project Manager and Central Coordinator have administrative, organizational and scientific responsibilities for the day-to-day operation of the study. The Project Manager/Central Coordinator position must be fully backed-up on all work days.

Specific responsibilities of the Project Manager include the following:

- To serve as a non-voting member of the Executive/Steering Committee;
- To facilitate collaboration with the Chairman's Office, Resource Centers, Clinical Centers and study committees;

16-4 Coordinating Center

- To insure accurate and timely invoicing of Clinical Center activities;
- To monitor budgets of the Coordinating Center and Clinical Centers and to develop, in collaboration with the Director, budgets for annual continuation applications;
- To assist in the development of an informational study web site for the Full Investigative Group and study patients;
- To assist in the preparation of study documents including the Manual of Procedures, brochures, study forms, training and certification materials, study presentations and publications;
- To assist in the preparation of recurrent and ad hoc reports including annual NIH progress reports, quarterly performance reports to Clinical Centers and semi-annual reports to the Executive/Steering Committee;
- To assist in scheduling and organizing meetings/teleconferences of the Executive/Steering Committee, Endpoint Committee and writing committees.

Specific responsibilities of the Central Coordinator include the following:

- To train and certify OHTS Clinic Coordinators and Investigators for protocol knowledge and measurement of IOP, blood pressure, visual acuity and contrast sensitivity;
- To provide telephone support to Clinical Center staff with questions regarding the study protocol and to refer appropriate questions to the Coordinating Center Director, Study Chairman and/or Reading Center Directors;
- To assist Clinical Centers with retrieval of contact information and/or vital status of participants lost to follow-up using a tracing service;
- To supervise quality assurance activities at the Coordinating Center and Clinical Centers with input from the Director;
- To collate data from Clinical Centers and Reading Centers for masked review by the Endpoint Committee for POAG conversion and progression;
- To perform site visits to the Clinical Centers as needed and write summary reports;
- To query Clinical Center staff about missing and delinquent data;

Biostatisticians:

Ling Chen, Ph.D and J Phillip Miller, A.B.

Study biostatisticians work closely with the Director and Study Chairman with regard to data analysis and interpretation. Specific responsibilities of the Biostatisticians include the following:

- To perform analyses aimed at detection of outliers and data patterns that may indicate irregularities in data collection procedures;
- To develop analyses of the data required for study specific aims in consultation with the Director and Study Chairman;
- To prepare accurate and timely analyses of the data for presentations and publications;
- To develop new statistical methodology as indicated and to present and publish such

methodology appropriately;

- To perform other data analytic tasks as directed by Director and Study Chairman;
- To attend weekly meetings of the Analysis Team.

Senior Statistical Data Analyst:
Statistical Data Analyst:

Julia B. Huecker, MS.
Bradley Wilson, BA

Statistical Data Analysts work closely with the biostatisticians and Director with regard to data analysis and interpretation. Specific responsibilities include the following:

- To provide programming support (custom data bases) for statistical analyses;
- To generate recurrent and ad hoc performance reports on enrollment, consent status, data quality, timeliness of transmission and protocol adherence for review by Clinical Centers, Reading Centers, Director, Study Chair and the Executive/Steering Committee;
- To be assist Biostatisticians in the statistical analysis of data for study publications/presentations and local and national meetings;
- Responsible for generating monthly SAS data sets from REDCap;
- To maintain study databases, and comprehensive documentation of variables, formats and program code used in reports;
- To generate and maintain invoicing database for Clinical Center activities;
- To monitor adjudication of endpoint attribution by the Endpoint Committee;
- To annotate and archive datasets/program code of mainline publications reporting specific aims;
- To create document archive datasets and to create de-identified datasets for public sharing.

Database Programmer:

Leonard Haertter, BA

- Responsible for REDCap data entry and editing screens for all study forms;
- Responsible for setting up REDCap user accounts, online permissions and for training and certifying users on data entry in REDCap;
- Responsible for constructing and maintaining REDCap on-line certification surveys and certification log database of certified Clinical Center personnel;
- Responsible for constructing and maintaining the database of IRB submissions and renewals;
- Create and maintain a secure website for the Endpoint Committee to review masked data for the adjudication process;
- Maintain the “Request Tracker” query/response system;
- At study close-out create the archive website.

Systems Analyst

Karen Clark Laseter, MS.

- To insure that adequate procedures have been established and maintained for preserving the integrity and security of the data files;
- To install upgrades to statistical and data management software;
- To insure integrity and efficiency of data transmission from Clinical Centers to Resource Centers;
- Responsible for receiving/converting and editing all data sent from the resource centers into SAS data sets;
- To maintain the local area network.

16.4 Protocol and Systems Development Months 0-6

The Coordinating Center plays an active role, along with the Chairman's Office, the Executive/Steering Committee, and the Full Investigative Group in protocol refinement, including:

- Completing and distributing Manual of Procedures;
- Completing an participant brochure describing OHTS Phase 3;
- Developing patient consent documents and IRB protocol for local IRB submission;
- Providing Clinical Centers with listing of presumed survivors to schedule for OHTS Phase 3 and assisting Clinical Centers to trace participants lost to follow-up;
- Distributing study equipment and supplies to Clinical Centers, specifically, but not limited to OMRON automated blood pressure cuffs, memory sticks and light meters;
- Training and certifying Clinical Center Coordinators, technicians, photographers, Directors, and reading center personnel;
- Creating database(s) for Clinical Center regulatory binders that include IRB approval, renewal dates, directory of certified personnel and certification dates;
- Completing systems and procedures for receiving, editing and generating reports in REDCap (Research Electronic Data Capture) secure, web-based system for use by Clinical Centers and Resource Centers;
- Completing programming for monthly reports of unit cost payment system to Clinical Centers and quarterly invoice payments;
- Completing programs for quarterly performance reports to Clinical Centers, semi-annual reports to the Executive/Steering Committee;
- Completing website for Endpoint Committee review of clinical data and adjudication;
- Completing an informational study website for use by OHTS personnel at Clinical Centers and Resource Centers;

- Organizing Full Investigative Group meeting attended by Clinical Center Investigators, Clinic Coordinators, Resource Center Principal Investigators and Coordinators.

16.5 Study Initiation and Patient Visits Months 6-30

Data collection will start in Month 6 and continue through Month 30. During the active data collection phase, Coordinating Center activities can generally be categorized as:

- 1) administrative, 2) data collection and management, 3) data analysis and reporting and, 4) quality assurance. Coordinating Center responsibilities are summarized for each category.

Study Administration

- Managing Clinical Center invoices, preparing monthly/quarterly summaries of invoices, reconciling differences and insuring timely payments to Clinical Centers;
- Assisting Clinical Centers with initial IRB submissions and renewals;
- Organizing documents, tests and measures for Endpoint Committee review;
- Participating in standing committees;
- Coordinating and providing the necessary materials in support of study meetings and teleconferences;
- Coordinating communications among the various functional units and committees;
- Maintaining accurate study archives, including study history and proceedings of committee meetings;
- Preparing and distributing to Clinical Centers reminders of overdue tests and measures;
- Maintaining an accurate OHTS personnel directory (telephone, address, fax, and e-mail directory), database of IRB approvals and database of personnel certifications;
- Publishing and distributing study newsletters for patients and Clinical Center staff.

