Ocular Hypertension Treatment Study (OHTS)

Manual of Procedures Version 3.0 9/24/01

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1. Introduction

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1.1 Synopsis of Study

Elevated intraocular pressure (IOP) is a common condition and is thought to be the leading risk factor for the development of open-angle glaucoma. There is conflicting evidence as to whether early medical treatment is effective in preventing or delaying the onset of glaucomatous damage in individuals with elevated intraocular pressure (referred to as ocular hypertensive individuals or glaucoma suspects). The proposed study is a long-term, randomized, multicenter, clinical trial to determine whether medical reduction of intraocular pressure prevents or delays the onset of glaucomatous optic nerve and/or visual field defects in ocular hypertensive individuals. 1500 participants with IOPs \geq 24 mm Hg but \leq 32 mm Hg in at least one eye (IOPs ≥ 21 mm Hg in the fellow eye) as determined by two separate determinations taken at least two hours, but not greater than 12 weeks apart, and normal visual fields and optic discs in both eyes will be assigned randomly to receive stepped medical treatment to both eves or to close observation only to both eves. At this level of intraocular pressure, the participants are considered to be at moderate risk for the development of openangle glaucoma. The participants will be followed twice-yearly with automated, threshold, central static perimetry (Humphrey program 30-2) and once-yearly with stereoscopic optic disc photographs. The study endpoints are reproducible optic nerve damage and/or reproducible glaucomatous visual field loss in either eye of an individual. All visual fields and optic disc photographs will be read in masked fashion in Reading Centers. The participants will be followed for a minimum of five years with follow-up continuing until study termination.

1.2 Specific Aims

Primary Aim: To determine whether medical reduction of IOP prevents or delays the onset of glaucomatous visual field loss and/or optic nerve damage in ocular hypertensive individuals judged to be at moderate risk for developing open-angle glaucoma.

Secondary Aims: To identify risk factors that predict which ocular hypertensive individuals are most likely to develop glaucomatous visual field loss and/or optic nerve damage. Potential risk factors include age, cup/disc ratio, intraocular pressure, myopia, systemic vascular disease, family history of glaucoma, and African American heritage.

1.3 Background and Significance

In all surveys, glaucoma is among the leading causes of blindness in the United States and other industrialized countries.^{1,2} It is estimated that 2 million people in the United States have glaucoma and that 80,000 of these individuals are legally blind from the disease.^{1,2} The prevalence of glaucoma is higher in some subsets of the population such as diabetics, myopes, and African Americans. It is now clear that glaucoma is the leading cause of blindness in African Americans.³⁻⁹ In the recently published Baltimore Eye Survey, African Americans had a prevalence of open-angle glaucoma four to five times higher than did whites. The prevalence of open-angle glaucoma among African Americans ranged from 1.23% in those age 40 to 49 years to 11.26% in those 80 years or older.¹⁰

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It is estimated that 3 to 6 million people in the United States, including 4% - 7% of the population above age 40, have elevated IOP without detectable glaucomatous damage using current clinical tests. Thus, these individuals are at an increased risk for developing open-angle glaucoma. Up to now there has been no consensus on how to manage this large group of people, who are referred to as ocular hypertensives or glaucoma suspects. Ouigley and coworkers reported that up to 50% of the optic nerve fibers can be lost before glaucomatous visual field defects are detected by routine kinetic perimetry.¹¹ The studies of Quigley and coworkers, the high prevalence of glaucoma, and the serious consequences of the disease suggest the need for widespread glaucoma screening and early treatment. This aggressive approach is strengthened by evidence from clinical studies as well as by the almost universal clinical impression that treatment initiated early in the course of glaucoma is far more effective in preventing progressive visual loss than is treatment initiated late in the course of the disease.¹ However, this approach of widespread glaucoma screening and early treatment has been challenged by investigators who point out that there is insufficient scientific information to support a major health initiative.¹⁶ One of the prerequisites for any screening program is that there must be an effective treatment for the disease. Surprisingly, there is relatively little information on the efficacy of medical treatment in preventing or delaying the onset of glaucomatous damage.¹

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Table 1 Studies of Medical Treatment in Glaucoma Suspects

Investigator	Sample Size	Treatment	Developed Visual Field Loss	Comments
Graham ¹⁷	201	1% pilocarpine and/or 1%	1 person developed visual field loss	Low rate of conversion to glaucoma
		epinephrine bid		Short follow-up
				regularly
				Very small IOP differential between treated and untreated individuals
Norskov ¹⁸	110	not specified	0/68 untreated people	Retrospective design
			3/42 treated people	Nonrandomized treatment assignment
			1 1	Not a well-coordinated study
				Low rate of conversion to glaucoma
Levene ¹⁹	59	2% pilocarpine qid or	1/59 untreated eyes	Low rate of conversion to glaucoma
		phospholine iodide	3/59 treated eyes	Small sample size
			·	Little pressure differential between treated and untreated eves
David ²⁰	61	2%-4% pilocarpine tid or gid:	3/67 untreated eyes	Variable follow-up
		some patients also received	9/50 treated eves	Nonrandomized treatment assignment, with
		epinephrine and/or carbonic	5	eves at greatest risk receiving treatment
		anhydrase inhibitors		Nonstandardized treatment regimen
Chisholm ²¹	101	not specified	unclear	Uninterpretable study as published
Chauhan ⁵⁰	143	.25%5% timolol bid	25/70 untreated people	Treatment limited to a single drug
			22/73 treated people	Unusually high rate of conversion to glaucoma
Becker ²³	50	2% epinephrine bid	7/50 untreated eyes	Small sample size
			2/50 treated eyes	Variable follow-up due to side effects
				Treatment limited to a single drug
Shin ²⁴	19	1%-2% epinephrine bid	6/19 untreated eyes	Small sample size
			0/19 treated eyes	Unresponsive patients dropped from trial
Kitazawa ²⁵	52	.25%5% timolol bid	1/26 untreated people	Small sample size
			2/26 treated people	Low conversion rate to glaucoma
				Short follow-up
				Treatment limited to a single drug
Epstein ²⁶	107	.25%5% timolol bid	7/54 untreated people 4/53 treated people	Treatment limited to a single drug
Kass ²⁷	62	.25%5% timolol bid	10/62 untreated eyes	Small sample size
			4/62 treated eyes	Treatment limited to a single drug

In addition, the published studies are almost equally divided between those that find early medical treatment to be effective in preventing or delaying glaucomatous damage ²³⁻²⁷ and those that do not.¹⁷⁻²² Furthermore, most of the published studies are limited by such factors as small sample size, limited ethnic representation, short follow-up periods, nonrandomized treatment assignment, outdated definitions of glaucoma, insensitive techniques for detecting glaucomatous damage, and limitation to a single drug for lowering IOP.

Despite the lack of convincing evidence for the efficacy of medical treatment in ocular hypertension, it is estimated that 1.5 million glaucoma suspects in the United States are nonetheless being treated with ocular hypotensive medications. The majority receive a topical beta blocker. If we estimate that each patient uses eight bottles of drops per year at \$25 per bottle (both estimates are quite conservative), the total cost is \$300 million per year (personal communication, David Fellows, Director of Marketing, Allergan Pharmaceuticals). There is little information about the health benefits of this major expenditure. It should also be stressed that topical ocular hypotensive medications produce a variety of side effects that can be serious and even life-threatening. Thus, the costs to society and to the individual in terms of disability, dollars spent, time consumed, and lost productivity are even greater than indicated above.

From the above discussion, it seems clear that there is a need for a well controlled, randomized clinical trial to determine whether medical reduction of IOP can prevent or delay the onset of glaucomatous damage in ocular hypertensive individuals. The trial must include a variety of medications and must be of sufficient power and robustness to provide a definitive answer to this issue. Only then can clinicians and patients make rational choices and health care planners ensure that limited medical resources are being allocated in a cost-effective manner.

This trial is designed to study the efficacy and safety of early medical treatment in ocular hypertension. However, there will be other spin-offs or additional benefits of the trial. It is clear from the previous discussion that African Americans have a much higher prevalence of open-angle glaucoma than do whites. However, there are no prospective data on the conversion rate of African American ocular hypertensives to open-angle glaucoma. The proposed trial will include 400 African American ocular hypertensives and, thus, will provide good data on this issue.

Another important issue is to identify ocular hypertensive individuals most likely to develop open-angle glaucoma. In previous studies, we developed quantitative estimates of risk for individual ocular hypertensive individuals. The proposed study should allow us to refine and validate these estimates in a large, national sample. Thus, at the end of the proposed study, practitioners should have useful information about which ocular hypertensive individuals are most likely to develop open-angle glaucoma and which are most likely to benefit from early medical treatment. One additional matter deserves emphasis. The 5-Fluorouracil and Glaucoma Filtering Surgery Study (FFSS) and the Advanced Glaucoma Intervention Study (AGIS) included individuals with advanced glaucoma. The Glaucoma Laser Trial (GLT) focused on patients with early to moderate glaucomatous damage. The Ocular Hypertension Treatment Study includes individuals with the earliest stage of open-angle glaucoma, i.e., before damage is detectable by present clinical methods. Thus, when all of these clinical trials are completed, physicians and health planners will have information about all stages of open-angle glaucoma to judge the efficacy, safety, and cost-effectiveness of treatment.

1.4 Progress Report/Preliminary Studies

1.4.1 Long Term Timolol Study

The Principal Investigator/Study Chairman and coworkers recently completed a long-term, double-masked, randomized, clinical trial on whether topical timolol treatment prevents or delays the onset of glaucomatous damage in ocular hypertensive individuals.²⁷ Sixty-two participants with IOPs between 24 and 35 mm Hg in both eyes were enrolled in the study. All participants had normal visual fields and normal optic discs at baseline. The participants were considered to be at moderate risk for developing open-angle glaucoma on the basis of elevated IOP as well as a high prevalence of other risk factors, including a family history of glaucoma, decreased outflow facility, large cup/disc ratio, and systemic vascular disease. For each participant, one eye was assigned randomly to receive timolol 0.25% twice daily while the fellow eye received placebo eyedrops. The participants were examined three times yearly with applanation pressures and perimetry. Stereoscopic optic disc photographs were taken once yearly.

The mean duration of follow-up was 56.1 ± 26.5 months. Timolol administration reduced IOP from baseline by 4.8 mm Hg in the treated eyes. Timolol administration also reduced IOP from baseline by 2.8 mm Hg in the fellow, placebo-treated eyes. The mean difference in IOP between the timolol-treated and the placebo-treated eyes over the course of the study was 2.3 ± 2.6 mm Hg.

Reproducible glaucomatous visual field loss (as determined by a committee of clinicians masked as to treatment assignments) developed in four timolol-treated eyes and ten placebo-treated eyes (p = 0.039, one-tailed McNemar test). Over the course of the trial, visual field loss developed in 11 of the 62 participants, or 17.7% of the sample. Progressive optic nerve damage (as determined by a committee of clinicians masked as to treatment assignments) developed in four timolol-treated eyes and eight placebo-treated eyes (p = 0.11, one-tailed McNemar test). Optic disc pallor was quantified from baseline and final optic disc photographs using a computerized image analysis system in 42 participants who completed a minimum four-year follow-up. In these 42 participants, the increase in optic disc pallor over the course of the study in the timolol-treated eyes was

 $0.86\% \pm 2.4\%$ as opposed to $1.80\% \pm 3.6\%$ in the placebo-treated eyes (p = 0.02, onetailed, paired Student's t test). We concluded that topical timolol administration had reduced the incidence of glaucomatous damage in participants with ocular hypertension. The limitations of the trial included a relatively small sample size (n = 62), a substantial loss of subjects because of voluntary withdrawal as well as the development of exclusion criteria and drug-related side effects, and a contralateral IOP reduction which reduced the pressure differential between treated and "untreated" eyes. The restriction to a single drug also meant that some treated eyes had little or no reduction of IOP and that serious drug-related side effects required withdrawal from treatment.

1.4.2 Risk Factors in Ocular Hypertension

The Principal Investigator/Study Chairman and coworkers did two studies on risk factors for the development of glaucomatous visual field loss in ocular hypertensive individuals. In a retrospective study, 92 participants with ocular hypertension, i.e., intraocular pressure of 21 mm Hg or higher and no evidence of glaucomatous visual field defects, were observed for five years. Visual field defects developed in one or both eyes of 33 participants during the five-year follow-up period (35.8% of the sample). Values for suspected risk factors, determined at the outset of the follow-up period, were subjected to a multivariate analysis with use of linear discriminant analysis and a multiple logistic function. Models of risk providing maximum separation of the two participant groups (visual field loss vs. no visual field loss) found that the risk factors having the greatest significance for prediction of visual field loss included vertical estimates of cup/disc ratio, mean IOP during the period of observation, a positive family history of glaucoma, and age.

These risk factors were then validated in a prospective study using a different cohort of participants. We estimated the risk of developing glaucomatous visual field loss for each of 243 ocular hypertensive participants (IOP 21-35 mm Hg).²⁹ The risk coefficient was estimated using a logistic regression analysis that took into consideration baseline IOP, family history of glaucoma, age, and baseline vertical cup/disc ratio by color. The participants were followed without treatment for a median time of 63 months. During the study, 18 participants (7.4% of the entire sample) developed glaucomatous visual field loss in one or both eyes. The participants were separated into four categories of risk. Over the follow-up period, glaucomatous visual field loss developed in 3 of 143 subjects (2.1%) judged to be in the lowest category of risk, 3 of 41 participants (7.3%) in the next higher category, 5 of 33 subjects (15.1%) in the third category and 7 of 26 subjects (26.9%) in the highest category of risk. This study clearly demonstrated that participants who developed glaucomatous visual field loss had higher coefficients of risk at baseline than did the participants who maintained normal visual fields (p = 0.0011).

1.4.3 Humphrey Visual Fields Criteria for Reliability and Normality

Almost all investigators utilize < 33% false positive and false negative responses as indices for reliable Humphrey visual fields. This consensus, however, does not include the rate of fixation losses as some investigators utilize a < 20% fixation loss criterion while other investigators have recommended relaxing the fixation loss criterion to

< 33%.^{30-33,52} The Planning Committee asked Drs. John Keltner and Chris Johnson and associates to assess the impact of relaxing the fixation loss criterion on the reproducibility and retest rate of the visual field endpoints chosen for OHTS. Keltner and Johnson and coworkers examined data from normal and ocular hypertensive patients followed at UC Davis and ocular hypertensive patients followed at Washington University.

Relaxing the fixation loss criterion from < 20% to < 33% increased the number of ocular hypertensive individuals who would be eligible for OHTS by 10% to 20% in both data sets. Fortunately relaxing the fixation loss criterion did not reduce the reproducibility of the visual field data or increase the retest rate. Using the < 20%fixation loss criterion, 17.5% of the visual fields would have required retesting to confirm a visual field defect. If the < 33% fixation loss criterion was used, 17.0% of the visual fields would have required a confirming test. Furthermore, the rate at which the defects would have been confirmed was essentially identical with both fixation loss criteria. Thus, relaxing the fixation loss criterion from < 20% to < 33% should aid recruitment without diminishing the quality or reproducibility of the visual field data.

1.4.4 Clinical Trials

The investigators for this study have extensive experience in multicenter clinical trials. The Principal Investigator/Study Chairman, Michael A. Kass, M.D., served on the Planning Committee and the Steering Committee for the 5-Fluorouracil and Glaucoma Filtering Surgery trial (FFSS). He was also the principal investigator of the St. Louis Clinical Center for this project. Dr. Kass served also on the Planning Committee for the proposed trial entitled "Collaborative Initial Glaucoma Treatment Study."