Data Collection and Management

- Assisting Clinical Centers in tracing participants and arranging transportation and/or alternative Clinical Centers for completion of OHTS Phase 3 examinations when necessary;
- Serving as a liaison with professional tracing agency for participants for whom contact information is not current;
- Providing logistical and scientific support to Clinical Centers, the Visual Field Reading Center (VFRC), Optical Coherence Tomography Reading Center (OCTRC), and the Optic Disc Reading Center (ODRC), and the Endpoint Committee;
- Receiving data electronically submitted from the Clinical Centers and Resource Centers;
- Performing edit checks and resolving queries to ensure high quality data;
- Assisting Clinical Center staff with patients for whom visit completion is a problem;

16-8 Coordinating Center

- Receiving and maintaining SAS datasets of all data records created by the graders at Reading Centers;
- Providing on-going support to the Clinic Coordinators regarding data collected at the Clinical Center and data retrieved from OHTS and non-OHTS sites after the last OHTS visit.

Data Analysis and Reporting

- Preparing monthly/quarterly Clinical Center performance reports on consent status, completed tests and measures, data quality and timeliness of transmission to Resource Centers and data retrieval from OHTS and non-OHTS sites (Appendix A);
- Generating semi-annual performance reports for the Executive/Steering Committee (Appendix A);
- Participating in the drafting of all study publications;
- Performing analyses deemed appropriate by the Executive/Steering Committee and other Study units as time permits;
- Assisting in dissemination of results via scientific publications including social media;
- Reporting to appropriate audiences statistical and methodological innovations developed during the course of the study.

Quality Assurance

- Completing study certifications on-line and by an initial face-to-face training sessions at the kick-off Full Investigative Group Meeting prior to study enrollment for clinic personnel to review study design, examination procedures, data entry/editing data collection, tracing of participants;
- Conducting weekly/monthly telephone troubleshooting calls with Clinical Centers as necessary;
- Assisting Clinical Center personnel to interpret and to follow the protocol and procedures documented in the *Manual of Procedures*;
- Maintaining documentation of all procedures and operations at the Coordinating Center;
- Maintaining the data files in a secure manner to assure their integrity and adherence with HIPAA requirements;
- Backing up the data files to assure that data are not lost;
- Cooperating with any individual or group assigned to review operations at the Coordinating Center;
- Conducting site-visits to Clinical Centers, the Visual Field Reading Center, Optical Coherence Tomography Reading Center, and Optic Disc Reading Center as needed.

16.6 Close-out of Clinical Centers and Reading Centers

Clinical Centers and Reading Centers complete OHTS Phase 3 data collection by Month 30 and complete closeout by Month 36. The Coordinating Center continues function through Month 60.

Close-out includes:

- Helping to arrange patient follow-up and care after study exit;
- Final data editing, archival storage of consent forms, study documents and administrative forms at Clinical Centers;
- Insuring that Reading Centers document and archive datasets and transmit archive dataset to the Coordinating Center;
- Assisting in the preparation of presentations, manuscripts and Power Point slide sets for dissemination of results;
- Closing-out of Clinical Centers, the VFRC, the ODRC, the OCTRC;
- Insuring that IRB approvals remain active for at least 3 years after Clinical Center close-out.

16.7 Termination Phase

During the termination phase, study datasets have essentially undergone final editing. Coordinating Center continues to function through Month 60. This phase includes:

- Completing analyses for specific aims;
- Preparing, submitting, publishing and annotating manuscripts for specific aims and distributing companion Power Point slide sets to Clinical Center Investigators and Coordinators;
- Dissemination of results among Clinical Centers via Share point, among participants via Facebook, e-mail and letters, and to the general public via Facebook and YouTube;
- Completing annotation of published papers;
- Implementing interactive website for the prediction of glaucoma risk;
- Documenting and de-identifying datasets for resource sharing;
- Archiving data files and study documents;
- Completion of website for archival purposes: narrative description of study, MOP, clinic directory, bibliography, papers in PDF, PDF's of companion Power Point presentations, instructions for data sharing queries;
- Serving as OHTS communications center;
- Insuring that IRB approvals remain active for 3 years after Clinical Center close-out.

16.8 Computer Resources and Remote Data Entry

The Division of Biostatistics' computing resources are organized around an Ethernet LAN. A cluster of Intel compatible servers (all running Linux) form the core of the shared use machines. The Linux cluster currently consists of 15 dual processor compute servers with SAS and R installed, nine file servers, supporting a total of 50 Terabytes of storage, and 9 other servers (mostly dual processor) supporting web serving, mail processing and other administrative uses. A Penguin Beowulf compute cluster consisting of a head node and 21 compute nodes, each of which has two quad-core processors and 32 GB of memory and local disk storage. A compute farm consisting of 13 dual Intel Xeon 3.06 GHz or dual Opteron 2.2GHz systems is primarily devoted to genetic epidemiology related projects and is configured to utilize Gridware for efficient parallel utilization of the computing power. All of these servers plus all desktop systems are on the Medical School private network protected from the rest of the university network. Three Linux based systems handle the mail processing for the Division and an additional 3 system provides access to public websites and password controlled access areas which do not contain PHI. Another webserver located within the private zone is used for all applications with PHI, including data entry systems. Ten additional servers (mostly dual processor systems) support various security and administrative needs. These systems are administratively organized as a Division-wide computing resource (WUBIOS) with the costs shared by its users.

In addition, the Division of Biostatistics maintains an updated library of the latest versions of a variety of genetic analysis programs and packages. Although a few are proprietary packages (most notably S.A.G.E.) most are freeware and shareware that are contributed by various statistical geneticists and genetic epidemiologists. These include data cleaning and quality control programs (e.g. PEDSYS, PEDCHECK, ASPEX, GRR, etc.), linkage programs (e.g. MERLIN, SOLAR, GENEHUNTER, SEGPATH, MLINK, LOKI, FASTLINK, MX, etc.) association/LD analysis programs (e.g. FBAT, QTDT, TRANSMIT, etc.) haplotype analysis (e.g. PHASE, HAPLO.SCORE, HAPLORE, etc.) and many others. A current list can be found at: <http://www.biostat.wustl.edu/genetics/geneticssoft/>.

Each faculty or staff member of the Division has a networked desktop computer. These Intel compatible systems run Windows 7 and support a variety of applications including word processing. All systems have the necessary software installed to provide an integrated client/server computing environment.

16.8.1 REDCap secure web data entry:

OHTS phase 3 will use REDCap (Research Electronic Data Capture) secure web data entry system for building and managing online surveys and databases. REDCap was developed specifically to be in compliance with HIPAA-Security guidelines. All web-based information is encrypted. Data will be stored on a private, firewall protected network located in Washington University Division of Biostatistics. All users are assigned individual user ID's and passwords. User rights will be restricted on a role-specific basis. User rights include: access to study calendar, data import, data comparison, file repository, data quality checks, graphical data view and statistics, report viewing/generating, and creating new records. Data entry rights will be set to none, read only, or view and edit.