The vice-chair, Dale K. Heuer, M.D., served on the Planning and Steering Committees for the 5-Fluorouracil and Glaucoma Filtering Surgery Study. He was also the principal investigator of a Clinical Center for this project.

The vice-chair, Eve J. Higginbotham, M.D., participated in a Clinical Center in the 5-Fluorouracil and Glaucoma Filtering Surgery Trial and served on the Steering Committee and as a principal investigator for a Clinical Center in the Advanced Glaucoma Intervention Study (AGIS).

The vice-chair, Richard K. Parrish, II, M.D., was principal investigator of the 5-Fluorouracil and Glaucoma Filtering Surgery Study.

1.4.5 Planning Sessions

It seemed obvious that a large, randomized, multicenter clinical trial would be necessary to determine the efficacy and safety of medical treatment in ocular hypertensive individuals. This would only be possible if there was strong interest in such a trial among glaucoma clinical researchers. Michael A. Kass, M.D. and Mae E. Gordon, Ph.D. called a meeting during ARVO 1989 and sent invitations to 100 clinical glaucoma investigators. Fifty-eight investigators attended the meeting. Many other investigators indicated a strong interest in participating in such a trial but were not able to attend the meeting because of conflicts during the busy ARVO week. 45 investigators from 36 medical centers indicated an interest in participating as a Clinical Center, and 45 investigators indicated a desire to participate in a planning meeting.

On July 14-16, 1989, 14 clinicians and scientists met in St. Louis as a Planning Committee to develop the general guidelines for the clinical trial. The current grant proposal is a direct outgrowth of the meeting in St. Louis.

On July 12-14, 1991, eight clinicians and scientists met as a Planning Committee to consider the recommendations of the NEI Vision Research Review Committee and the NEI Council in formulating a revised application. The current grant proposal is a direct outgrowth of the meeting.

On July 6, 1992, Drs. Gordon and Kass met with NEI staff to discuss streamlining the trial and incorporating features of a community-based trial.

On August 28, 1992, Drs. Gordon, Kass, Caprioli, Higginbotham, Heuer, and L. Jay Katz met with NEI staff to refine the protocol.

On May 1, 1993, Drs. Kass, Gordon, Caprioli, Heuer, Higginbotham, Johnson, Keltner, Parrish, and Schechtman met with NEI staff to discuss Clinical Center applications, protocol refinement, and ancillary studies.

On July 29, 1993, Drs. Kass, Gordon, Caprioli, Heuer, Higginbotham, Johnson, Parrish, and Schechtman met with NEI staff to discuss funding and responsibilities of the Optic Disc Reading Center.

1.4.6 Study Milestones

November 4, 1993	First meeting of the Data and Safety Monitoring Committee in St. Louis, Missouri.
January 21, 1994	First Full Investigative Group Meeting in St. Louis, Missouri.
February 21, 1994	Optic Disc Reading Center moved to Bascom Palmer, Dr. Richard Parrish, Director.
February 28, 1994	First participant randomized at Devers Eye Institute.
December 1, 1994	Endothelial Cell Density Ancillary Study funded, Dr. William Bourne, Principal Investigator, Mayo Clinic/Foundation (Chapter 17).
July 1, 1995	Confocal Scanning Laser Ophthalmoscopy Ancillary Study funded, Dr. Robert Weinreb, Principal Investigator, UC-San Diego (Chapter 17).
July 1, 1995	Short Wave-Length Automated Perimetry Ancillary Study funded, Dr. Chris Johnson, Principal Investigator, UC-Davis (Chapter17).
October 31, 1996	Last participant randomized at Kresge Eye Institute.
June 1, 1997	Data and Safety Monitoring Committee recommends an increase in the number of abnormal visual fields required to confirm an abnormal visual field for POAG Endpoint determination. To be considered for endpoint review participants must present with three abnormal visual fields in a row with the same defect in the same location.
October 1, 1997	Short Wave-Length Automated Perimetry Ancillary Study moved to Devers Eye Institute, Dr. Johnson, Principal Investigator.
December 1, 1997	National Eye Institute awards administrative extension to OHTS Coordinating Center and Chairman's Office. Project period to run through November 30, 2003.
October 9, 1998	Data and Safety Monitoring Committee approves addition of pachymetry measurements to the OHTS protocol.
March 5, 1999	First pachymetry measurement performed at UC-Davis.

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May, 1999	Manuscript entitled "The Ocular Hypertension Treatment Study: Design and Baseline Description of Participants" is published in <i>Archives of Ophthalmology</i> .
July 1, 2000	National Eye Institute approves continuation grant for Confocal Scanning Laser Ophthalmoscopy Ancillary Study. Project period to run through June 30, 2005.
July 1, 2000	National Eye Institute approves continuation grant for Short Wave- Length Automated Perimetry Ancillary Study Project period to run through June 30, 2005.
September, 2000	Manuscript entitled "Confirmation of Visual Field Abnormalities in the OHTS" is published in <i>Archives of Ophthalmology</i> .
October, 2000	Manuscript entitled "Contralateral Effect of Topical β -Adrenergic Antoganists in Initial One-eyed Trials in the OHTS" is published in the <i>American Journal of Ophthalmology</i> .

Summary of Revisions

Chapter 2 - Study Design

Section		Date	Description
2.2.1	Entry Criteria	1/21/94	Prestudy VF & photos can be performed by non-certified
			personnel so long as they meet protocol.
		4/25/94	Individuals ineligible for unreliable or abnormal (9/5/95)
			VF's can be retested after 12 weeks.
		10/27/94	Individuals ineligible for IOP can be retested after 12
			weeks.
		2/14/95	Qualifying IOP's must be consecutive.
<u>2.2.3</u>	Rationale for Entry and	1/21/94	Prestudy VF & photos can be performed prior to wash-out.
	Exclusion Criteria		
<u>2.5.1</u>	Stepped Medical	3/1/95	Target treatment goal is 20% reduction from average of
	<u>Regimen</u>		Qualifying IOP and Baseline IOP, not from Baseline IOP
			alone.
2.5.3	Adverse Events and	7/28/95	SF-36 is administered at semi-annual follow-up exams.
	Drug Related Side	9/5/95	Adverse Events form should be completed for each ocular
	<u>Effects</u>		or systemic complex, not necessarily each symptom.
2.5.3	Hospital Discharge	9/6/96	DSMC requests retrieval of hospital discharge summary for
			each inpatient hospitalization.
<u>2.5.3</u>	Participant Death	9/6/96	In event of participant death, send Adverse Event form and
			Patient Death form to Coordinating Center.
2.6	Participant Follow-Up	1/31/94	ETDRS V/A is added to annual follow-up exams.
	and Retention	1/1/99	Pachymetry measurement is added as a one-time measure of corneal thickness.
2.7	POAG Endpoints	4/16/99	DSMC permits Endpoint Committee to review both eyes,
			rather than just the affected eye.
		1/1/00	Confirmation testing for participants already at POAG will
			occur at regularly scheduled visits, not at expedited
			confirmation visits.
<u>2.7.1</u>	POAG Endpoint	7/28/95	Red reflex photograph is added to document lens opacities
	by Optic Disc		at annual follow-up visits.
		10/24/97	Macular photographs are added at annual visits when stereo
			photos are taken to assist Endpoint Committee attribute
			cause of visual field abnormality.
		5/1/98	DSMC requires disc progression to be "clinically
			significant" for participants to be defined as reaching a
			POAG endpoint.
2.7.3	POAG Endpoint	10/24/97	Confirmation of visual field abnormality now requires three
	by Visual Field		consecutive visual fields with a defect of the same character
		c /a /c =	in the same location. Previously, this number was two.
2.10.4	<u>Kısks</u>	6/1/95	Trusopt side effects added
		7/1/98	Azopt side effects added
		7/1/98	Cosopt side effects added
		11/1/00	Rescula side effects added

2. Study Design

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2.1 Synopsis of Study Design

Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. In fact, glaucoma is now recognized to be the number one cause of blindness in African Americans. Glaucoma is one of the most common causes of irreversible blindness in individuals above age 60, one of the fastest growing groups in the United States. Elevated intraocular pressure (IOP) is a key risk factor for the development of open-angle glaucoma. There is no consensus on whether early treatment of elevated IOP prevents or delays the onset of open-angle glaucoma.

The OHTS is a long-term, randomized, multicenter clinical trial to determine whether medical reduction of intraocular pressure prevents or delays the onset of glaucomatous optic nerve damage and/or visual field defect in ocular hypertensive individuals. 1500 participants with IOPs \geq 24 mm Hg but \leq 32 mm Hg in at least one eye (IOPs \geq 21 mm Hg in the fellow eye) as determined by two separate determinations taken at least two hours, but not greater than 12 weeks apart, and normal visual fields and optic discs in both eyes are randomly assigned to receive stepped medical treatment to both eyes or to close observation only to both eyes. The participants are followed through study end (a minimum of five years) with automated, threshold, central static perimetry (Humphrey program 30-2) twice yearly and stereoscopic optic disc photographs once yearly. The study endpoints are reproducible optic nerve damage and/or reproducible glaucomatous visual field loss in either eye of a subject. All visual fields and optic disc photographs are read in masked fashion in Reading Centers.

While this trial is designed to study the efficacy and safety of early medical treatment in ocular hypertension, there will be other benefits as well. This study will allow us to refine and validate estimates of risk for individual ocular hypertensive patients in a large national sample. Furthermore, this study will also determine the conversion rate of African American ocular hypertensive individuals to open-angle glaucoma. At the conclusion of this study, practitioners should be able to make reasonable estimates of risk for individual ocular hypertensive patients and determine which ocular hypertensive individuals are most likely to benefit from early prophylactic medical treatment.

The Study Chairman's Office and the Coordinating Center are at Washington University. The Visual Field Reading Center (VFRC) is at UC-Davis, and the Optic Disc Reading Center (ODRC) is at Bascom Palmer Eye Institute. The various Clinical Centers were chosen by the NEI using an RFA mechanism.

Resource centers to support ancillary studies include the Short Wave-Length Perimetry (SWAP) Reading Center at Devers Eye Institute, Confocal Scanning Laser Ophthalmoscope (CSLO) Reading Center at UC-San Diego, and the Corneal Endothelial Cell Morphology (ENDO) Reading Center at Mayo Clinic/Foundation. These ancillary studies are described in greater detail in Chapter 10, Study Organization. Manual of Procedures for these ancillary studies are included in appendices to the OHTS Manual of Procedures.

Timetable For OHTS

Year 1	Refinement of protocol and Manual of Procedures			
	Request for applications (RFA) for Clinical Centers			
	Selection of Clinical Centers			
	Development and pretesting of forms			
	Development of quality control procedures including training, certification, recertification			
	Public relations campaign			
Year 2-3	Training and certification of Clinical Center personnel Participant recruitment			
	Public relations campaign			
	Participant follow-up			
Year 4-7	Participant follow-up			
Year 8	Complete participant follow-up and close study			
Year 9	Data analysis			
	Publication of primary results			

2.2 Participant Selection

2.2.1 Entry Criteria

- a. The qualifying IOP in at least one eye of each individual must be ≥ 24 mm Hg but ≤ 32 mm Hg calculated from two separate consecutive determinations taken at least two hours, but not greater than 12 weeks apart. A determination consists of either the mean of two measurements or the median of three measurements (see chapter 7). The fellow eye must have a qualifying IOP ≥ 21 mm Hg on two determinations. All IOP readings are taken by two certified study personnel, recorder and operator, at approximately the same time of day to minimize diurnal fluctuations. If IOP falls outside the qualifying range, individuals may be reevaluated for inclusion **once and only once** twelve weeks after the date of the last Qualifying Assessment visit. All IOP readings are performed after appropriate washout of prestudy topical ocular medications as follows:
 - 1) miotics 1 week
 - 2) beta-blockers 4 weeks
 - 3) epinephrine/dipivefrin 4 weeks
 - 4) alpha 2 agonist 2 weeks
 - 5) topical carbonic anhydrase inhibitors 2 weeks
- b. Age 40 to 80 years, inclusive.
- c. Normal and reliable Humphrey 30-2 visual fields for both eyes as determined by the VFRC. Individuals undergo a minimum of two and a maximum of three visual field tests, and all but prestudy visual fields must be done by certified study technicians.

Two of the three tests must meet reliability criteria of < 33% false positives, < 33% false negatives, and < 33% fixation losses. Two of the three visual fields must be judged to be normal by the VFRC, including all STATPAC II global indices (mean defect [MD], pattern standard deviation [PSD], short-term fluctuation [CSF], and corrected pattern standard deviation [CPSD] being within the 95% age-specific population norm, and glaucoma hemifield test [GHT] being within the 97% age-specific population norm). Individuals who are ineligible due to unreliable and/or abnormal visual fields may be reevaluated for inclusion **once and only once** 12 weeks after the last Qualifying Assessment visit.

d. Normal optic discs in both eyes on clinical examination and on stereoscopic photographs as determined by the ODRC. The optic discs of both eyes must have intact rims and there should be no disc hemorrhages, notches, localized pallor, or asymmetry in the cup/disc ratios of the two eyes > 0.2. All <u>but</u> prestudy photographs must be taken by certified study photographers.

2.2.2 Exclusion Criteria

- a. Best-corrected visual acuity worse than 20/40 in either eye on qualifying examination.
- b. Previous intraocular surgery, as determined by subject history and examination, including laser trabeculoplasty, laser iridotomy, filtering surgery, combined cataract/filtering surgery, penetrating keratoplasty, retinal detachment repair. The following are not exclusionary surgical procedures: A previous uncomplicated extracapsular cataract extraction with PC-IOL and no escape of vitreous to the anterior chamber, strabismus, cosmetic lid surgery (including blepharoplasty and ptosis repair), and radial keratotomy.
- c. A life-threatening or debilitating disease that limits the individual's ability to return a minimum of twice yearly until study end (a minimum of five years).
- d. Secondary causes of elevated IOP, i.e., exfoliation syndrome, pigment dispersion, systemic or ocular corticosteroid use, iridocyclitis, trauma. After discontinuation of corticosteroid use, individuals may be re-evaluated for study eligibility.
- e. Angle-closure glaucoma or anatomically narrow angles 75% of the circumference of the angle must be grade II or more by Shaffer criteria.
- f. Other diseases that cause visual field loss, i.e., pituitary lesions, demyelinating diseases, ischemic optic neuropathy, stroke.
- g. Background diabetic retinopathy, defined as a single microaneurysm seen on direct ophthalmoscopy with a dilated pupil. Retinal hemorrhage is **not an exclusion** unless associated with background or proliferative diabetic retinopathy.
- h. Inability to visualize or photograph the optic discs.
- i. Optic disc abnormalities that can produce visual field loss or that can obscure the interpretation of the optic disc, i.e., optic disc drusen, pits, colobomas, or other severe anomalies as determined by the ODRC.

- j. Individual's unwillingness to undergo random assignment to medication or close observation, failure to sign informed consent form.
- k. Pregnant or nursing women as determined by subject self-report and testing. Baseline pregnancy tests will be performed on all premenopausal women who have not been sterilized. Pregnant or nursing women can be reconsidered for inclusion after the period of pregnancy or nursing has ended.