REDCap will be used in OHTS Phase 3 to:

1. Maintain a database of current certifications of OHTS personnel in good standing to perform i.e. visual fields, optic disc photography, OCT scans, IOP, ETDRS visual acuity, refraction, Pelli-Robson Contrast Sensitivity, etc... MOP Chapter 5.1.1).
2. Maintain a database of IRB approvals and renewals that triggers auto-reminders to Clinical Centers.
3. Enter clinical data with an audit trail, on-line edit queries, range checks, and real time validation.
4. Pre-populates test schedule reflecting POAG status of each eye. When Reading Centers enter that a retake is needed due to poor quality or suspected conversion, the patient test schedule will be automatically updated.
5. Generate Clinical Center performance reports
6. Generate Clinical Center invoicing system based on completion of protocol visits. Support review of data by Endpoint Committee for determination of whether confirmed conversion and confirmed progression is due to POAG. Data entry screens will record votes, tally consensus and report need for 2nd round of voting
7. Export data into common statistical packages (SAS, R, STATA or SPSS).

16.9 Request Tracker

Request Tracker (RT) (RT 3.8.13 Copyright 1996-2010 [Best Practical Solutions, LLC](#)) is an automated system, the Coordinating Center (CC) will use to monitor, prioritize, reliably answer, and document problems/questions pertaining to OHTS protocol, clinical testing procedure, REDCap data entry, sending data to the resource centers, or report generating.

Both web and e-mail interfaces can be used to interact with RT. (email OHTS@rt.biostat.wustl.edu). OHTS Project Manager will assign a unique username and password to OHTS certified personnel for access to RT. When RT receives a request, a ticket is created, and assigned a ticket number. The requestor will receive a confirmation of the new ticket by email. The RT ticket number will be included in the subject line of the email and in all subsequent emails. Once the new ticket has been created, the Project Manager assigns the ticket to the appropriate individual to resolve the request and, if necessary, get in touch with the requestor to ask questions. Once a request has been resolved, the CC will close the ticket. When the ticket is closed, the requestor will be informed by email that it has been resolved and asked if the resolution was satisfactory. All correspondence between the CC and the requestor is saved in the history of each ticket for future reference.

All correspondence for all tickets will be stored in a MySQL database. This will allow for an audit trail and help the CC determine how quickly different types of requests are resolved. The CC will use this metadata to report on the number of requests by subject (REDCap data entry, protocol questions, etc...) and performance of the CC in areas such as timeliness of resolution.

16.10 Form Design

Forms for the study were designed, field tested and revised during the prior phases of OHTS. All study forms will be programmed into the REDCap system and entered remotely at the Clinical Center.

16.11 Data Management

Data from REDCap will be output into SAS data sets. The SAS system is used for virtually all computer processing within the Coordinating Center. The use of SAS software allows the use of a single software system across a broad spectrum of hardware platforms.

In the OHTS database, all instances of each form type are grouped together as a single SAS Version 9.3 dataset, cross-indexed by patient ID. The entire collection of datasets (a SAS library) resides on a single shared-use computer. Data extraction SAS programs are written on a regular or as needed basis for accessing this library for the production of those management reports which the Executive/Steering Committee and Coordinating Center to develop jointly. Other SAS programs extract analysis subsets for interim analyses and quality control monitoring.

Appendix A

The backbone of protocol adherence and good data quality is the cycle of data transmission from Clinical Centers to Resource Centers coupled with timeliness of feedback/support from Resource Centers back to Clinical Centers. The recurrent reports below provide a cross-sectional and longitudinal overview of Clinical Center and Resource Center performance.

Recurrent reports augment real-time quality control protocols which are in place for grading each visual field, stereoscopic optic disc photograph and OCT scan as they are received by their respective Reading Center. The response time from test completion to Reading Center quality feedback for visual fields and stereoscopic optic disc photos is 14 days (7 days from Clinical Center test to transmission to Reading Center and 7 days from receipt by Reading Center to feedback to Clinical Centers). This time frame will enable feedback and corrective action to be taken by Reading Centers in a timely manner to minimize degradation of subsequent tests given the data flow expected. The REDCap web-based data entry system will provide real-time quality assessment during data entry.

A. Certification Status Report

Generator: Coordinating Center
Receiver: Clinic Coordinator, PI or person certified when certification is completed
Documents: Certification report completed by the Central Coordinator

B. Reports To Clinical Centers

1. Monthly Consent Status Report

Generator: Coordinating Center
Receiver: Monthly to Clinical Center PI & Coordinator
Semi-annually to the Executive/Steering Committee
Data bases: Checklist on Consent forms
a. # of participants who consented to each component of Phase 3 by clinic.

2. Monthly Completed Tests/Visit Report

Generator: Coordinating Center
Receiver: Monthly to Clinical Center PI & Clinic Coordinator,
Reimbursement specialist
Data bases: FV, ODRC, VFRC and OCTRC data
a. % of expected patient visits/tests completed by Clinical Centers and overall
b. frequency distribution of days from patient visit to receipt of data at
Resource Centers

3. Quarterly and Semi-Annual Clinical Data Quality

Generator: Coordinating Center
Receiver: Quarterly to Clinical Center PI & Coordinator
Semi-annually to Executive/Steering Committee
Data bases: FV, VFQ, FM OCRD, VFRC and OCTRC data.
a. % of forms with edit queries,
b. frequency distribution of days to resolution of edit query.

4. Quarterly and Semi-Annual Optic Disc Photography Quality

Generator: Optic Disc Reading Center
Receiver: Quarterly to Clinical Center PI, Coordinator, Photographer,
Coordinating Center

- Semi-annually to Executive/Steering Committee
- Documents: ODRC Grading Forms & ODRC log
- a. #, % of stereo pairs with clarity and stereo on scale from 1-5, where grade 4 and 5 require retakes, by Clinical Center, last 6 months and total to date
 - b. time for repeat photography due to poor quality
 - c. time interval for confirmation photography
 - d. #, % of stereophotographs with labeling errors
 - e. % of stereo pairs that are received by ODRC within 3 days of photography

5. Quarterly and Semi-Annual Visual Field Test Quality

- Generator: Visual Field Reading Center
- Receiver: Quarterly to Clinical Center PI, Coordinator, Visual Field Technician, and Coordinating Center
Semi-annually to Executive/Steering Committee
- Documents: VFRC Grading Screen & VFRC log
- a. #, % of visual fields that have reliability errors, last 6 months, total to date
 - b. #, % of visual fields with incorrect test parameters (refraction, age correction, reliability indices, OHTS perimeter)
 - c. #, % of visual fields that need to be repeated due to quality
 - d. distribution of days for repeat fields due to poor quality
 - e. distribution of days for confirmation fields

6. Clinical Center Site Visit Reports

- Receiver: As needed to Clinical Center PI & Coordinator, Study Chairman, Coordinating Center Director
- Documents: Site Visit Form

C. Semi-Annual Performance Report of Visual Field Reading Center

- Generator: Visual Field Reading Center
- Receiver: Semi-annually to the Executive/Steering Committee
- Documents: Weekly and monthly VFRC transmissions
- a. Time ticks in VFRC performance
VFRC receipt of field to grading for quality
VFRC receipt of field to grading for conversion or progression
 - b. Grader agreement of quality, conversion and progression
 - c. Agreement on QC set for secular trend