2.2.3 Rationale for Entry and Exclusion Criteria

- Newly diagnosed versus previously followed individuals. A major issue was a. whether the OHTS should use only newly diagnosed ocular hypertensive individuals or individuals previously followed. In some respects it was appealing to use only newly diagnosed individuals. However, the Planning Committee rejected this choice because it would be extremely difficult to recruit an adequate number of newly Furthermore, newly diagnosed individuals are generally diagnosed individuals. younger, and age is a substantial risk factor for the development of open-angle glaucoma. Finally, there is no evidence that the risk of developing glaucomatous damage declines over time, i.e., an ocular hypertensive individual who has been followed for five years without developing damage is not at lower risk over the next In fact, studies performed in five years than a newly diagnosed individual. Scandinavia with a 20-year follow-up demonstrated that the incidence of glaucoma in ocular hypertensive individuals appears to be relatively constant over long periods of time.¹
- b. **Previous treatment or not.** A second major concern was whether to include individuals who have previously received medical treatment. Once again, it was appealing to limit the study to "virgin" eyes. However, the Planning Committee decided it would be extremely difficult to recruit enough such individuals to complete the study. Many practitioners in the community routinely treat all patients with elevated IOPs.
- c. Qualifying IOP. An obvious question is, why choose these levels of IOP as entry criteria? To some extent the choice was arbitrary and balances ease of recruitment with adequate conversion rates to glaucoma. The study could include ocular hypertensives whose qualifying IOPs are ≥ 21 or 22 mm Hg. This choice would have simplified participant recruitment. However, individuals with borderline IOPs have a low incidence of glaucoma (approximately 0.5% per year); thus, the sample size would need to have been increased substantially. Choosing a qualifying IOP ≥ 28 or 30 mm Hg would have increased the incidence of glaucoma, but would have made it more difficult to find suitable participants. The Planning Committee decided that a qualifying IOP ≥ 24 mm Hg was a reasonable compromise.

Individuals with qualifying IOPs > 32 mm Hg are excluded from the study as a safety measure. Such individuals are generally started on medical treatment because they have a high incidence of conversion to glaucoma. Many practitioners believe it is unethical to randomize individuals with very high IOPs.

Perhaps the most important reason to choose these IOP levels (24-32 mm Hg) for study entry is that this is the IOP range that creates the greatest uncertainty for Version 3.0 9/24/01

practitioners. Individuals with borderline IOPs (IOP 20-23 mm Hg) have a low incidence of glaucoma and most clinicians follow such patients without treatment. Patients with markedly elevated IOPs (IOP > 32 mm Hg) are usually started on medical treatment by clinicians. The group whose IOPs fall in between (IOP 24-32 mm Hg, inclusive) causes the most uncertainty. Because of this uncertainty most clinicians begin medical therapy despite the lack of evidence of treatment efficacy.

- d. **Refractive error.** The Planning Committee decided not to use refractive error, including astigmatic correction, as an exclusion factor provided the individual has a corrected visual acuity of 20/40 or better in both eyes, has reliable Humphrey visual fields, and has optic discs that can be photographed and examined clinically. The major reason to exclude individuals for refractive error is the fear that it will interfere with visual field testing.
- e. **Risk factors.** The Planning Committee decided not to require risk factors (family history of glaucoma, larger cup/disc ratio, systemic vascular disease) other than elevated IOP as entry criteria. It is obvious that many individuals recruited for the study will have one or more risk factors besides elevated IOP. However, a qualifying IOP of ≥ 24 mm Hg should identify individuals at sufficient risk for developing openangle glaucoma that it is not necessary to require additional risk factors. Furthermore, the use of other risk factors as entry criteria might inhibit participant recruitment and might limit the generalizability of the results, i.e., skew the sample. Because glaucoma is the leading cause of blindness in African Americans, the study will attempt to enroll 400 (26.7%) African Americans. This should yield important information about the incidence of glaucoma in African American ocular hypertensives and the protective effect of prophylactic treatment.
- f. **Systemic medications.** The Planning Committee decided to include individuals taking systemic medications that can lower IOP such as beta adrenergic antagonists, clonidine, and angiotensin-converting enzyme inhibitors. These medications are not exclusion factors provided the individual meets the qualifying IOP. These drugs are used so commonly that if we exclude all individuals who are using them we might exclude as many as 25% of the potential enrollees. Furthermore, African Americans are at higher risk for both glaucoma and systemic hypertension. If the study excludes medications used to treat systemic hypertension, it would result in a systemic exclusion of African Americans from the trial. Individuals receiving systemic corticosteroids at baseline are excluded from the study as the drug may be the cause of the ocular hypertension. (Inhaled and topical dermatologic corticosteroids are not included in the definition of systemic corticosteroids.)
- g. **Diabetic retinopathy.** The Planning Committee decided to exclude individuals with diabetic retinopathy, including mild background retinopathy, because diabetic retinopathy is often associated with abnormal visual fields. These abnormalities could confound interpretation of the visual field endpoint.
- h. **Visual fields.** The Planning Committee decided that the visual field entry criteria should perform two functions: (1) to exclude individuals with preexisting visual field loss, and (2) to exclude individuals whose fields are not reliable enough to allow detection of early glaucomatous damage either at baseline or in the future. The

Planning Committee decided that it was important to exclude individuals who had visual field loss at baseline as a few such individuals, if undetected, could substantially reduce the statistical power of the trial.³⁷

The Planning Committee decided to use a clinical assessment of the fields by the VFRC and the STATPAC II criteria for abnormality: all global indices within the 95% age-specific population norm and GHT within the 97% age-specific population norm. The advantages of these analysis procedures are that they are based on large population studies, have known sensitivity and specificity characteristics, are evaluated automatically as part of STATPAC II analysis, and are readily recognized by clinicians familiar with automated perimetry. The committee also decided to use reliability criteria of false positives < 33%, false negatives < 33%, and fixation losses < 33%. These criteria for false positives and false negatives are generally accepted. Some investigators have suggested a 20% criterion for fixation losses. However, research from several laboratories has suggested that the 20% criterion is too stringent and eliminates many individuals who are capable of providing useful data. Preliminary analysis of data from normals and ocular hypertensives suggests that using a criterion of 33% fixation losses does not diminish the quality of the data and does not increase the retest rate.

Humphrey program 30-2 was chosen instead of program 24-2 because there is greater experience with the 30-2 test and better age-specific comparison data.

The qualifying visual fields are faxed to the VFRC for review within one day to ensure that the individuals meet the entry criteria. The floppy disks are sent once weekly to the VFRC. The first set of visual fields may be from a prestudy visit within 12 weeks of the first qualifying visit if the fields were performed according to the OHTS protocol. All other qualifying fields must be performed within the 12 week qualifying assessment period. The individual does not have to be washed out for the prestudy visual field completed prior to qualifying assessment. However, the individual must be "washed out" for visual fields completed during qualifying visits. **No individual may be randomized until the fields are reviewed and accepted by the VFRC.**

i. **The optic discs.** The Planning Committee decided that the optic disc entry criteria should perform two functions: (1) to exclude individuals with preexisting glaucomatous damage, and (2) to exclude individuals with optic nerve diseases or conditions that could produce optic nerve damage in the future or that could obscure future development of glaucomatous optic nerve damage. The Planning Committee recognized that it was important to exclude individuals who had glaucomatous optic nerve damage at baseline as a few such individuals, if undetected, could substantially reduce the statistical power of the trial.³⁷ The committee defined preexisting nerve damage as an optic disc hemorrhage, a localized optic disc notch or thinning of the rim, a localized area of pallor, and/or an asymmetry between an individual's two eyes such that the cup/disc ratios differ by > 0.2. Conditions that could cause damage in the future or that could obscure future glaucomatous damage include optic disc drusen, pits, colobomas, atrophy, and other severe anomalies.

The Planning Committee decided not to use nerve fiber layer dropout as an exclusion criterion. It is difficult to visualize the nerve fiber layer adequately in many eyes, and

nerve fiber layer dropout is sometimes found in normal eyes;^{38,39} thus, the sensitivity and specificity of this sign is not entirely clear at this time.

The qualifying optic disc photographs are reviewed within one week of receipt by the ODRC to ensure that the individual meets the entry criteria. Optic disc photographs taken within 12 weeks of the first qualifying visit that meet all study criteria can be used to assess eligibility. An individual does not have to be "washed out" for prestudy optic disc photographs. No individual may be randomized until the disc photographs are reviewed and accepted by the ODRC.

2.3 Recruitment

Efficient and cost-effective recruitment of 1500 volunteers within a 24-month period requires a multifaceted approach. Studies have shown that no one technique yields all the volunteers needed for trials such as OHTS; rather, there must be a continuing recruitment effort.

In order to develop and direct such a program, OHTS has retained the services of a public relations consulting firm with a proven record. The general approach is to cast as wide a net as possible to inform the general public, as well as selected target audiences, about the study. This includes a program of national activities to reach health professionals and the lay public, but the primary focus will be on local support activities.

2.3.1 Audiences

It is essential to inform ophthalmologists, optometrists, and the general medical community about the study at its outset. Health professionals should be aware of the study before they hear about it from their patients. The number of referrals that practitioners will make to the study will vary from center to center. Some centers that have very good relations with community practitioners will receive a good number of referrals for the study. It may be possible to conduct screenings in selected hospital clinics (general medical, geriatric) to identify potential candidates. In some areas, a program of providing mutual referrals may be possible, with community practitioners sending glaucoma suspects to the study and the study sending screenees (who have no eye doctor but are found to need other types of eye care) to community practitioners.

2.3.2 National Activities

At the national level, the study will develop a limited media campaign with materials and contacts for selected national professional and lay publications, ranging from professional journals to USA Today. The Chairman's Office will use a public relations firm to develop a display to be used at national, regional, and local professional meetings. The public relations firm will also identify other public awareness opportunities and provide counsel as needed to the Chairman's Office.

2.3.3 Local Activities

The most important component of the public relations campaign is at the local level, providing counsel and training to the coordinators and principal investigators of all Clinical Centers on the conduct of a public awareness and recruitment campaign. Each Clinical Center is encouraged to telephone the study public relations firm for personalized telephone consultation and materials

related to recruitment. The diverse activities recommended over the two-year recruitment period might include: counter displays with tear-off pads placed in optical stores, screenings at churches frequented by African Americans, screenings at community-based senior citizen centers, and flyer distribution at local health fairs.

2.4 Qualifying and Baseline Studies

One or more qualifying examinations performed within a 12-week period determine the individual's eligibility for the trial.

2.4.1 History and Examination

As part of the qualifying process, the Clinical Center personnel obtain a detailed medical history including medications, and a detailed ocular history including previous ocular disease and treatment, and allergic or other untoward reactions to ocular medications. The Clinical Center personnel obtain best-corrected visual acuity and refraction, and perform pupillary and motility examinations, slit-lamp examination, applanation tonometry, clinical optic disc examination, optic disc photography, gonioscopy, and Humphrey 30-2 visual field studies.

2.4.2 Intraocular Pressure

Intraocular pressure is measured by two certified study personnel, the operator and recorder, using a calibrated Goldmann applanation tonometer in order to reduce potential bias in the measurement of IOP. Measurement bias is a concern since the investigator, technician and participant are aware of the randomization assignment. The operator looks through the slit-lamp and adjusts the dial while the recorder reads and records the results. The qualifying IOP in at least one eye of each participant must be ≥ 24 mm Hg but ≤ 32 mm Hg calculated from two separate consecutive determinations taken at least two hours, but not greater than 12 weeks, apart. **Pre-existing IOP data cannot be used.** The eye with the lower pressure must have an IOP ≥ 21 mm Hg on two separate determinations. A determination consists of either the mean of two measurements or the median of three measurements. All IOP readings are performed after appropriate washout of prestudy topical ocular medications as follows:

- 1) miotics 1 week
- 2) beta-blockers 4 weeks
- 3) epinephrine/dipivefrin 4 weeks
- 4) topical alpha-2 agonists 2 weeks
- 5) topical anhydrase inhibitors 2 weeks
- 6) topical prostaglandin agonists 4 weeks

The baseline IOP is defined as the IOP determination at the randomization visit and is distinguished from the qualifying IOP. This approach should minimize regression to the mean.

2.4.3 Visual Field

Qualifying visual fields must be normal and reliable in both eyes as determined by the VFRC. A reliable visual field is defined as < 33% false positives, false negatives, and fixation losses. A normal field is determined by clinical review at the VFRC and by STATPAC II criteria for global indices within the 95% age-specific population norm and GHT within the 97% age-specific population norm. Two out of a maximum of three visual fields for each eye must meet entry criteria. http://www.vrcc.wustl.edu/mop/mop.htm VFRC

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The visual fields testing sessions during qualifying assessments must be separated by a minimum of one hour and a maximum of 12 weeks. The first set of visual fields may be from a prestudy visit within 12 weeks of the first qualifying visit if the fields were performed according to the OHTS protocol. The individual does not have to be washed out for the prestudy visual field.

2.4.4 Rationale for Visual Field Assessment

The Planning Committee decided to use automated static threshold visual field tests in order to detect early glaucomatous defects and protect the participants. Automated perimetry should find earlier defects than would be detected using traditional kinetic suprathreshold strategies. The Humphrey perimeter was chosen because it is widely available and used by more practitioners than any other automated perimeter. The 30-2 program was chosen over the 24-2 because the 30-2 has been used more extensively and gives more information. Using the 30-2 program will create a few more "rim defects," but these can be minimized by careful technician training, placing lenses close to the eye, and reminding participants not to back away from the perimeter. The Planning Committee chose to exclude peripheral visual field tests because of time, cost, and subject fatigue. It is possible that detection of some early visual field defects will be delayed, but automated threshold central static perimetry and optic disc photography should be more than adequate to protect the participants and protect the trial. Visual field abnormality due to primary open angle glaucoma (POAG), as determined by the Endpoint Committee, is a study endpoint with respect to decisions regarding treatment and with respect to the analysis of the primary hypothesis.

2.4.5 Optic Disc

All but prestudy stereoscopic optic disc photographs must be performed by certified study photographers. The photographs are developed and mailed to the ODRC. All individuals must be judged qualified by the ODRC before being randomized. The readers at the ODRC estimate baseline cup/disc ratio. The cup/disc ratio is used to describe the sample at baseline and to provide a quantitative estimate for risk analysis, but will not be used to detect progressive cupping in the future.

Individuals are excluded from the study if the photographs document an optic disc hemorrhage, a localized notch or thinning of the rim, a localized area of pallor, or an asymmetry between the two eyes > 0.2. Individuals are excluded also if they have optic disc drusen, pits, colobomas, atrophy, or other severe anomalies. Preexisting optic disc photographs that meet all quality control and entry criteria performed within 12 weeks of the first qualifying visit can be utilized to assess eligibility.

2.4.6 Rationale for Optic Disc Assessment

Many practitioners consider it unethical to randomize subjects exhibiting evidence of glaucomatous optic nerve damage to an observation group. Results from a survey of the American Glaucoma Society showed that 97% (142/147) of the respondents would initiate treatment in individuals with evidence "suggestive of progressive glaucomatous optic disc damage."

Progressive optic nerve damage due to primary open angle glaucoma, as determined by the Endpoint Committee, is a study endpoint with respect to decisions regarding treatment and with respect to the analysis of the primary hypothesis. When confirmed progressive optic nerve damage due to POAG develops in a participant randomized to the close observation group, it is unethical to withhold treatment. Similarly, when confirmed progressive optic nerve damage due to POAG Version 3.0 9/24/01

develops in participants randomized to treatment, more aggressive treatment may be indicated. Optic disc assessment needs to be made on a time-urgent basis on all participants over the course of follow-up.