D. Semi-Annual Performance Report of Optic Disc Reading Center

- Generator: Optic Disc Reading Center
- Receiver: Semi-annually to Coordinating Center and Executive/Steering Committee
- Documents: Weekly and monthly ODRC transmissions
- a. Time ticks:
ODRC receipt of photo to grading for quality
ODRC receipt of photo to grading for abnormality
Time interval for adjudication
 - b. Grader Agreement on quality, change from baseline and change from conversion
 - c. Grader Agreement on QC set for secular trend

E. Semi-Annual Performance Report of Optical Coherence Tomography Reading Center

Generator: OCT Reading Center

Receiver:

Documents: Weekly and monthly OCTRC transmissions

- a. Time ticks in days for OCTRC performance
- OCTRC receipt of field to grading for quality
- OCTRC receipt of field to grading for abnormality time interval

F. Semi-Annual Performance Report of Coordinating Center

Generator: Coordinating Center

Receiver: Semiannually to the Executive/Steering Committee

Documents: Directory, REDCap logs, study databases

- a. Certification status of Clinical Center and reading center personnel
- b. Number and types of files received last 6 months, total to date
- c. Number and types of edit checks initiated/resolved by Coordinating Center

Ocular Hypertension Treatment Study

OHTS

MINI MOP For Certifications

OHTS Coordinating Center

Address:

Washington University School of Medicine
Ocular Hypertension Treatment Study
Campus Box 8096
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St. Louis MO 63110
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Central Coordinator

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REDCap Manager

Brad Wilson
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Project Manager

Ellen Fischbach
314-747-7692
ellen@wustl.edu

Database Manager-WUSTL Box

Karen Clark Laseter
314-362-2349
laseter@wustl.edu

Frequently Asked Questions

1. Where do I send my OCT images and Optic Disc Photos?

There are two methods for submitting OCT images and Optic Disc Photos.

- a. WUSTL Box System www.app.box.com (Washington University Box System (WUSTL Box) is the preferred way to submit OCT images and Optic Disc Photos) The OCT Reading Center (OCTRC) and Optic Disc Reading Center (ODRC) will download the data from WUSTL U Box System
- b. Mail encrypted flash drives provided by OHTS Coordinating Center with OCT images and Optic Disc Photos to the Coordinating Center along with transmittal logs. The OHTS Coordinating Center will upload your images to the WUSTL Box System. ***NOTE: Only clinic sites with limited access to the internet should mail OCT images and Optic Disc Photos to the OHTS Coordinating Center.***

Washington University School of Medicine
 Sam Pistorius
 Campus Box 8096
 660 South Euclid Ave
 St. Louis MO 63110

2. Who do I contact for USB/flash drives for OCT images and Optic Disc Photos?

OHTS Coordinating Center will furnish USB/flash drives. Contact one of the Central Coordinators at the OHTS Coordinating Center to obtain additional USB/flash drives.

3. Where do I send my visual field data and PDF/print out?

There are two ways to submit visual fields.

- a. VFRC Website www.perimetry.com (Preferred method to submit visual fields & PDF/print out) ***Important: Please do not mail visual fields data/images to the OHTS Coordinating Center***
- b. US Mail:

Visual Field Reading Center
 University of Iowa
 2501 Crosspark Road
 B148-MFK
 Coralville, IA 52241

4. Who do I contact for flash drives and diskettes for visual fields?

Please contact VFRC to obtain Flash Drives and/or Diskettes.

NOTE: Please remember to label all visual fields, OD Photos and OCT images according to the OHTS Protocol.

5. Who to contact if I have questions?

Questions about the OHTS Study:

OHTS Coordinating Center

Pat Morris

morris@vision.wustl.edu

Sam Pistorius

pistoriuss@vision.wustl.edu

Ellen Fischbach

ellen@wustl.edu

Questions about Visual Fields:

Visual Field Reading Center

Tana Wagschal

tana-wagschal@uiowa.edu

Questions about OCT images:

OCT Reading Center

Please include ALL 3 staff members on your e-mail:

Keri Dirkes, M.P.H.

kdirkes@ucsd.edu

Suzanne Vega, M.P.H.

smvega@ucsd.edu

Maria Hunsicker

mhunsicker@ucsd.edu

Questions about OD Photos:

Optic Disc Reading Center

Eleonore Savatovsky, PhD

esavatovsky@med.miami.edu

Visual Field Reading Center (VFRC) Certification

Certification Check List

- Study OHTS MOP Chapter 11 and VFRC "Protocol for Submission Upload"
- Be able to successfully demonstrate knowledge of the OHTS protocol and VFRC's "Protocol for Submission Upload"
- Call VFRC to schedule a certification phone interview
- Request a user name and password for the VFRC website
- You will need to use a phone near the Humphrey Field Analyzer for the phone interview
- Submit visual fields on 2 Patients/4 Eyes (Non-OHTS Patients)
- Submit visual field data and visual field print outs via VFRC website (**preferred method**) or by mailing diskette or USB/ flash drive directly to VFRC
- Label visual fields according to the OHTS protocol
- IMPORTANT TO REMEMBER: visual field data and visual field PDF printouts need to be uploaded on separate diskettes and/or USB/Flash Drives**
- VFRC will notify the OHTS Coordinating Center with certification status

To become certified for OHTS visual field testing, a technician must demonstrate competency in the following:

- calibrating the Humphrey perimeter and formatting a diskette
- measuring pupil size
- adjusting the comfort features for the participant, 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 participant data
- performing a 30-2 SITA Standard Full Threshold visual field test
- being sensitive to participant fatigue -- allowing the participant to rest during the test
- saving and printing the test data
- making a back-up diskette and copying visual field files onto another diskette

Please call VFRC with all visual field related questions or issues.

Mini MOP 17-2

Tana Wagschal

(P) 319-467-4538

E-mail: tana-wagschal@uiowa.edu

E-Mail: vfr@uiowa.edu

Mailing Address:

Visual Field Reading Center

University of Iowa

2501 Crosspark Road

B148-MTF

Coralville, IA 52241

(P) 319-467-4539

Website:

www.perimetry.com

Optic Disc Reading Center (ODRC)

Certification Check List

- Study OHTS MOP Chapter 12 ODRC Protocol
- E-mail Karen Clark to request access to the WUStL Box System**
- E-mail ODRC when ready to submit OD Photos for certification
- Submit all OD photos to the WUStL Box System www.app.box.com (Preferred method)
- Or- Mail Flash Drive containing images along with transmittal log to OHTS Coordinating Center
- Photographer takes two pairs of stereo photographs of each eye, of two patients who are not part of OHTS 3: Patient 1: right eye - two stereo pairs; left eye - two stereo pairs and Patient 2: right eye - two stereo pairs; left eye - two stereo pairs
- ODRC also contacts the Coordinating Center with the new photographer certification information
Label images according to the OHTS protocol

Please call ODRC for OD Photos questions or issues.