2.5 Treatment

2.5.1 Stepped Medical Regimen

Using a randomized permuted block design, eligible participants are assigned to either close observation only or a stepped medical regimen at a randomization visit. The stepped medical regimen begins in most participants with a topical beta-blocker twice daily (timolol, levobunolol, metipranolol, carteolol, or betaxolol). All new treatments begin with a therapeutic trial in one eye. Generally, treatment is started with a low concentration of the drug and increased as necessary. If a drug is ineffective or minimally effective (IOP reduction < 10% from average of Qualifying IOP and Baseline IOP), it should be stopped and another substituted. If a drug is moderately effective (IOP reduction 10%-20% from average of Qualifying IOP and Baseline IOP), the clinician has the choice of substituting another drug or adding a drug. In most cases, an alpha-2 agonist, a prostaglandin agonist or a topical carbonic anhydrase inhibitor is the second choice. The third class of drugs to be added or substituted is a standard miotic or an adrenergic agonist. A fourth choice is an alpha-2 agonist (brimonidine or apraclonidine) or a prostaglandin analogue (latanaprost or uniproston). This stepped regimen reflects standard clinical practice in the United States at this time. Participants return in 4 ± 2 weeks for an IOP Confirmation Visit to evaluate therapeutic response.

All study drugs are provided free of charge to the participants from the Chairman's Office. The drugs have been donated to the study by Alcon Laboratories, Allergan Pharmaceuticals, Merck Research Laboratories, Bausch and Lomb, Otsuka Pharmaceutical, and Pharmacia & Upjohn.

As new ocular hypotensive drugs become commercially available, the Executive/Steering Committee will consider redesigning the stepped medical regimen. It is important to include new drugs so that the stepped medical regimen reflects current practice and is not outdated. This strategy is consistent with the primary goal of the trial, i.e., to determine whether medical reduction of IOP prevents or delays the onset of glaucomatous damage in moderate-risk ocular hypertensive individuals. This trial is not intended to be a test of a specific drug or a specific medical regimen, but rather a test of the efficacy of medical treatment.

2.5.2 Goals of Treatment

The treatment goals for both eyes are (1) an IOP ≤ 24 mm Hg, and (2) a 20% reduction in IOP from the average of the Qualifying IOP and Baseline IOP. The 20% reduction in IOP is not required if IOP ≤ 18 mm Hg. Medical therapy is changed and/or added until <u>both</u> of these goals are met or until the participant is receiving maximum tolerated topical medical therapy. Participants who do not meet these goals despite maximum tolerated topical medical therapy continue to be followed in the trial.

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A markedly elevated IOP is not an endpoint for the study, but it does raise safety and ethical issues. The Planning Committee decided on the following course of treatment when markedly elevated IOP is a concern:

- If the IOP is > 35 mm Hg on two consecutive visits in a participant assigned to the close observation group, the clinician, after discussion with the Medical Monitor, can start the participant on the stepped medical regimen.
- If the IOP is > 35 mm Hg on two consecutive visits in a participant receiving maximum tolerated topical therapy, the clinician, after discussion with the Medical Monitor, can add systemic carbonic anhydrase inhibitors or suggest laser trabeculoplasty or filtering surgery if it seems appropriate.

An IOP > 35 mm Hg on two consecutive measurements is not an endpoint, but this procedure allows clinicians to intervene if they believe the pressure is so high that it is unethical to continue within the confines of the randomized treatment regimen. In these instances, the Medical Monitor can approve the "deviation" from the participant's randomized therapeutic assignment as described above. The Medical Monitor completes a Treatment Change form (TC) to report the deviation from protocol to the Coordinating Center.

2.5.3 Adverse Events and Drug-Related Side Effects

The clinician completes an Adverse Event form (AE) whenever a participant:

- requires a change in therapy because of side effects
- experiences a condition (ocular or systemic) in which the participant is unable to work or perform their usual activities.
- is hospitalized
- experiences a condition requiring medical or surgical intervention
- experiences a permanent or substantial disability or dies.

The Adverse Event form (AE) indicates the nature of the medical problem, its severity, and whether the problem was likely caused by the drug. An Adverse Event form must be completed <u>for</u> <u>each</u> ocular or systemic complex.

All participants in the trial, regardless of their randomization assignment complete the selfadministered ocular and systemic Symptom Checklist form (SY) at six- and twelve-month examinations, confirmation visits and unscheduled visits. Quality of life is assessed using the selfadministered form SF-36 at baseline, six months after baseline, and every 12 months thereafter.

A hospital discharge summary is requested for each inpatient hospitalization (> 24 hour stay) the participant reports during the six-month follow up visit.

In the event of a participant death, the clinic coordinator calls the Coordinating Center to report the death. This call should be followed with an Adverse Event form (AE) and a Confirmation of Death form (DT).

2.5.4 Medication Adherence

The clinicians and coordinators will take a number of steps to increase adherence to the medical regimen and to decrease possible adverse effects of the drugs:

- Clinicians will prescribe the simplest regimen that meets therapeutic goals, i.e., the least number of medications, the least number of administrations, and the lowest concentrations. One way to keep the regimen simple is to change or add medications in a one-eyed therapeutic trial.
- On the basis of the history and examination, clinicians will choose drugs less likely to cause side effects, i.e., avoid nonspecific beta blockers for participants with asthma, or avoid miotics for participants with posterior subcapsular cataracts.
- Clinic coordinators will instruct the participants in the proper technique of eyedrop administration, including punctal occlusion or simple eyelid closure for two minutes.
- Clinic coordinators will educate the participants, spouses, and significant others about elevated IOP and glaucoma, the need for adherence with the treatment regimen, the purpose of the medication, and the need for proper drug administration.
- Clinic coordinators will assist the participants in cueing medication administration to daily activities, i.e., choosing times for medication administration that are easy to remember and are linked to other daily activities such as meals, the 6 o'clock news program, bedtime, etc.
- Clinic coordinators will fill out and update a chart listing medications, times of administration, and tips for more effective administration.
- Clinic coordinators will remind participants to bring their medications to all office visits. The medication can then be checked for accuracy and proper labeling.
- Clinicians will review medications at each visit and ask participants about potential side effects and problems. Treatment will be altered as necessary.
- Whenever possible, medications with participant reminder caps will be used.

2.5.5 Rationale for Stepped Treatment Regimen

a. Placebo eyedrops. The Planning Committee decided not to use placebo eyedrops for the following reasons: (1) It is impossible to mask participants and physicians as to treatment assignment because many medications produce effects that are obvious, including miosis from drugs such as pilocarpine, or conjunctival erythema and mydriasis from epinephrine/dipivefrin, etc. (2) If participants were prescribed placebo eyedrops they might want to know why their therapy has not been altered if IOP is still elevated. Furthermore, participants might be discouraged if their IOP is elevated and they might seek other medications from physicians outside the trial (treatment crossover). It is possible to mask participants as to their IOP readings, but it is difficult and participants can have their IOP measured at health screenings, optical shops, etc. It seemed better not to mask participants as to their pressure readings and to explain that it is unclear whether reducing IOP is useful in ocular hypertension. (3)
Placebo eyedrops are not necessary to protect the trial since IOP is not an endpoint. The optic disc and visual fields are evaluated by Reading Centers masked as to treatment assignments.

- b. Laser trabeculoplasty. The Planning Committee decided not to include a laser arm in the trial for the following reasons: (1) A substantial proportion of participants treated with laser would require ocular hypotensive medications. Only 80% of glaucoma patients get an adequate reduction in IOP after laser trabeculoplasty and this effect diminishes with time. Published data from the Glaucoma Laser Trial demonstrated that 50% of the laser-treated eyes required medical treatment within two years.⁴² (2) Laser trabeculoplasty is not standard care for ocular hypertensive individuals in the United States at this time; therefore, including a laser arm might inhibit individual referral and recruitment. (3) Laser trabeculoplasty is not safe in all individuals. Some individuals treated with laser develop side effects such as iritis, peripheral anterior synechiae, and a few might even require urgent filtering surgery for uncontrollable post laser IOP elevations.
- c. Treatment goals. The Planning Committee chose these goals to reflect common medical practice for this group of individuals, i.e., if an ocular hypertensive individual starts with an IOP of 26 mm Hg, a 20% reduction in IOP yields a treated pressure of approximately 21 mm Hg (20.8 mm Hg). Most practitioners would judge this to be a good response, continue the same therapy, and follow the patient, checking for visual field loss or optic disc deterioration. A 20% IOP differential between the medication and close observation groups should be adequate to show a treatment effect. In a recent trial by Kass and coworkers, a treatment effect was seen with a mean 2.3 mm Hg pressure differential between treated and untreated eyes.²⁷

One could choose treatment goals with IOP reductions < 20%; however, the Planning Committee decided that a small pressure differential between the medication and close observation groups might not be an adequate test of the primary study hypothesis. One could choose treatment goals with IOP reductions > 20%; however, the Planning Committee decided that this would deviate from common clinical practice, would require more medication, and would produce a greater incidence of drug-induced side effects.

d. No charge for medication. The Planning Committee decided that recruitment would be aided if there were no direct charges to participants for medication. Free study medication may also increase compliance with the treatment regimen. Medication is supplied to the study without charge by Alcon Laboratories, Allergan Pharmaceuticals, Merck Research Laboratories, Bausch and Lomb, Otsuka Pharmaceutical, and Pharmacia & Upjohn. Medication is distributed by the Study Chairman's Office.

2.6 Subject Follow-up and Retention

The participants are examined every six months from the date of randomization for the duration of the study (a minimum of five years). The clinic coordinators will contact participants by phone or letter four weeks prior to appointments to confirm the appointments and to reschedule within the study windows if necessary. The participants will also receive a letter or phone reminder

one week prior to the appointment. Participants randomized to medication should be reminded to take their medication.

Tests and measures performed at <u>every</u> regularly scheduled follow-up visit:

- Symptom checklist (SY)
- Update Patient Tracking (TR) (retained at clinic)
- Review of medications
- Updated medical and ocular history
- External examination
- Slit-lamp examination
- Direct ophthalmoscopy
- Applanation tonometry
- Humphrey program 30-2.
- Completion of follow-up visit form (FV)
- Dispense medication to participants in medication group

Additional tests and measures performed at annual follow-up visits (12, 24 months, etc.):

- Participant completed Quality of Life (SF-36) form
- Snellen visual acuity with current refraction
- Dilated ophthalmoscopic exam
- Stereoscopic optic disc photographs
- Macular photographs and red reflex photographs

Additional tests and measures performed at semi-annual follow-up visits (6, 18 months, etc.):

- Refraction
- Best corrected visual acuity Snellen and ETDRS
- Gonioscopy (completed every two years at non-photo visits)

Beginning January, 2000, one-time pachymetry measurements to determine corneal thickness were added. Measurements are performed for participants at either an annual or semi-annual visit prior to dilation. The measurements will be repeated only in those participants who sustain trauma or who undergo intraocular or refractive surgery after which corneal thickness is likely to be altered (Chapter 17).

Beginning April 2001, additional measures are collected including the participant completed National Eye Institute 25-item Visual Function Questionnaire. Additional information collected includes exercise history, smoking history, more specific African derived origin, more specific family history of glaucoma.

2.7 **POAG Endpoint Determination**

2.7.1 Optic Disc POAG Endpoint

Stereoscopic optic disc photographs and single 30° and 1X macular photographs and single red reflex photographs are taken once yearly, developed, and mailed to the ODRC. All but prestudy photographs must be taken by certified study photographers.

An optic disc progression is defined (based on a masked comparison to baseline stereo photographs) 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
- an overall thinning of the rim

The magnitude of change must meet or exceed that illustrated by the series of standard photographs. As a general rule, thinning of the rim should be > 0.1 disc diameter to be considered significant. A disc hemorrhage, nerve fiber layer dropout, or a change in the depth of the cup are not considered optic disc endpoints.

The ODRC grades photographic quality and provides reports to the Clinical Centers and to the Coordinating Center about stereo, focus, magnification, clarity, labeling, and timeliness. If a set of optic disc photographs is ungradable, the coordinator of the ODRC contacts the Clinical Center to request that a new set of photographs be taken within four weeks.

If the ODRC suspects the occurrence of progressive change in the optic disc, the ODRC calls the Clinical Center to request that a repeat set of photos be taken within 4 ± 2 weeks. The ODRC coordinator notifies the clinic coordinator of the results. If the progression is confirmed by the repeat set of photos, the ODRC will call the Coordinating Center to convene the Endpoint Committee. The ODRC sends the Coordinating Center a description of the progressive optic disc damage and photographs of the affected eye and fellow eye from the Qualifying Assessment to date.

The Coordinating Center sends the following to the Endpoint Committee: 1) masked copies of QA medical history page and all follow-up examination forms as well as pertinent Adverse Event (AE), Unscheduled Visit (UN) forms and Confirmation Visit (CF) forms; 2) all visual fields, stereoscopic optic disc photographs, macular photographs and red reflex photographs for both eyes to date. The Endpoint Committee will make a determination as to whether progression is due to POAG or not. If the Endpoint Committee determines that the change is due to POAG, the Coordinating Center notifies the clinician to place the participant in the open arm of the study. If the change is not clinically significant ("No Change") or the change is not POAG, the Coordinating Center notifies the clinician to continue follow-up per randomization group assignment.

A close observation group subject reaching a POAG optic disc endpoint in one or both eyes is followed in the open arm of the trial and begins the stepped medical regimen. A medication group participant reaching a POAG optic disc endpoint in one or both eyes is followed in the open arm of the trial; in most such participants additional medications, including systemic carbonic anhydrase inhibitors, may be added to reduce IOP. In some cases clinicians may advise laser trabeculoplasty or filtering surgery. Participants continue their regularly scheduled follow-up visits and continue optic disc photographs in the open-arm of the study.

If a clinician is concerned about the occurrence of progressive optic disc damage and the participant is not scheduled for photographs at that visit, the clinician may perform an additional set of disc photographs. (The clinician is limited to one additional set of photographs per year.) The clinician calls the coordinator of the ODRC and asks for expedited review. The ODRC coordinator places the new photographs in the next batch scheduled for reading. The two readers are not told of the expedited review. The ODRC coordinator calls the Clinic Coordinator and sends a letter with the results. If the photographs are judged unchanged, the participant is followed according to the routine schedule of visits. If progressive change is confirmed by the repeat set of photos, the ODRC will call the Coordinating Center to convene the Endpoint Committee to institute an endpoint review.

2.7.2 Rationale for Optic Disc POAG Endpoints

- **a.** The optic disc as an endpoint. It would have been possible to design this trial with visual field loss as the only outcome for a POAG endpoint; however, most clinicians believe that progressive cupping precedes a visual field defect in many participants with open angle glaucoma. Thus, the Planning Committee believed that it would be unethical and unsafe to exclude optic disc progression.
- **b. Reading Center.** An additional issue is whether an ODRC is really needed. There have been multiple studies of disc interpretation and it is clear that clinicians do not interpret or grade discs in reproducible or consistent fashion.⁴³ Only an ODRC (where the readers have been trained, and the techniques and criteria are standardized) can yield reproducible results for entry criteria and progressive glaucomatous damage. The ODRC also allows for the initial training and certification for the photographers, quality control, and masking of readers as to treatment assignment.
- **c. Readers.** The Planning Committee decided to use trained technicians as readers. The Planning Committee decided not to perform automated disc analysis because the technique is time-consuming, expensive, and unproven in large-scale clinical trials. If the technique of automated disc analysis improves in the future, an ancillary study could and should be performed.
- **d. Repeat photographs.** The Planning Committee decided that a repeat set of optic disc photographs was likely to improve sensitivity and specificity. Requesting a repeat set of photographs does not add significantly to the cost, nor does it significantly delay the decision to pursue treatment (or more vigorous treatment) in participants showing deterioration.
- e. Disc hemorrhages. The Planning Committee decided that optic disc hemorrhages would not be a POAG endpoint. Some individuals who experience disc hemorrhages develop localized rim defects and visual field loss, and these will be detected in subsequent visits. However, the majority of ocular hypertensive individuals with disc hemorrhages do not develop disc or field abnormalities within six to 12 months. Thus, while a disc hemorrhage is a risk factor, it is not synonymous with glaucomatous damage.

One obvious question is why the Planning Committee decided that an optic disc hemorrhage is an exclusion criterion for entry into the study, but is not a study endpoint. In any study with a relatively low conversion rate, it is important to exclude individuals with preexisting disease or those who are at the threshold of developing disease. Inclusion of such individuals diminishes the opportunity to detect a treatment effect. Because an optic disc hemorrhage may herald imminent conversion to glaucoma, the Planning Committee decided that optic disc hemorrhage is an exclusion factor. On the other hand, optic disc hemorrhage is not synonymous with optic disc cupping or visual field loss — more than 50% of ocular hypertensive individuals with optic disc hemorrhages do not develop glaucomatous visual field defects within six to 12 months. Thus, the Planning Committee decided not to consider optic disc hemorrhage as a study endpoint.

- **f.** Nerve fiber layer dropout. The Planning Committee decided that nerve fiber layer dropout is not a POAG endpoint. It is very difficult to visualize the nerve fiber layer in some individuals. Furthermore, it is known that nerve fiber layer dropout is found in some normal individuals; thus, the sensitivity and specificity of this sign is unclear.
- **g. Optic cup depth.** The Planning Committee decided not to use optic cup depth as a POAG endpoint. The appearance of cup depth is greatly influenced by the position of the eye and the plane of focus; thus, it is neither a reliable nor a reproducible sign of progressive cupping.

2.7.3 Visual Field POAG Endpoint

Humphrey 30-2 visual fields are done every six months by certified study technicians. The fields are sent via floppy disks and hardcopy to the VFRC. The VFRC receives the fields, processes them, and evaluates quality. The visual fields are considered abnormal if p < 5% for the CPSD or if the GHT is outside normal limits (p < 1%) as determined by the VFRC.

The VFRC grades visual field quality and provides feedback to the Clinical Centers and the Coordinating Center. If a set of visual fields does not meet reliability standards, the VFRC notifies the Clinical Center and requests a retest of the participant.

Since ninety percent of the first abnormal, reliable visual fields that occur during the study are normal on retest, a single isolated abnormal visual field does not generally warrant accelerated retesting. The next (second) visual field should be performed at the next regularly scheduled follow-up visit.

If the VFRC considers the second field abnormal and reliable, the VFRC calls the Clinical Center to schedule a repeat (third) visual field in 4 ± 2 weeks. If the defect is confirmed by the repeat (third) visual field, the VFRC contacts the Coordinating Center to convene the Endpoint Committee. **The defect on the confirming** (third) **field must be of the same character and location as the defects** in the two previous abnormal fields. If the defect is confirmed, the VFRC sends the Coordinating Center a description of the defect and copies of visual fields of the affected eye and fellow eye from the Qualifying Assessment to date.

The Coordinating Center sends the following to the Endpoint Committee: 1) masked copies of the QA medical history page and all follow-up examination forms and pertinent Adverse Event (AE), Confirmation Visit (CF) and Unscheduled Visit (UN) forms, 2) all visual fields, stereoscopic optic disc photographs, macular photographs and red reflex photographs for both eyes to date. The Endpoint Committee will make a determination as to whether the abnormality is due to POAG or not. If the Endpoint Committee determines that the change is due to POAG, the Coordinating Center notifies the clinician to place the participant in the open arm of the study. If the change is not POAG, the Coordinating Center notifies the clinician to continue follow-up per randomization group assignment.

A close observation group participant reaching a POAG visual field endpoint in one or both eyes is followed in the open arm of the trial and begins the stepped medical regimen. A medication group participant reaching a POAG visual field endpoint in one or both eyes is followed in the open arm of the trial; in most such participants additional medications, including systemic carbonic anhydrase inhibitors, are added to reduce IOP. In some cases clinicians may advise laser trabeculoplasty or filtering surgery. Visual fields will still be performed on subjects in the open arm of the study. The participant continues the regular schedule of follow-up visits and visual field testing.

If a clinician is concerned about an abnormality on a visual field, the clinician may retest the participant prior to the next regularly scheduled visit.

2.7.4 Rationale for Visual Field POAG Endpoint

- **a. A Visual Field Reading Center.** One important issue was whether a VFRC is necessary. The Planning Committee decided that in a large trial it is crucial to standardize entry and endpoint criteria. This is best done by a Reading Center. Visual fields can be checked by technicians in the Clinical Center and, in effect, these technicians become a reading center, but one without expertise or backup. The use of a VFRC also allows for the initial training and certification of technicians, quality control, and masking of readers as to randomization assignment.
- **b. Readers.** The VFRC will use trained, certified, highly skilled and experienced readers.
- c. Unreliable follow-up visual fields. Past experience indicates that once participants have qualified for the study with reliable visual fields they will continue to have reliable fields on the vast majority of the tests. If a visual field does not meet reliability standards, the Clinical Center should retest the participant. The retest can be the same day if the participant gets a one hour break, and also, the retest must be completed within 8 weeks. Careful training of technicians should reduce the number of unreliable visual fields. Therefore, unreliable visual fields should not be a significant factor in visual field POAG endpoints.
- **d. Other visual field endpoints.** A variety of other outcomes, such as cluster analysis, nerve fiber bundle analysis, etc., could have been chosen for the visual field endpoint. However, the STATPAC II analysis has the longest track record, and it is available to practitioners who will want to apply the lessons of this trial to their practices. The advantages of these analysis procedures are that they are based on large population studies, have known sensitivity and specificity characteristics, are evaluated

automatically as part of STATPAC II, and are readily recognized by clinicians familiar with automated perimetry. The use of the 5% cutoff for CPSD was considered conservative. Since the Glaucoma Hemifield Test is based on five regions, the stricter 1% cutoff was chosen. This study focuses on the appearance of abnormal findings, and the rate of change is not critical.

The Planning Committee decided not to use mean defect (MD) as an indicator of visual field abnormality. Mean defect is very sensitive to media opacities, which are common in the age group involved in this trial. The Planning Committee believed that an isolated decrease in mean sensitivity is far more likely to be caused by cataract than by glaucoma. The exclusion of mean defect may cause us to delay the detection of a few cases of glaucoma. However, cases of early glaucoma that have no focal signs are likely to be detected by stereoscopic optic disc photography. The exclusion of mean defect may slightly decrease sensitivity in detecting glaucoma, but should greatly increase specificity.

e. **Psychophysical tests.** The Planning Committee decided not to use a variety of other potential endpoints such as color vision loss, pattern ERG abnormalities, pattern VER abnormalities, etc. None of these tests are in common clinical use so we have little information about false positives, false negatives, or predictive capabilities. Furthermore, most of the tests are expensive, time-consuming, and require specialized equipment and trained personnel. Finally, these tests are not available to practitioners who will want to incorporate the results of this trial into their practices. There does not seem to be sufficient information to include any of these tests at present.

2.7.5 When POAG Endpoint is Confirmed

Participants who develop primary open angle glaucoma triggered by a confirmed visual field abnormality and/or by an optic disc progression continue to be followed in the study in the open arm of the trial until study close-out. The same follow-up schedule and the same tests and measures continue to be performed. Data are sent to the Coordinating Center, VFRC and ODRC as stated in the protocol.

For participants already at POAG endpoint in one or both eyes, subsequent abnormalities in the visual fields and/or optic discs will be confirmed at regularly scheduled follow-up visits. Expedited confirmation visits will not be required to confirm subsequent suspected abnormalities in the affected or fellow eye for these participants. In some cases, confirmation photographs may need to be taken at the semi-annual rather than the annual visit.

2.7.6 Statistical Analysis of Participants Who Cannot be Evaluated

For the purposes of statistical analyses, a participant who is ascertainable for either the optic disc endpoint or visual field endpoint in at least one eye is not considered censored in the analysis of the primary hypothesis. Only participants who are not measurable for both the optic disc endpoint and visual field endpoint in both eyes are considered censored in analysis of the primary hypothesis. This decision rule is consistent with current standards of practice in that the development of abnormality in either visual field or optic discs would be reason for changing participant management. Participant safety is adequately protected so long as either endpoint is measurable in either eye.

2.7.7 Open Arm

Participants are moved to the open arm of the trial if any of the following occur:

- When the Endpoint Committee attributes confirmed optic disc progression to **POAG.** The Coordinating Center notifies the clinician of the Endpoint Committee decision. If the participant is in the close observation group, the participant begins the stepped medical regimen. If the participant is in the medication group, medical therapy is altered to achieve lower IOP. If the participant is receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors, argon laser trabeculoplasty or glaucoma surgery.
- When the Endpoint Committee attributes confirmed visual field abnormality to POAG. The Coordinating Center notifies the clinician of the Endpoint Committee decision. If the participant is in the close observation group, the subject begins the stepped medical regimen. If the participant is in the medication group, medical therapy is altered to achieve lower IOP. If the participant is receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors, argon laser trabeculoplasty or glaucoma surgery.

Participants moved to the open arm of the study continue their regularly scheduled follow-up visits and continue to complete all routine tests and measurements including visual fields and stereo optic disc photography until study closure. All study data continue to be collected.

2.7.8 Masking

The Visual Field Reading Center and the Optic Disc Reading Center are responsible for determining the presence of abnormalities in a masked fashion i.e., using only the fields or stereoscopic optic disc photographs respectively and without knowledge of the participant's randomization assignment or clinical status including medical history, ocular comorbidity, etc.

Clinic personnel must be careful to guard against inadvertent disclosure of information to reading center personnel i.e., the participant's randomization status, ocular or systemic conditions or POAG endpoint status. Clinic personnel need to route questions pertaining to the participant's clinical status that affect visual field or optic disc assessment to the Coordinating Center.

Visual Field Reading Center staff and Optic Disc Reading Center staff must be vigilant and deter inadvertent disclosure by clinics of the participant's clinical or POAG endpoint status.

The Visual Field Reading Center and Optic Disc Reading Center are not permitted to exchange information unless specifically approved to do so by the Data and Safety Monitoring Committee.

2.8 Clinical Centers

The Clinical Centers were chosen by an RFA mechanism developed jointly by the Study Chairman, the Coordinating Center, and the NEI staff. Each Clinical Center demonstrated that it is qualified to participate in the trial by virtue of its personnel, equipment, and recruitment potential.

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In each Clinical Center the personnel consist of a principal investigator, clinic coordinator, technician, and photographer. Each of these positions requires backup, although in some cases a person can play 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.

Each Clinical Center needs standard ophthalmic equipment such as slit-lamps, gonioprisms, and ophthalmoscopes. The Centers must also have specific equipment including calibrated Goldmann tonometers, Humphrey perimeters modified with the OHTS chip with STATPAC II, and fundus cameras for stereoscopic optic disc photography.

Because glaucoma is such an important health problem in African Americans, the study will attempt to enroll African Americans so that they comprise approximately 25% of the study sample (400 participants). Thus, the ability to enroll African Americans was an important consideration in selecting Clinical Centers.

2.9 Data Analysis

2.9.1 Unit of Analysis: Eyes or Participants?

The Planning Committee agreed unanimously that the sampling unit should be participants, not eyes. The primary hypothesis tests a treatment strategy; therefore, external validity is compromised when the treatment strategy in the clinical trial departs from standard practice. Randomizing eyes (one eye to medication and one eye to close observation) would constitute a serious departure from practice. Furthermore, the assumption is made in the primary analysis (intent to treat) that the treatment intervention affects only those randomized to the treatment arm. Results from Kass et al²⁷ clearly show a substantial long-term treatment effect of topical beta blockers on the placebo-treated fellow eye. Similar effects have been reported for epinephrine/dipivefrin. Furthermore, participants are apt to confuse treatment of each eye so that eyes in the close observation group may receive active drug and vice versa. Pharmacologic cross-over and subject initiated cross-over could seriously compromise assessment of treatment efficacy. Randomizing participants rather than eyes circumvents this problem.

2.9.2 Sample Size

The following was estimated in order to estimate the sample size required to provide adequate statistical power: (1) the endpoint event rate in the close observation group, and (2) the endpoint event rate in the medication group. The primary study endpoint is glaucomatous damage as indicated by either abnormal Humphrey visual fields or progressive optic nerve damage as determined by Reading Centers and an Endpoint Committee.

2.9.2.1 **Projecting the Incidence of POAG in the Control Group**

The following tables were presented to the Planning Committee so that they could advise the statistical staff as to the expected event rate in the close observation group. The Planning Committee reviewed both published and unpublished *randomized* clinical trials of the efficacy of medical therapy in preventing or delaying glaucomatous visual damage in ocular hypertensive individuals. The review included only randomized studies to avoid the pitfalls of biased selection, differential

ascertainment, and follow-up. This review did not include studies in which the primary outcome variable was intraocular pressure, since intraocular pressure is not the primary outcome of interest in this trial. Eight trials were located that satisfied the above criteria. The trial reported by Chauhan et al in a 1988 publication⁵⁰ was replaced by a more recent publication by Schulzer et al²² which reported on the same study sample with longer follow-up. However, we did exclude the trial by Graham¹ because the Globuk field screener employed was considered too insensitive a measure of glaucomatous visual field damage. The remaining seven clinical trials are included in the following table which gives baseline (not eligibility) intraocular pressure, duration of follow-up, number and percent of participants developing visual field damage over the study observation period, annual rate of visual field defects, and a comparison of the incidence of visual field damage in the treatment group to the control group expressed as a change measure (treatment incidence-control incidence/control incidence). We assumed that the incidence rate of visual field defects was smooth over the mean/median observation period and made no adjustment for variable follow-up. It is noteworthy that of these seven trials, no trial used more than one topical medication concurrently for treatment. In each of the following trials, the control patients received either a placebo or no treatment.

Table 1

Randomized Clinical Trials of Medical Treatment of Ocular Hypertension

Author	Baseline IOP mm Hg	F/Up months	Visual Field Defect T=Treatment (%) C=Control (%)	Incidence of VFD/Yr.	Percent Reduction in Incidence of VFD <u>Treatment-Control</u> Control
Levene ¹⁹	21	55	T: 4/59 eyes 7% C: 2/59 4%	1.5% 0.8%	+0.75%
Becker ²³	20	50	T: 2/50 eyes 4% C: 7/50 14%	1.0% 3.4%	-0.71%
Shin ²⁴	27	38	T: 0/19 eyes 0% C: 6/19 31%	0.0% 10.1%	>-1.00%
Kitazawa ²⁵	26	12	T: 1/27 pts 4% C: 2/27 7%	4.0% 7.4%	-0.42%
Epstein ²⁶	24	56 51	T: 4/53 pts 8% C: 9/54 17%	1.7% 3.9%	-0.52%
Kass ²⁷	26	56	T: 4/62 eyes 6% C: 10/62 16%	1.3% 3.4%	-0.62%
Schulzer ²²	26	72	T: 15/67 pts 22% C: 13/70 18%	3.7% 2.2%	+0.22%

The expected incidence of visual field damage in the control group of the proposed trial was projected using the incidence rates reported in the control groups of the above trials. Five of the seven trials above report an incidence of visual field defects in the control group that is 3% or greater per year using a crude estimate which does not take variable follow-up into account. Of the two studies reporting an event rate lower than 3%, one study enrolled participants whose mean baseline IOP was 21 mm Hg and the other study enrolled participants whose mean baseline IOP was 26 mm Hg. The median annual event rate for visual field damage in the above control groups is 3.9% per year. This incidence rate is much higher than would be expected given the generally accepted incidence rates across trials is somewhat surprising given the different risk characteristics of the study samples.