Eleonore Savatovsky, PhD

(P) 305-243-5488

E-mail: esavatovsky@med.miami.edu

WUStL Box System:

www.app.box.com

OCT Reading Center (OCTRC)

Certification Check List

- Check with your PI to find which instrument will be used for the OHTS study. Spectralis or Cirrus.
 - **Spectralis:** 2 RNFL Circle scans, and 2 P.Pole scans of each eye or
 - **Cirrus:** 2 Optic Disc Cube 200x200 and 2 Macular Cube 512x128 scans of each eye

- Study OHTS MOP Chapter 13 OCTRC Protocol for Spectralis or Cirrus
- Contact Karen Clark to request access to WUStL Box System**
- Contact the OCTRC to schedule a phone interview
- On the day of the phone interview, the TECHNICIAN will call the OCTRC to initiate the telephone interview
- To become certified for OHTS Spectralis or Cirrus imaging, a technician must demonstrate an understanding of the correct procedures for all aspects of image acquisition and processing, to include:
 - Adjusting the comfort features for the participant, such as the chin rest and chair
 - Adjusting the laser target and monitoring fixation during imaging
 - Entering Participant Data
 - Operating the Spectralis or Cirrus instrument; choosing the appropriate focus parameters and obtaining an image
 - Saving and archiving images
 - Exporting images for transfer to the OCTRC
 - Completing transmittal logs
- IMPORTANT:** The telephone "test" asks the technician to walk through a series of mock images (i.e. explain any issues and how to improve the scan). Before the telephone interview, make sure your Clinical Center has the certification PDF files (containing Spectralis or Cirrus example scans) and the scans can be viewed on a computer. **If the Clinical Center does not have these image files, contact the OCTRC**
- After successfully completing the phone interview, you will be instructed to upload images to the WUStL Box System. **Do NOT acquire certification scans prior to the phone certification.**
- Submit all OCT images to the WUStL Box System www.app.box.com (Preferred method)**
- OR-** Mail encrypted Flash Drive, containing OCT images, along with **transmittal log** to OHTS Coordinating Center
- OHTS Coordinating Center will upload OCT images to the WUStL Box System
- Label OCT image folder according to the OHTS protocol**
- Send an e-mail to the following OCTRC staff members to notify them the scans have been uploaded or shipped
- Certification will be awarded if the images are of satisfactory quality.

Please call OCTRC for all OCT related questions or issues.

Linda Zangwill, Ph.D., Director
(P) 858-534-7686

E-mail: lzangwill@ucsd.edu

Keri Dirkes, M.P.H., OCTRC Supervisor
(P) 858-822-3156

E-mail: kdirkes@ucsd.edu

Suzanne Vega, M.P.H., OCTRC Coordinator
(P) 858-822-6670

E-mail: smvega@ucsd.edu

Maria Hunsicker, OCTRC Coordinator
(P) 858-822-4104

E-mail: mhunsicker@ucsd.edu

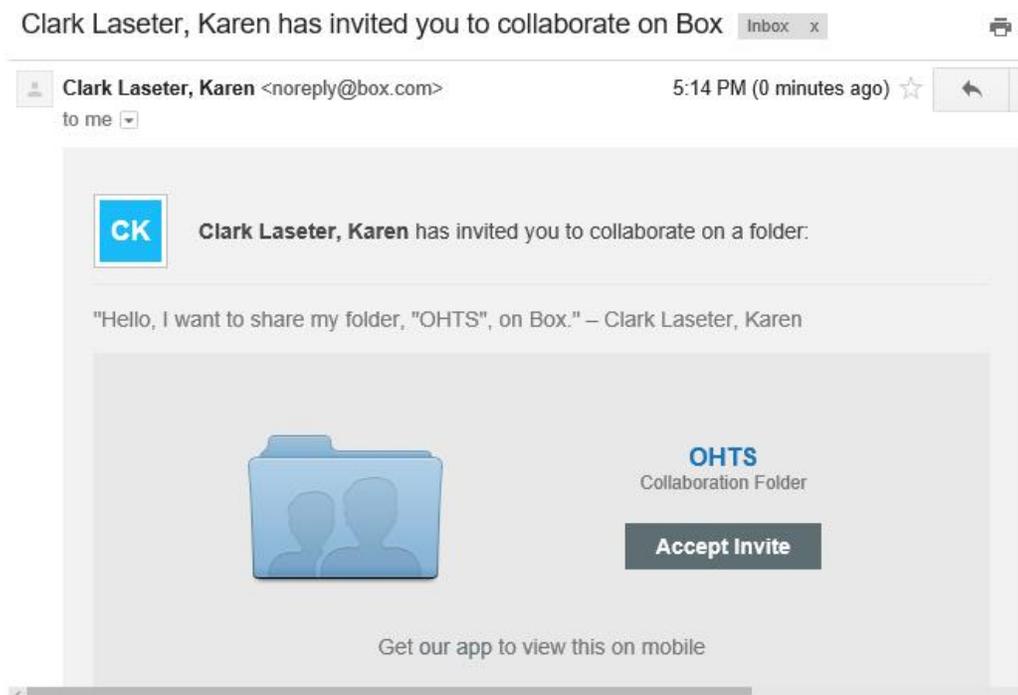
Submitting OCT Images and Optic Disc Photos

Clinical Centers can transfer Optic Disc Photos and OCT images to the Coordinating Center in two ways:

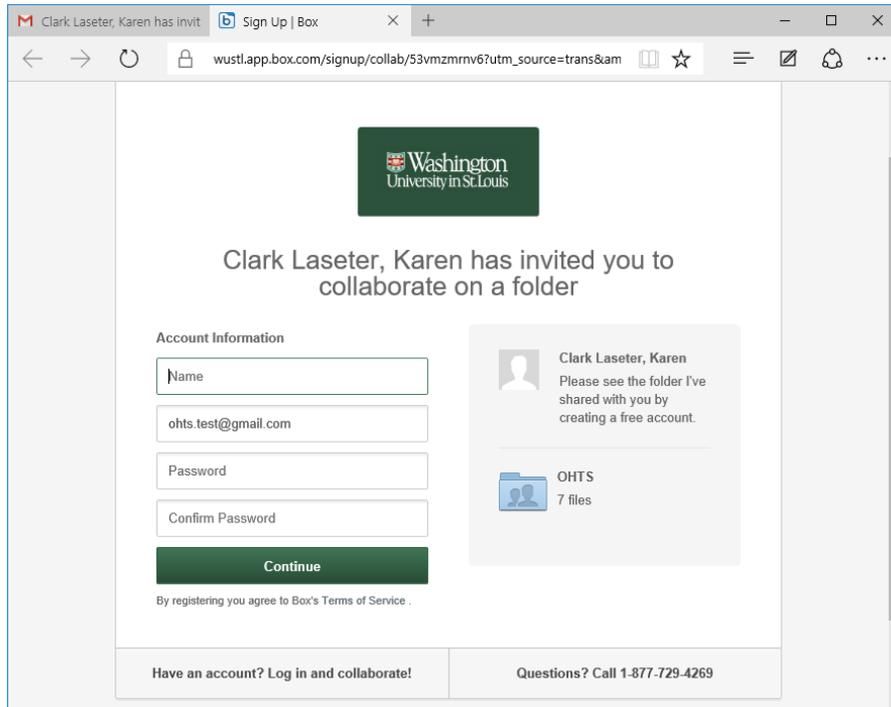
1. Uploading data electronically using WUStL Box <http://www.app.box.com> (Preferred method)
2. Password-protected flash drive (described later)

Setting up a WUStL Box account

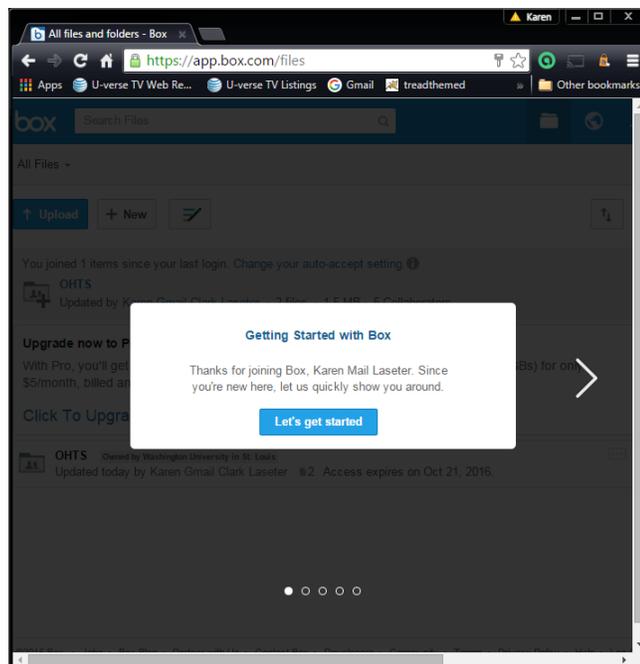
1. Coordinating Center will create an account for each Clinical Center that uses WUStL Box. This needs to be done only once, and will allow access to the Reading Center folders.
2. Each individual/technician/photographer transmitting data from the Clinical Center will receive their own invite/username/password.
3. Each clinic will confirm acceptance of the Box account by responding to an e-mail inviting them to collaborate on Box. Each clinic will receive a separate invitation for OD Photos and OCT Images. See example e-mail below:
4. Be sure to label all OD photos and OCT images according to the OHTS protocol.



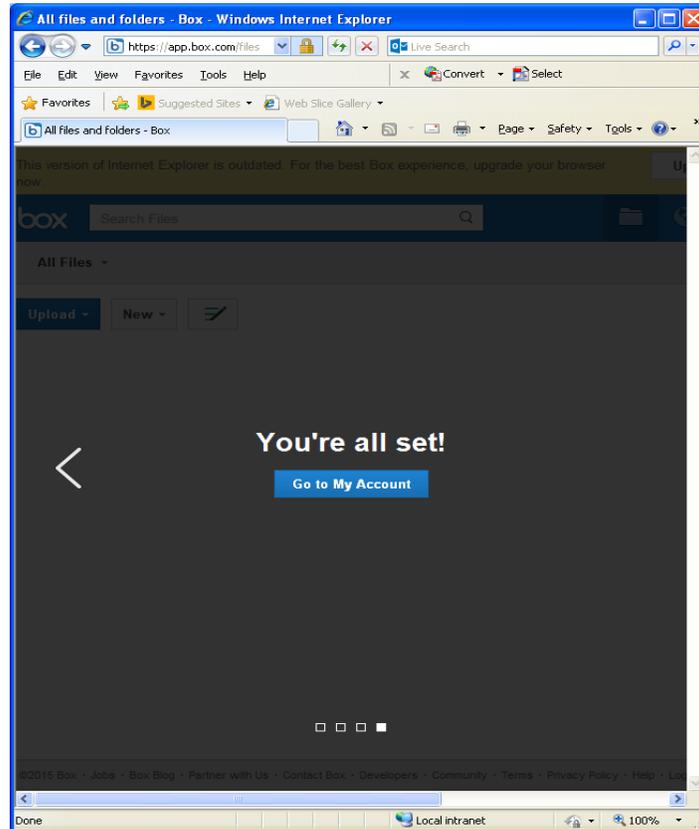
5. Click on **Accept Invite**. It will take you to the Washington University Box System (Clark Laseter, Karen)



6. Your e-mail address will be pre-filled. Enter your name and create a password. Once logged in, it will offer you a brief walk-through of the features:

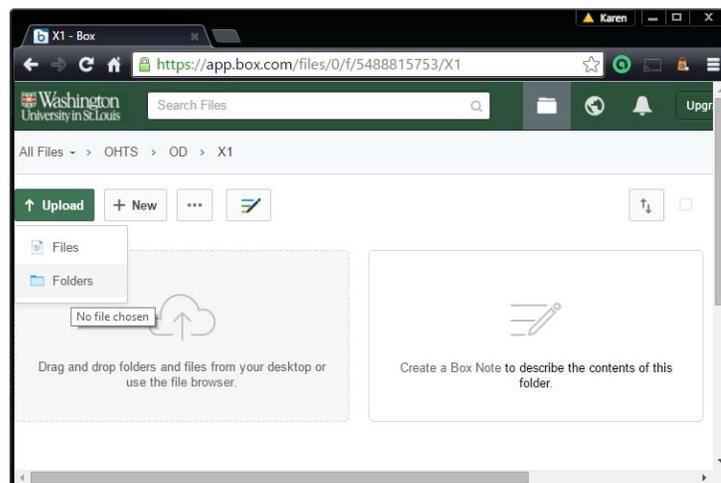


7. Scroll through 3 more screens by clicking on the right arrows. On the 4th screen, choose **Go to My Account**

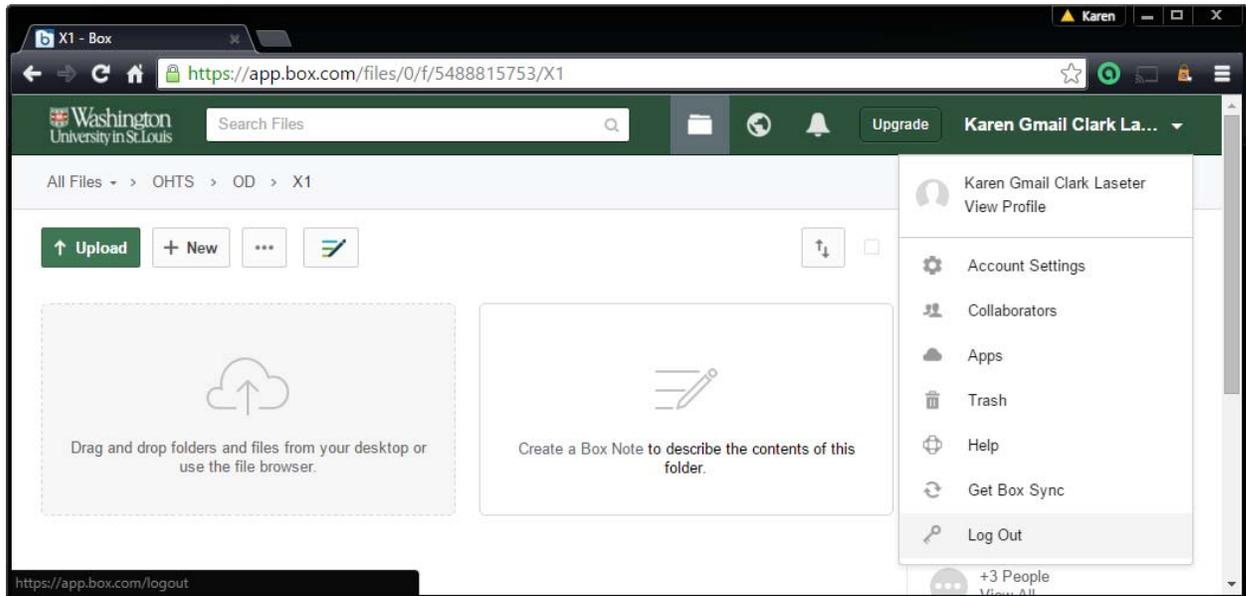


Accessing WUSTL Box Drives: Use app.box.com

You will see your OCT and clinic-specific OD folders. Click on the folder you need, and then **Click on the Upload tab** to upload folders.