Projections of the endpoint event rate based on small trials, all with small selective samples, often do not hold up when larger studies with more representative subject samples are conducted. Participants enrolled into these small clinical trials may be at higher risk than implied by the study inclusion criteria; thus, the event rates in these trials may be higher than event rates that would be observed in a larger scale trial. As an example, the lower bound for the IOP eligibility criteria in the Epstein trial was 22 mm Hg, whereas the mean observed baseline IOP of the randomized participants was 24 mm Hg. Similarly, in the Kass trial, the lower bound for IOP eligibility criteria was 24 mm Hg, but the mean baseline IOP of the randomized participants was 26 mm Hg. Thus, we must be concerned that the incidence of visual field damage in a less selective, larger sample would be lower.

To assess this possible source of error in the projected event rate in the control group, we investigated the Collaborative Glaucoma Study,⁵¹ which is one of the few prospective, well-conducted studies of the incidence of glaucomatous visual field loss. The age- and IOP-specific incidence rates for glaucomatous visual field damage (Goldmann visual fields) for a median follow-up period of about 3.5 years in the Collaborative Glaucoma Study, was as follows in their Table IV.4.

Table 2

Incidence of Visual Field Loss in Collaborative Glaucoma Study

<u>IOP mm Hg</u>	Age		
	40-49	<u>50-59</u>	60+
20-23	1.4	2.4	9.3
24+	6.9	7.9	11.1

Accuracy of estimated annual incidence depends critically on an accurate estimate of duration of follow-up. Median duration of follow-up was estimated from the follow-up table reported on Table IV.1 of their report. The incidence of visual field loss in the 24 mm Hg group for ages 50-59 is 7.9% for a median follow-up of 3.5 years, or 2.6% per year of follow-up. The Planning Committee felt that the Collaborative Glaucoma Study yielded an incidence rate for abnormal visual fields using the Goldmann perimeter that was comparable to the projected 3%-per-year incidence of glaucomatous damage using Humphrey visual fields.

Projection of the event rate also requires estimation of the incidence of progressive optic nerve damage. The incidence of progressive optic nerve damage is more difficult to document. Of the above studies, a systematic effort to document the status of the disc in a masked fashion was made in the Epstein, Kass, and Schulzer trials. In the Epstein trial, only one participant out of 54 participants in the control group developed progressive optic nerve damage prior to visual field loss, or 0.4% per year. The incidence for the combined visual field and optic disc endpoint in the Epstein trial would be 4.3% per year. The combined endpoint is not necessarily the sum of the two incidence rates because the same eye/participant can have both endpoints. In the Kass trial, 8 out of 62 eyes in the placebo group developed progressive optic nerve damage, but all 8 eyes also developed visual field loss. Thus, in the Kass trial the annual incidence for the combined visual field and optic disc endpoint would be 3.4%, the same as for visual field alone. In the Schulzer trial, 6 out of 70 participants in the control group developed progressive optic nerve damage at some time in the trial, but it is not possible to determine the degree of overlap with visual field abnormalities, so it is not possible to estimate the combined endpoint event rate, except to assume that the event rate of 2.2% per year for visual field damage alone is the lower bound for the combined endpoint event rate. The Planning Committee felt that the Epstein and Kass trials, along with the Collaborative Glaucoma Study, provided adequate support for the projection of a 15% incidence rate over five years for the combined glaucomatous damage endpoint as indicated by either glaucomatous visual field abnormality or glaucomatous optic disc cupping.

The endpoint event rate observed in a trial is very sensitive to the specific inclusion and exclusion criteria of the trial and the method of endpoint ascertainment. We recognized that the stringent visual field inclusion criteria proposed for the OHTS trial might exclude a large number of individuals at risk of developing visual field damage and consequently substantially reduce the observed event rate. We conducted a pilot study to determine what the incidence of visual field http://www.vrcc.wustl.edu/mop/mop.htm Version 3.0 9/24/01

abnormality is likely to be if we imposed both the proposed study visual field entry criteria <u>and</u> the proposed visual field abnormality criteria. We collaborated with University of California-Davis Visual Field Reading Center to reanalyze Humphrey visual field data from over 100 untreated ocular hypertensive individuals participating in a natural history study who met the visual field entry criteria of the proposed OHTS and who had about 30 months of data available for analysis. (The eligibility IOP in the natural history study was 21 mm Hg, which is lower than the IOP criteria proposed for the OHTS trial.) This reanalysis suggests that the proposed Humphrey visual field criteria for eligibility and endpoint will yield an incidence rate of abnormal visual field of about 16% over five years.³² This pilot study strongly suggests that the projected incidence of glaucomatous damage of 15% over five years is realistic given the specific study Humphrey visual field entry and endpoint criteria.

2.9.2.2 Estimating Treatment Effect on Incidence of POAG

The Planning Committee decided that prophylactic treatment must make a marked difference in prognosis of the target sample to justify chronic treatment. The Planning Committee felt that the endpoint event rate should be reduced by at least 40% if the treatment effect is to be clinically significant. Only the Epstein and Kass trials provide an estimate of the treatment effect on a glaucomatous damage endpoint consisting of both visual field abnormality and/or optic disc progression. The Schulzer trial reported the incidence of both visual field abnormalities and optic disc progression separately but did not clarify their joint occurrence. Furthermore, in the Schulzer trial the treatment effect was in the opposite direction for visual field and optic disc progression. Treatment was associated with a 22% increase in the incidence of visual field damage and a 65% decrease in the incidence of optic disc progression. The net effect of treatment in the Schulzer may be null. The remaining four trials either did not report an optic disc outcome or failed to report its joint occurrence with visual field abnormalities. In the Epstein trial, treatment was associated with a 40.5% reduction in the combined glaucomatous damage endpoint from an overall incidence of 18.5% (10/54) in control group to 11% (6/53) in the treatment group. In the Kass trial, treatment was associated with a 39.8% reduction in the overall incidence of the combined glaucomatous damage endpoint from 16.1% (10/62) in the control group to 9.7% (6/62) in the treatment group. The consistency in treatment effect of the Epstein and Kass trials suggest that, if a clinically significant treatment effect exists, the effect is probably in the range of a 40% reduction in glaucomatous damage.

The initial Planning Committee, which included three biostatisticians in addition to the ophthalmologists, concluded that a one-tailed test was the appropriate test for the trial given the lack of evidence that treatment might induce visual field damage and the nature of the clinical question being posed. However, since that meeting in July 1989, the publication by Schulzer et al²² raises questions as to whether treatment increases damage. A two-tailed test is therefore the most appropriate test.

2.9.2.3 Assumptions for Calculating Sample Size

The sample size projected is based upon the projected proportion of the medication group who develop glaucomatous visual field loss and/or optic disc cupping as compared to the proportion in the close observation group. The sample size calculations are based on a comparison of two proportions using an arcsine transformation.^{53,54} Because the sample size calculations assume a comparison at a fixed time, statistical power will probably be slightly higher in analyses that take failure time into consideration. The sample size calculations assume the following:

- a. power = 0.90 the probability of detecting a 40% difference in the five-year incidence of glaucomatous damage, assuming this difference exists.
- b. alpha = 0.05 the probability of concluding there is a difference between the medication and close observation groups when there is no difference
- c. two-tailed test

Given the above assumptions, and assuming a five-year incidence of the combined glaucomatous damage endpoint of 15% in the close observation group and 9% in the medication group, 607 participants would be required in each group. A sample size of 607 participants per group also provides power of 0.90 to detect the differences between the medication and close observation group in the face of a 10% cross-over from the close observation group to the medication group. ⁵⁵ With an allowance for a rate of 15% loss to follow-up, this would yield a sample of 698 participants per group or a total sample size of 1396. The following table gives the sample size required, given the above assumptions, to detect a range of event rates in the medication and close observation groups.

Table 3

Number of Participants per Group

Event Rate in	Ev	ent Rate i	n Close O	bservatio	n Group
Medication Group	0.13	0.14	0.15	0.16	0.17
.07	514	392	311	254	213
.08	779	561	427	338	275
.09	1276	846	607	460	363
.10	2367	1378	911	652	493
.11	5539	2545	1477	974	695

The proposed minimum target sample of 25% (approximately 400) African American study participants will provide adequate power to detect overall subgroup differences for most clinical outcomes of interest, e.g., differences between proportions greater than 10% and differences greater than 0.2 standard deviation between means.

2.9.3.4 Effect of Medication Defaulting on Statistical Power

The work of Kass and coworkers points to the importance of compliance to medication as a key factor mediating treatment efficacy and hence statistical power of the trial. No special compliance enhancing strategies were reported in any of the above studies. Therefore, the sample size penalty for the effect of noncompliance in reducing treatment efficacy is already incorporated in the sample size estimate. If medication compliance can be enhanced in this trial over and above the level attained in the published trials, the statistical power of the trial might be higher than estimated, assuming medication is effective. Furthermore, if the efficacy of medical treatment can be enhanced by increasing type or number of topical hypotensive medications available to the clinician, statistical power will probably be increased. All of the seven trials reviewed used only a single topical

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medication. Therefore, all treated participants who had no IOP reduction or who had serious drugrelated side effects that required cessation of therapy, were unlikely to show any treatment benefit. In the proposed trial, the medication group can be prescribed any topical medication available to the clinician and approved by the Steering Committee.

2.9.4 Data Analysis

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

- a. to provide a regular mechanism for evaluating data quality, protocol adherence, and side-effect patterns including adverse reactions.
- b. to monitor recruitment targets in subgroups of interest (African Americans) and to monitor balance between the medication and close observation groups with regard to prognostic factors.
- c. to refine statistical modeling procedures, particularly to respond to unique attributes of the clinical measures; for instance, analysis of paired longitudinal data by methods described by Rosner⁵⁶ and Liang and Zeger⁵⁷ for the analysis of risk factors.
- d. to determine whether the study should be terminated early. Negative results could suggest that there is no possibility of ever establishing significant between-group differences. Alternatively, larger than anticipated between-group differences could indicate that there is no need to continue the study. In view of the steepness of the power curve at the event rates projected for the trial, we will intensely monitor endpoint incidence with the Data and Safety Monitoring Committee (DSMC). We do not know precisely how trial entry and endpoint criteria will impact event rates. It is clear that a high event rate in the close observation group, assuming the same treatment differential, will increase statistical power of the trial substantially; conversely, a low event rate will reduce statistical power substantially.
- e. to assess the possibility that a positive but nonsignificant trend might require an increase in the originally projected sample size or an increase in the study duration.

Beginning at the end of the fourth year of the study (i.e., 18 months after recruitment has ended), interim analyses will be conducted on an annual basis. Thus, there will be a total of five analyses which will occur at the end of each year from year 4 to year 8. These analyses will be timed to coincide with meetings of the monitoring board so that the board can play its essential role in all decisions regarding the future conduct of the study. With need-to-know individuals at the Coordinating Center being the only exception, all investigators will be masked as to the results of interim analyses.

The primary purpose of the interim analyses will be to provide regular opportunities to make decisions regarding the possible need to terminate the study early or to modify the study protocol. Issues to be addressed by the interim analyses will include the possibility that (1) the medication is clearly effective so that it is unnecessary to continue to the planned termination point insofar as the primary endpoint is concerned; (2) the medication appears so ineffective that continuation of the study would provide little or no chance of ever reaching statistical significance; (3) there is a trend toward medication effectiveness that is less pronounced than that projected in our sample size calculations, but which is sufficient to suggest that a modest increase in the sample size might yield a http://www.vrce.wustl.edu/mop/mop.htm

significant trial; and (4) excessive side effects demand an early end to the study or a modification of the intervention. Each of the interim analyses will evaluate both safety and efficacy.

While subjective considerations of many aspects of the trial will be a part of any decision to alter the planned protocol, objective group sequential statistical testing will play an important role should the possibility of early stopping due to a greater than expected treatment effect arise. Among the many stopping rules that are available, the two most widely used are those of Pocock and O'Brien and Fleming. As with all other early stopping rules, these approaches account for the effect on Type I error of repeated looks at the data by requiring that nominal p-values be less than 0.05 in order to claim true significance at the 0.05 level. Because the Pocock stopping rule assigns the same nominal significance level at each interim analysis, we prefer the O'Brien-Fleming method. Under this approach, significance levels form an increasing sequence, with the later interim analyses being associated with larger nominal significance levels and with the final value of this increasing sequence being relatively close to the significance level assigned to the study as a whole (0.05 in this case). We find this approach more appealing because we believe on first principles that early termination should be more difficult at the beginning of the study, i.e., early significance levels should be lower. Based on the results of Geller and Pocock,⁰¹ the O'Brien-Fleming rule yields nominal significance levels for termination at the 5 analysis points of, respectively, 0.00001, 0.0013, 0.008, 0.023, and 0.041.

We emphasize that the above p-values will serve as guidelines only, and that no decision to stop the study early will be based only on an O'Brien-Fleming p-value having been reached. Other considerations will include the availability of desired information about other trial endpoints, the consistency of the primary result with other findings in the trial and with other studies, and the consistency of the primary outcome across important subgroups.

The primary analysis in this study will be a logrank test which will compare the Kaplan-Meier survival curves which describe the time to the development of POAG. A logrank test will be used in preference to a generalized Wilcoxon test because the Wilcoxon test is most sensitive to early events whereas we expect the separation of the survival curves to occur relatively late in OHTS. The unit of analysis will be the participant and the endpoint will be defined to have been reached when POAG has been determined to have occurred in either eye. Such damage is defined to be present if either the visual field or the optic disc endpoint is reached. The participant will be the unit of analysis because when conversion to glaucoma is achieved in either eye according to either outcome measure, the protocol requires that the participant be treated as deemed appropriate by his physician without regard to randomization group assignment. This reflects standard medical care.

The above analysis will be performed using the intention-to-treat principle. Thus, participants who drop out of the study, who crossover from one group to another, or who are not compliant with the medication regimen will be analyzed as part of the group into which they had originally been randomized. Data from participants who drop out of the study will be censored at the time of their last evaluation. If disease or trauma makes it impossible to collect endpoint data regarding one eye, the participant will not be censored and the development of glaucoma will be determined on the basis of the second eye only. Similarly, if circumstances are such that it is possible to collect information about only one of the two endpoints, the participant will not be censored and the development of glaucoma will be defined in terms of the available endpoint only. To the extent that either of the latter two circumstances arise, our estimates of the rate at which glaucoma develops in these participants will be understated. However, because we can think of no circumstances, which would cause the stated events to occur differentially in the two groups, our decision not to censor these

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participants will not bias the primary analysis. We emphasize that so long as at least one of the two outcome measures can be ascertained in at least one eye, participants will not be censored.

To determine whether the medication has a differential effect on important subgroups, interactions between medication and a set of predefined covariates will be evaluated. The predefined covariates are race, age, baseline cup to disc ratio, a family history of glaucoma, the presence of systemic hypertension, and the presence of vascular disease (including peripheral or cardiovascular). In addition, based on the work of Hart²⁸ et al. and Kolker,²⁹ we will determine the value of a logistic risk function for each participant and will treat that function as a covariate. Statistically, the significance of these covariates will be determined through an evaluation of interaction terms within a proportional hazards regression model. As secondary analyses, proportional hazards models will be fit to close observation group participants to describe the natural history of the development of POAG and to describe the role of the above stated risk factors.

Other questions to be addressed as part of our secondary analyses include the following:

- 1. Is change in IOP related to change in visual field?
- 2. Is change in IOP related to the time at which conversion occurs?
- 3. To what extent are changes in IOP and changes from baseline to final measurement in cup to disc ratio predictive of changes in visual field as measured continuously and conversion as measured by a threshold?

During the study year 3-5, we will explore in detail both the statistical methodology and the availability of software which can address these questions. Inherently, these are paired longitudinal analyses which, because data will sometimes be missing in one eye only, will be unbalanced. When time to conversion or time to some visual field threshold is the endpoint, survival models must be considered. If models which can correctly handle these survival analyses cannot be identified or cannot be reasonably implemented, we will implement simulation studies aimed at assessing the impact on statistical power of various compromises. For example, if we can implement a paired and balanced survival analysis but not a paired and unbalanced survival analysis, we will explore the relative power of analyzing the data (1) using balanced survival methods which use maximum likelihood extrapolations for missing data as compared to (2) treating the endpoint as dichotomous and using longitudinal analyses which ignore the differences in follow-up time between participants. All such analyses will explore the impact on the power comparisons of varying assumptions about relevant parameters; e.g., the amount of missing data and the temporal pattern of the occurrence of endpoints.

2.10 Human Participants

The study is limited to ocular hypertensive participants who have qualifying IOPs ≥ 24 mm Hg but ≤ 32 mm Hg in one eye and IOP in the fellow eye of ≥ 21 mm Hg as determined by two separate consecutive determinations taken at least two hours, but not greater than 12 weeks, apart. The participants are 40 and 80 years of age, inclusive, at entry into the study. There are no limitations based on gender, ethnic group, or religious affiliation. The study excludes fetuses, pregnant or nursing women, children, prisoners, institutionalized individuals, or individuals unable to give fully informed consent. It is anticipated that a total of 1500 participants will be enrolled in

various Clinical Centers. The study goal is to recruit 400 African American participants in the trial (26.7% of the volunteers).

2.10.1 Entry Criteria

- a. The qualifying IOP in at least one eye of each individual must be ≥ 24 mm Hg but ≤ 32 mm Hg on two separate consecutive determinations taken at least two hours, but not greater than 12 weeks, apart. A determination consists of either the mean of two measurements or the median of three measurements (See chapter 7). The fellow eye must have a qualifying IOP ≥ 21 mm Hg on two consecutive determinations. All IOP readings are taken by certified study technicians, an operator and recorder, at approximately the same time of day to minimize the influence of diurnal fluctuation. Individuals whose IOP falls outside the qualifying range may be reevaluated for inclusion **once and only once** after 12 weeks.
- b. Age 40 to 80 years, inclusive.
- c. Normal and reliable Humphrey 30-2 visual fields in both eyes as determined by the VFRC. Individuals undergo a minimum of two and a maximum of three visual field tests, and all but prestudy visual fields are done by certified study technicians. Two of the three visual fields must meet reliability criteria of < 33% false positives, < 33% false negatives, and < 33% fixation losses. The same two visual fields must also be judged to be normal by the VFRC, including all STATPAC II global indices (mean defect [MD], pattern standard deviation[PSD], short term fluctuation [SF], and corrected pattern standard deviation [CPSD] being within the 95% age-specific population norm, and glaucoma hemifield test [GHT] being within the 97% age-specific population norm).
- d. Normal optic discs in both eyes on clinical examination and on stereoscopic photographs as determined by the ODRC. The optic discs of both eyes should have intact rims and there should be no disc hemorrhages, notches, localized pallor, or asymmetry in the cup/disc ratios of the two eyes > 0.2. All but prestudy photographs must be taken by certified study photographers.

2.10.2 Exclusion Criteria

- a. Best-corrected visual acuity worse than 20/40 in either eye on qualifying examination.
- b. Previous intraocular surgery, as determined by history and examination, including laser trabeculoplasty, laser iridotomy, filtering surgery, combined cataract/filtering surgery, penetrating keratoplasty, retinal detachment repair. The following are not exclusionary surgical procedures: A previous uncomplicated extracapsular cataract extraction with PC-IOL and no escape of vitreous to the anterior chamber, strabismus, cosmetic lid surgery (including blepharoplasty and ptosis repair), and radial keratotomy.
- c. A life-threatening or debilitating disease that limits the individual's ability to return a minimum of twice yearly through study end (a minimum of five years).

- d. Secondary causes of elevated IOP, i.e., exfoliation syndrome, pigment dispersion, ocular or systemic corticosteroid use, iridocyclitis, trauma.
- e. Angle-closure glaucoma or anatomically narrow angles 75% of the circumference of the angle must be grade II or more by Shaffer criteria.
- f. Other diseases that cause visual field loss, i.e., pituitary lesions, demyelinating diseases, ischemic optic neuropathy, stroke.
- g. Background diabetic retinopathy, defined as a single microaneurysm seen on direct ophthalmoscopy with a dilated pupil. Retinal hemorrhage is not an exclusion unless associated with background or proliferative diabetic retinopathy.
- h. Inability to visualize or photograph the optic discs.
- i. Optic disc abnormalities that can produce visual field loss or that can obscure the interpretation of the optic disc, i.e., optic disc drusen, pits, colobomas, or other severe anomalies as determined by the ODRC.
- j. Individual's unwillingness to undergo random assignment to medication or close observation only, failure to sign informed consent form.
- k. Pregnant or nursing women as determined by subject self-report and testing. Pregnant or nursing women may be reevaluated for inclusion after the period of pregnancy or nursing has ended. Baseline pregnancy tests are performed on all premenopausal women who have not been sterilized.

2.10.3 Confidentiality and Protection of Subjects

The research data consists of written records, optic disc photographs, and visual fields. All material is kept in locked file cabinets and is available only to the physicians and coordinators at the various Clinical Centers and Reading Centers. No material will be published or released with a participant's name, social security number, or other identifier. Some information about the participant's previous medical history will be utilized in the study.

All participants are recruited by the principal investigator or designate at each Clinical Center. The individual obtaining consent explains the study, and the potential recruit reads a booklet and watches a videotape describing the study before being asked to sign the consent. The consent form has been approved by the Institutional Review Board of each participating institution. No waivers are requested.

2.10.4 Risks

The risks of this trial are relatively low and are, for the most part, connected to the individual's preexisting conditions. The primary risk of the study is that a participant will develop open-angle glaucoma with attendant visual loss. Of course, all of the individuals recruited are at moderate risk for developing the disease. It is anticipated that 10-20% of the individuals recruited will develop early open-angle glaucoma. By following the participant every six months and examining them carefully, all diagnoses should be made at an early stage of the disease when

treatment is most likely to be effective. It must be emphasized that the individuals are at risk whether they enter the study or not. It is possible that the risk of developing open-angle glaucoma is reduced in the medication group. It seems highly unlikely that the risk of developing open-angle glaucoma is increased in the medication group.

Another risk is the development of a side effect to one of the prescribed medications. The drugs and the more common side effects are listed below. The side effects of medication can be serious but can be reduced in frequency and severity by careful questioning of participants at baseline and throughout the study. Side effects are also reduced by punctal occlusion or simple eyelid closure after drug instillation. Furthermore, many of these participants might have been treated with the same drugs outside of the trial.

Topical beta adrenergic antagonists (timolol, betaxolol, metipranolol, levobunolol, or carteolol): Burning and stinging on instillation, blurred vision, asthma; **less commonly,** dry eyes, slowed heart rate, lung failure, congestive heart failure, hallucinations, trouble concentrating, problems with sexual function, depression.

Topical miotics (pilopine gel, Ocusert, pilocarpine, or carbachol): Burning and stinging on instillation, headache, dim vision, blurred vision; **less commonly,** retinal detachment, hemorrhage in the eye, acute rise in eye pressure.

Topical adrenergic agonists (epinephrine or dipivefrin): Burning and stinging on instillation, redness, allergic reaction of the lids; **less commonly,** rapid or irregular heartbeat, elevated blood pressure, stroke, heart attack.

Topical alpha-2 agonists (brimonidine or apraclonidine): Burning and stinging on instillation, redness, allergic reaction of the lids, watery eyes, dry mouth; **less commonly**, abnormal vision, abnormal heartbeat, facial swelling, drowsiness, nervousness, dry nose, shortness of breath, low blood pressure.

Topical carbonic anhydrase inhibitors (dorzolamide or brinzolamide): Burning and stinging on instillation, blurred vision, watery eyes, dry eyes, a bitter taste following instillation, allergic reaction of the lids, **less commonly**, headache, nausea, skin rashes, hair loss, diarrhea, dizziness, dry mouth, chest pain.

Topical prostaglandin analogue (latanaprost or uniproston): Blurred vision, burning and stinging on instillation, redness, foreign body sensation, itching, increased pigmentation of the iris, eye pain; **less commonly,** muscle and joint pain, skin rash, retinal edema, growth of eye lashes, inflammation of the eye.

Combination topical therapy (timolol and dorzolomide): Burning and stinging on instillation, blurred vision, asthma, watery eyes, dry eyes, a bitter taste following instillation, allergic reaction of the lids; **less commonly** slowed heart rate, lung failure, congestive heart failure, hallucinations, trouble concentrating, problems with sexual function, depression, headache, nausea, skin rashes.

These drugs are elective for participants who develop primary open angle glaucoma.

Systemic carbonic anhydrase inhibitors (diamox, diamox sequels, or neptazane): Malaise, fatigue, gastrointestinal upset, frequent urination, weight loss; less commonly, decreased libido, skin rash, renal colic, bone marrow depression.

It should be emphasized that many practitioners routinely treat moderate-risk and even lowrisk ocular hypertensive individuals with eyedrops; therefore, the side effects listed above could occur in ocular hypertensive individuals who are not entered in the study.

2.10.5 Ethics

A major question deals with the ethics of the randomized assignment to medication. We believe it is ethical to perform this randomized trial since we do not have conclusive evidence about the efficacy and safety of medical treatment in ocular hypertension. Given the controversy in this situation, a randomized trial appears ethical and appropriate.

Alternative approaches could include argon laser trabeculoplasty or filtering surgery, but these treatments are generally not performed on ocular hypertensive individuals in the United States at present.

All participants are examined carefully every six months. Thus, we should diagnose glaucoma at an early stage and adjust or initiate treatment appropriately to prevent further damage. In the medication group, participants are questioned carefully about their medical treatment and symptoms before selecting initial treatment or changing the treatment. On subsequent visits participants are questioned carefully to determine the presence of drug-induced side effects. Medication is altered to reduce or avoid serious or annoying side effects. Participants are also instructed in the proper technique of eyedrop administration, including punctal occlusion or simple eyelid closure for two minutes after drug instillation.

Confidentiality is maintained. The records are held in locked cabinets. No information is released with the participant's name, initials, social security number, or other identifier.

The data is monitored by the Coordinating Center and the DSMC for unusual or alarming side effects. In addition, the DSMC will determine whether sufficient evidence exists to terminate the trial early for reasons of safety.

2.10.6 Benefits

The potential benefits of this trial are great. Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. We lack conclusive information about the efficacy of early medical treatment in preventing or delaying the onset of POAG. Given the high prevalence of glaucoma in the population and the serious consequences of the disease, such information is crucial. The participant in this trial has the satisfaction of making a significant contribution to the care of ocular hypertensive individuals.

The participants will be followed with the best care possible. Their visual fields and optic disc photographs are reviewed by some of the top experts in the country at regular intervals. Participants are followed closely to detect evidence of glaucoma at the earliest possible stage.

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

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Chapter 2 Study Design: Appendix

Procedures for Confirmation of Abnormality and its Attribution to POAG

The primary endpoint is the development of a confirmed visual field abnormality or confirmed optic disc progression attributed to primary open angle glaucoma. It is the responsibility of the Endpoint Committee to determine whether the visual field defect and/or optic disc progression is attributable to primary open angle glaucoma or not. To do this, the Endpoint Committee is provided with the following:

- 1) Copies of all dated examination forms with pertinent medical/ocular histories. All pages are masked to randomization, IOP and endpoint status.
- 2) All visual fields performed to date for both eyes.
- 3) All photos taken to date for both eyes, including stereoscopic, macular and red reflex photos.
- 4) Narrative summary and description from the reading center convening the Endpoint Committee.
- 5) Endpoint Worksheet (EW) form.

With the information listed above, each Committee member independently checks one of the following options on the Endpoint Worksheet (EW) described below: 1) POAG, 2) Not POAG, 3) No Change, and makes a recommendation to the clinic and reading center for future testing of this eye for the type of abnormality being reviewed.

<u>1. POAG</u>

Recommendation	Clinic Action	Reading Center Action
a) Not Applicable		
 b) Continue follow-up and discontinue confirmation testing for this eye. 	Schedule unscheduled visit. Perform routine follow-up tests at future follow-up visits for this eye/modality. Do not perform confirmation testing for this eye/modality.	Expect routine follow-up tests in the future for this eye/modality.
c) Discontinue routine follow-up testing and discontinue confirmation testing for this eye.	Schedule unscheduled visit. Do not perform any further tests for this eye/modality.	Do not expect any further tests for this eye/modality.

2. NOT POAG (ocular, artifact, systemic, unknown, other)

Recommendation		
for Future Testing	Clinic Action	Reading Center Action
a) Continue routine follow-up and confirmation testing for this eye.	Schedule next follow-up visit. Perform routine follow-up tests at future follow-up visits for this eye/modality.	Expect routine follow-up tests in the future for this eye/modality. Request confirmation testing.
b) Continue follow-up and discontinue confirmation testing for this eye.	Schedule next follow-up visit. Perform routine follow-up tests at future follow-up visits for this eye/modality. Do not perform confirmation testing for this eye/modality.	Expect routine follow-up tests in the future for this eye/modality. Do not request confirmation testing for this eye/modality.
c) Discontinue routine follow-up testing and discontinue confirmation testing for this eye.	Schedule follow-up visit. Do not perform any further tests for this eye/modality.	Do not expect any further tests for this eye/modality.

3. NO CHANGE (Disease process unlikely or change not clinically significant)

-			
	Recommendation for Future Testing	Clinic Action	Reading Center Action
a)	Continue routine follow-up and confirmation testing for this eye.	Schedule next follow-up visit. Perform routine follow-up tests at future follow-up visits for this eye/modality.	Expect routine follow-up tests in the future for this eye/modality. Request confirmation testing.
b)	Continue follow-up and discontinue confirmation testing for this eye.	Schedule next follow-up visit. Perform routine follow-up tests at future follow-up visits for this eye/modality. Do not perform confirmation testing for this eye/modality.	Expect routine follow-up tests in the future for this eye/modality. Do not request confirmation testing for this eye/modality.
c)	Discontinue routine follow-up testing and discontinue confirmation testing for this eye.	Schedule follow-up visit. Do not perform any further tests for this eye/modality.	Do not expect any further tests for this eye/modality.







To protect masking, the Coordinating Center is the "go-between" for all communication involving endpoint processing for the Visual Field Reading Center and the Optic Disc Reading Center, clinics and Endpoint Committee. The reading centers and Endpoint Committee must remain masked to randomization, IOP and endpoint status.

Summary of Revisions

Chapter 3 - Eligibility and Exclusion Criteria

Section	Date	Description
<u>3.2 Eligibility Criteria</u>	10/27/94	Individuals whose IOP are outside qualifying range may be reevaluated for inclusion once and only once 12 weeks after the date of the last QA visit
	2/16/95	QA IOP's must be consecutive
	9/1/95	Individuals who are ineligible because of unreliable or abnormal visual fields may be reevaluated for inclusion once and only once 12 weeks after the date of the last QA visit.
	10/27/95	Two week washout for topical CAI's

3. Eligibility and Exclusion Criteria

3.1	Introduction	
3.2	Eligibility Criteria	
3.3	Exclusion Criteria	
3.4	Eligibility Review	

3.1 Introduction

All study personnel must be thoroughly familiar with the eligibility and exclusion criteria. Only a few of the participants enrolled in the study will develop primary open angle glaucoma (POAG); thus, entry of individuals who have glaucomatous damage at baseline or who have other forms of glaucoma could seriously compromise the statistical power and the conclusions of the trial.