- When finished uploading files, log out of Box by clicking on your name in the upper right corner, and choose **Logout**.



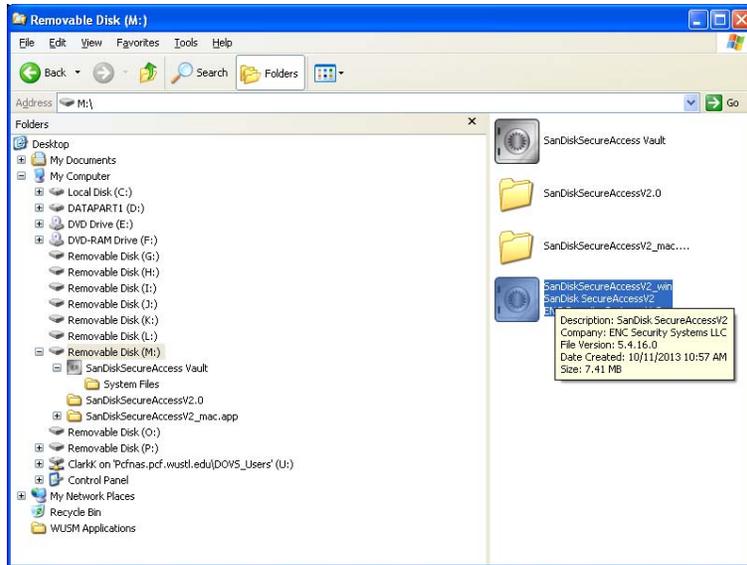
- To return to the BOX in the future, login at <https://app.box.com/login>

Using Encrypted Flash Drive to Send Optic Disc Photos and OCT Images to Coordinating Center

If a Clinical Center is unable to use the WUSTL Box system to upload OD photos or OCT images, the optional method is using a password-protected flash drive for this purpose, which the Coordinating Center will provide. The Coordinating Center will send you the password for the flash drive by e-mail. These instructions apply to Windows users. Mac users should contact to Coordinating Center to request Mac-appropriate flash drives.

Loading data onto USB flash drive

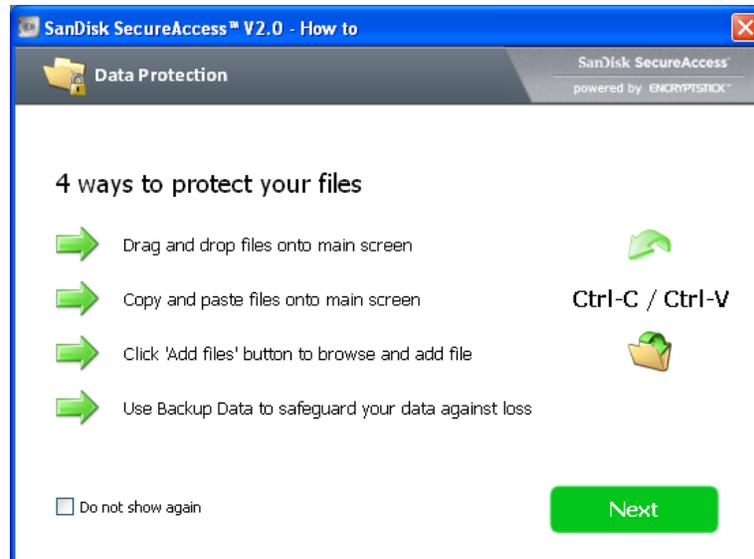
- Extend the retracted drive. Insert the flash drive into a USB port. If you have a USB 3.0 port, use this, as it will provide the fastest transfer speeds. If the drive does not automatically open, go to **My Computer** to find the drive, and click on the flash drive. See example below.



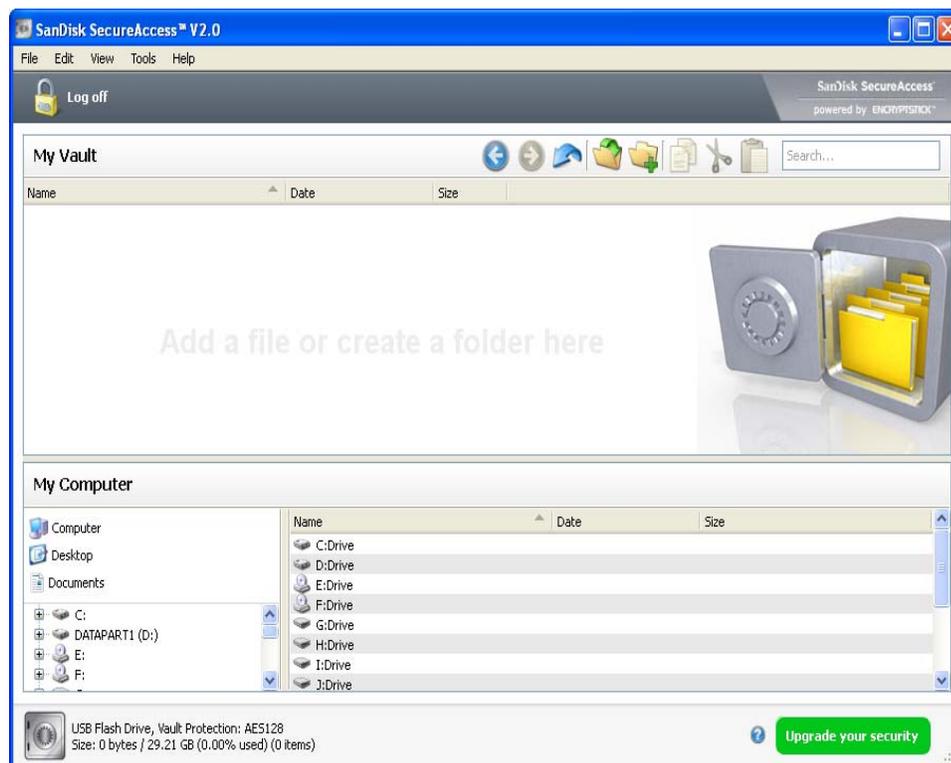
2. Click on the SanDisk SecureAccessV2-win (as highlighted above).
3. Enter the password to log in (provided via e-mail):



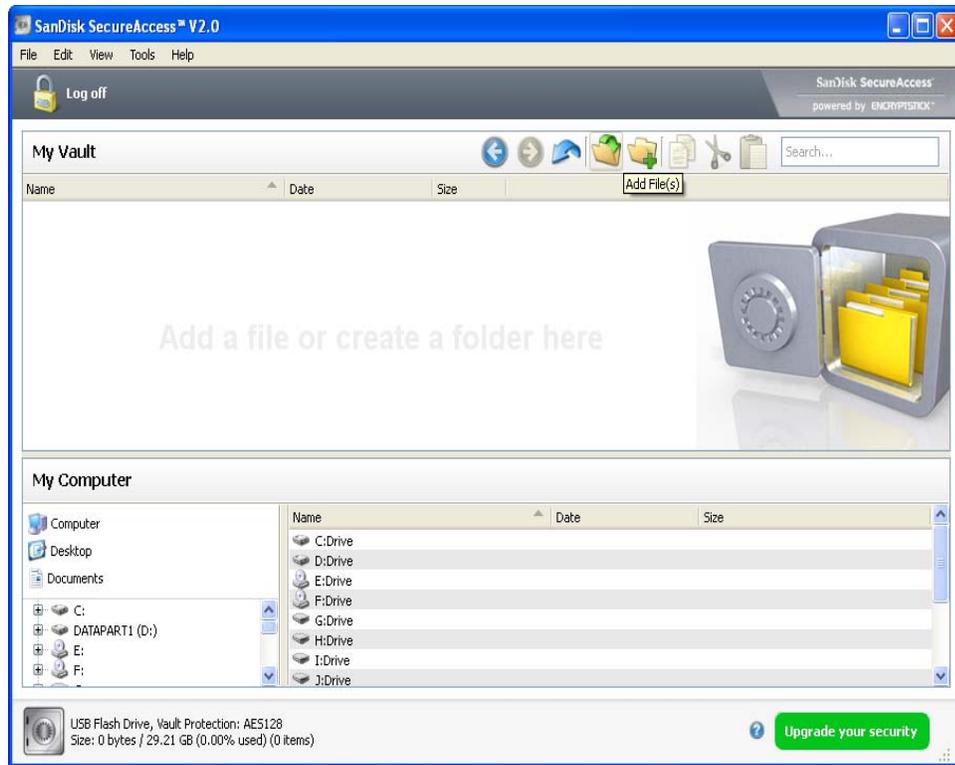
Introductory screen is shown:



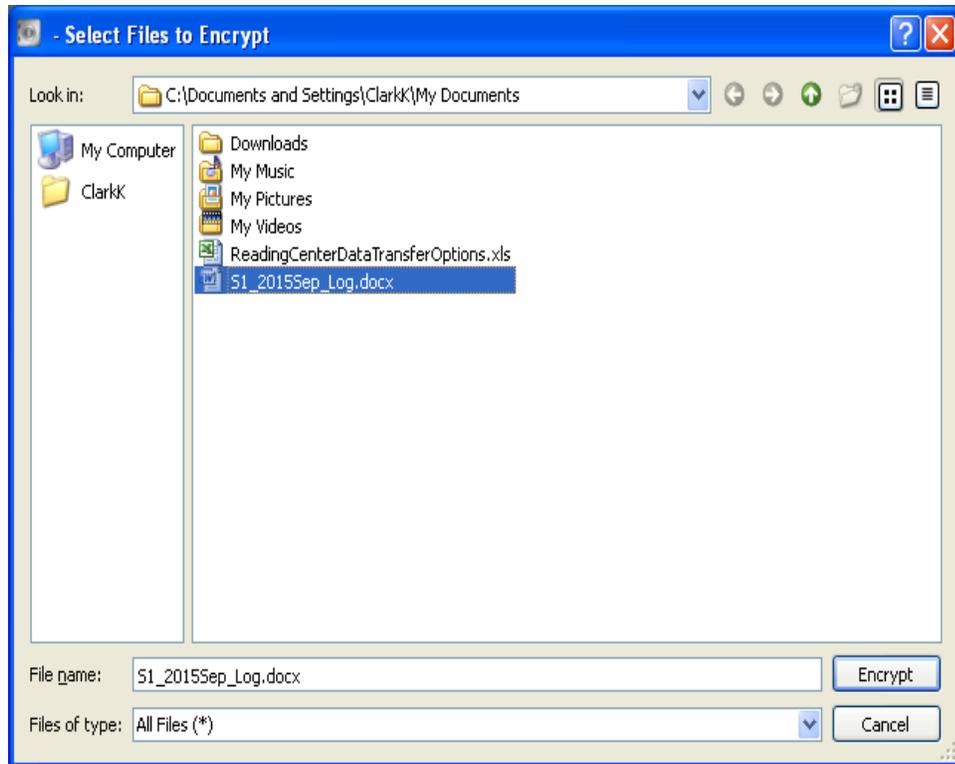
4. Click the green Next button
5. You will see **My Vault** as shown below.



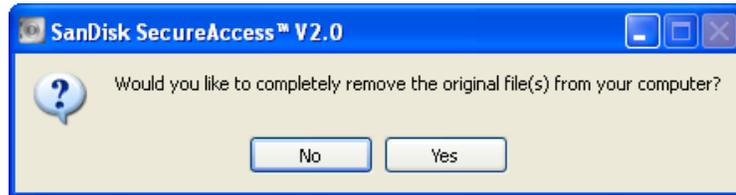
6. You may need to navigate to the OD or OCT subdirectory. Select files to be copied to drive by pressing the icon (in "My Vault") with the green arrow in the folder, or select an entire folder to be copied by pressing the folder with a green plus sign.



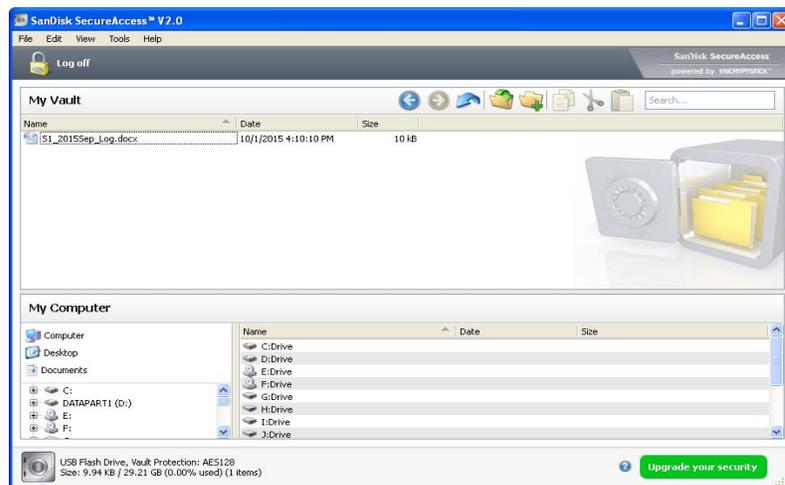
Identify the file(s) or folder(s) you want to transfer to the vault and select **Encrypt**



7. You are given an option to remove the original file from your computer. Select **“No”**



8. Confirm that the file is in your vault



9. When done transferring files/folders, select **Log off** in upper left corner.
 10. You can now remove the drive from your computer.

Please Call Karen Clark for any WUSTL Box System related questions or issues.

Karen Clark

(P) 314-362-2349

E-mail: Karen@wubios.wustl.edu

WUSTL Box: <http://www.app.box.com/>