3.2 Eligibility Criteria

Each participant enrolled in OHTS must meet the following requirements:

a. The qualifying IOP in at least one eye of each participant must be ≥ 24 mm Hg but ≤ 32 mm Hg calculated from two separate consecutive determinations taken at least two hours, but not greater than 12 weeks, apart. A determination consists of either the mean of two measurements or the median of three measurements. The fellow eye must have a qualifying IOP ≥ 21 mm Hg. All IOP readings are taken by certified study technicians, an operator and recorder, at approximately the same time of day to minimize the effect of diurnal fluctuations. Individuals whose IOP readings are outside the qualifying range may be reevaluated for inclusion once and only once 12 weeks after the date of the last Qualifying Assessment visit.

All IOP readings are performed after appropriate washout of prestudy topical ocular medications — one week for standard miotics, 2 weeks for alpha 2 agonists and topical carbonic anhydrase inhibitors and four weeks for beta blockers and epinephrine/dipivefrin.

- b. Age 40 to 80 years, inclusive.
- c. Normal and reliable Humphrey 30-2 visual fields in both eyes as determined by the Visual Field Reading Center (VFRC). Individuals will undergo a minimum of two and a maximum of three visual field tests. Visual fields must be done by certified study technicians. Two of the three tests must meet reliability criteria of ≤ 33% false positives, ≤ 33% false negatives and ≤ 33% fixation losses. Two of the three tests must be judged to be normal by the VFRC, including STATPAC II criteria of mean defect (MD) and corrected pattern standard deviation (CPSD) being within the 95% age-specific population norm and glaucoma hemifield test (GHT) being within the 97% age-specific population norm.

One set of 30-2 visual fields performed within 12 weeks of the first qualifying visit that is performed according to the OHTS protocol can be used as part of the

eligibility determination. The individual does not have to be washed out for the prestudy field.

Two visual field tests can be performed on the same visit provided they are separated by at least 1 hour. An individual determined to be ineligible because of unreliable or abnormal visual fields may be reevaluated for inclusion, once and only once 12 weeks after the last Qualifying Assessment visit.

d. Normal optic discs in both eyes on clinical examination and on stereoscopic photographs as determined by the Optic Disc Reading Center (ODRC). The optic discs of both eyes should have intact rims and there should be no disc hemorrhages, notches, localized pallor, or asymmetry in the cup/disc ratios of the two eyes >0.2 disc diameters. All but prestudy photographs must be taken by certified study photographers.

Preexisting optic disc photographs that meet all quality control and entry criteria performed within 12 weeks of the first qualifying visit can be used as part of the eligibility determination.

3.3 Exclusion Criteria

Individuals are excluded from participation in OHTS if any of the following are present:

- a. Best-corrected visual acuity worse than 20/40 in either eye on qualifying examination.
- b. Previous intraocular surgery, as determined by patient history and examination, including laser trabeculoplasty, laser iridotomy, filtering surgery, combined cataract/filtering surgery, penetrating keratoplasty and retinal detachment repair. The following are not exclusionary surgical procedures: A previous uncomplicated extracapsular cataract extraction with PC-IOL and no escape of vitreous to the anterior chamber, strabismus, cosmetic lid surgery (including blepharoplasty and ptosis repair) and radial keratotomy.
- c. A life-threatening or debilitating disease that limits the individual's ability to return a minimum of twice yearly for at least five years.
- d. Secondary causes of elevated IOP, i.e., exfoliation syndrome, pigment dispersion, ocular or systemic corticosteroid use, iridocyclitis, trauma. Individuals may be reevaluated for eligibility upon discontinuation of corticosteroid use.
- e. Angle-closure glaucoma or anatomically narrow angles 75% of the circumference of the angle must be grade II or more by Shaffer criteria.

- f. Other diseases that cause visual field loss, i.e., pituitary lesions, demyelinating diseases, ischemic optic neuropathy, stroke.
- g. Background diabetic retinopathy, defined as a single microaneurysm seen on direct ophthalmoscopy with a dilated pupil. Retinal hemorrhage is **not an exclusion** unless associated with background or proliferation diabetic retinopathy.
- h. Inability to visualize or photograph the optic discs.
- i. Optic disc abnormalities that can produce visual field loss or that can obscure the interpretation of the optic disc, i.e., optic disc drusen, pits, colobomas, or other severe anomalies as determined by the ODRC.
- j. Individual's unwillingness to undergo random assignment to medication or close observation only, or failure to sign informed consent form.
- k. Pregnant or nursing women as determined by self-report and testing. Baseline pregnancy tests will be performed on all premenopausal women who have not been sterilized. Pregnant or nursing women may be reevaluated for inclusion after the period of pregnancy or nursing has ended.

3.4 Eligibility Review

All qualifying visual fields are sent to the VFRC. The VFRC must determine that the qualifying visual fields meet entry criteria for reliability and normality. This information is transferred to the Coordinating Center and the Clinical Center.

The qualifying optic disc photographs are sent to the ODRC. The ODRC must determine that the photographs are gradable and that the discs meet entry criteria. The information is transferred to the Coordinating Center and the Clinical Center.

When the individual completes the qualifying assessment visits, the clinic coordinator sends the qualifying assessment form to the Coordinating Center. The Coordinating Center completes a separate eligibility report, cross-checking information with the clinic coordinator and makes the determination of eligibility. If there are unresolved questions about individual's eligibility, the Clinical Center and/or the Coordinating Center will contact the Study Chairman to request a resolution.

If the individual is eligible, the Coordinating Center provides the clinic coordinator with the participant's randomization assignment at the time of the participant's Baseline/Randomization visit.

Summary of Revisions

Chapter 4 - Participant Education and Informed Consent

Section	Date	Description
4.3 Informed Consent	10/27/94	Consent form needs to be signed before data is sent to VFRC, ODRC or CC
4.4 Decline to Participate	4/1/95	Only first page of Qualifying Assessment needs to be sent to Coordinating Center for individuals who are ineligible, who decline participation or are discontinued by the clinic.
4.6 Reconsenting Subjects	12/1/97	Funding of study extended through 2002. Participants will need to be reconsented if original consent form states a five-year follow-up period.
4. Participant Education and Informed Consent

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4.1 Introduction

In an effort to enroll all eligible individuals in OHTS, considerable attention is given to education of the individual and family members so that they have a good understanding of ocular hypertension, glaucoma, the treatment options available and the need for a randomized trial of this sort. Individual education is a key element in the informed consent process.

The informed consent process provides confirmation that the individual participated in a discussion of the study. The rationale for written informed consent is not solely legal or bureaucratic. The informed consent process protects the individual as well as the scientific integrity of the study. The discussion of study treatment, follow-up schedule, treatment side effects and reasons for randomization results in the selection of participants who are more likely to return for follow-up, to tolerate inconveniences associated with study participation and to adhere to the treatment assignment. This should diminish participant dropout and the number of subjects who wish to change to the other arm of the study.

4.2 Participant Education

The principal investigator and the clinic coordinator must explain to prospective participants about ocular hypertension, glaucoma, the treatment options available, and the need for a randomized trial and OHTS. Clinical Centers should make every effort to have available the services of interpreters for individuals who do not speak English. Discussion with the individual 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. Some people may be at higher risk of developing glaucoma, including individuals who are diabetic, nearsighted, African American, have a family history of glaucoma, or have systemic vascular disease.
- Glaucoma is a condition where high pressure in the eye can cause loss of vision and even blindness in some individuals.
- It is not clear whether medical treatment of ocular hypertension really helps. The studies done to date have been relatively small and inconclusive on this question. The medications used to treat ocular hypertension are well tolerated by most individuals, but can have side effects in some individuals.
- In OHTS, approximately half of the participants are assigned to receive medical treatment and the other half are assigned to close observation only. Randomization assignments are determined by the Coordinating Center using a preset formula.

- Participants are followed closely through study end (a minimum of five years) with examinations at least every six months.
- Participants undergo standardized tests, including medical history, refraction, visual acuity, intraocular pressure, visual field testing, gonioscopy, ophthalmoscopy and optic disc photography. If early evidence of glaucoma is detected, the participant is assigned to the open arm of the study and treated in whatever fashion is thought best. The tests utilized in this trial should detect glaucoma at the earliest possible stage, well before participants notice any visual deficit themselves.

Individuals also receive an education booklet and watch a videotape presentation summarizing this same information before being asked to sign the consent. The education booklet is available in a Spanish edition.

4.3 Informed Consent

After the educational discussions outlined in 4.2, the principal investigator asks the individual to sign the consent form. Individuals 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. Individuals are also told that they will not receive remuneration for participation in the study.

In signing the consent, the individual agrees to complete the tests to determine eligibility, to participate in the trial if eligible and to accept randomization. If an individual prefers to think about the trial at home, he or she is encouraged to do so. Additional questions can be answered in person or via telephone. A Spanish language edition of the consent form is available.

A consent is to be signed before data is sent to the ODRC, VFRC or Coordinating Center. Failure to obtain written informed consent, for any reason, makes the individual ineligible until written consent is obtained.

One copy of the signed consent is supplied to the and one is filed with the study records in the Clinical Center. To protect individual 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 participant ID is recorded on the ID Assignment Log and sent to the Coordinating Center.

The Planning Committee considered the option of using two consent forms, one for eligibility assessment and one for randomization, but concluded that this approach was counterproductive because it might elicit suspicion and confusion in some individuals. Dr. Higginbotham and other members of the committee believed that using two consent forms might discourage minority participation as a number of individuals might conclude that the second consent form represented a deviation from the previous agreement. Such individuals might withdraw from the trial.

4.4 Decline to Participate

For a potentially eligible individual, who declines to participate after initiation of the qualifying assessment, a Decline to Participate form is completed and he/she can choose to receive care where he/she wishes. The Decline to Participate Form is sent to the Coordinating Center. If an individual is found to be ineligible or the qualifying assessment is discontinued by the individual or clinic, it is necessary to send only the first page of the Qualifying Assessment (QA) form. The participant ID, date of visit and a brief explanation for discontinuing the individual must be given.

4.5 **Continuing Education**

During each visit the clinic coordinator reviews the medical regimen, including the method and time of medication administration and answers any questions the participant may have. Participants will also receive newsletters from the Study Chairman's Office containing educational material about ocular hypertension, glaucoma, vision and general health and the progress of the trials. Other educational materials to encourage subject involvement and continued study participation will be developed throughout the duration of the study.

4.6 **Reconsenting Participants**

The National Eye Institute extended the funding of OHTS through to 11/30/02. The Data and Safety Monitoring Committee, the Executive/Steering Committee, and the Full Investigative Group have approved this extension of funding. Clinical Centers whose consent form stated the study would last five years need to have participant sign a new consent form to continue follow-up beyond the five years of the first consent date. A sample consent form for study participation and a sample addendum for continued participation beyond five years are included in the appendix of this chapter.

Appendix

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participant	HSC Approval Number
Principal Investigator	
Title of Project: Ocular Hypertension Treatment Study	

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

You have been participating in a research project to determine whether reduction of intraocular pressure (IOP) with eye drop medicines prevents or delays the onset of glaucoma in individuals with increased eye pressure. This study has been reviewed for its scientific merit and is sponsored by the U.S. Government, (National Eye Institute, National Institutes of Health, Bethesda, Maryland). Based upon this review, the study has been extended because we are learning so much. All participants in the study are being asked to continue their participation. Your continued participation will enable the study to answer the question if eye drop medication to lower eye pressure is safe and effective in preventing or delaying glaucoma damage.

2. Your participation will involve:

Your examination schedule stays the same (every six months). During these visits, you continue to receive a complete eye examination at no charge above what your insurance normally pays. The complete examination continues to include visual field testing at each visit and optic disc photography yearly.

Participants in the Close Observation Group continue to be followed by close observation and examinations at least every six months until close of study. Participants in the Medication Group continue to be treated with eye drop medicines and followed by close observation and examinations at least every six months until close of study. All participants will continue to fill out a questionnaire at each visit.

Your visual fields and optic disc photographs are reviewed by a team of nationally recognized experts in the field.

Form date: 5/01

4-8 OHTS Procedure Manual

3. There are certain risks and discomforts that may be associated with this research. They include:

The primary risk of the study is that you will develop open-angle glaucoma with visual field loss. It must be emphasized, however, that you are at risk whether you participate in the study or not. It is not known whether the risk of developing open-angle glaucoma is reduced by medical treatment of increased eye pressure; the study will attempt to answer this question.

Another risk is the development of a side effect to one of the prescribed medications. The medications and their potential side effects are listed below. Other side effects not known at this time may occur.

Topical beta adrenergic antagonists (timolol, betaxolol, metipranolol, levobunolol, or carteolol): Burning and stinging on instillation, blurred vision, asthma; **less commonly,** dry eyes, slowed heart rate, lung failure, pulmonary failure, bradycardia, congestive heart failure, hallucinations, trouble concentrating, problems with sexual function/impotence, depression.

Topical miotics (pPilopine gel, Ocusert, pilocarpine, or carbachol): Burning and stinging on instillation, headache, blurred vision, dim vision, blurred vision, headache; **less commonly,** retinal detachment, hemorrhage in the eye, acute rise in eye pressure vitreous hemorrhage, angle-closure glaucoma.

Topical adrenergic agonists (epinephrine or dipivefrin): Burning and stinging on instillation, redness, allergic reaction of the lids, blepharoconjunctivitis; **less commonly**, rapid or irregular heartbeat, palpitations, elevated blood pressure, stroke, heart attack.

Topical alpha-2 agonists (brimonidine or apraclonidine): Burning and stinging on instillation, redness, allergic reaction of the lids, watery eyes, dry mouth; **less commonly**, abnormal vision, abnormal heartbeat, facial swelling, drowsiness, dry nose, shortness of breath, low blood pressure, allergic blepharoconjunctivitis, redness.

Topical carbonic anhydrase inhibitors (dorzolamide): Burning and stinging on instillation, blurred vision, watery eyes, dry eyes, a bitter taste following instillation, allergic reaction of the lids, **less commonly,** headache, nausea, skin rashes, malaise, fatigue, gastrointestinal upset, frequent urination, weight loss.

Topical prostaglandin analogue (latanaprost): Blurred vision, burning and stinging on instillation, redness, foreign body sensation, itching, increased pigmentation of the iris, eye pain; **less commonly,** muscle and joint pain, skin rash, retinal edema, growth of eye lashes, inflammation of the eye.

Systemic carbonic anhydrase inhibitors (Diamox, diamox sequels, or neptazane): Malaise, fatigue, gastrointestinal upset, frequent urination, weight loss; **less commonly,** decreased libido, skin rash, renal colic, bone marrow depression. (These drugs are elective for subjects who develop primary open angle glaucoma.)

4. The possible benefits to you and society from this research are:

As a participant in this federally funded study, you will receive eye care that meets or exceeds the standard quality of care. The benefits of this trial to society are great. Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. It is not known at this time whether medical treatment of ocular hypertension prevents or delays the development of glaucoma. Given the high prevalence of glaucoma and the serious consequences of the disease, such information is crucial.

- 5. Your participation is voluntary and you may choose not to participate in this research study or withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care and there will be no penalty or loss of benefits to which you are otherwise entitled. Other than non-participation in the research, available alternatives include:
- 6. All reasonable measures to protect the confidentiality of your records and your identity will be taken. Your identity will not be revealed in any publication that may result from this study. The confidentiality of all study related records will be maintained in accordance with State and Federal laws. There is a possibility that your medical record, including identifying information, may be inspected and photocopied by officials of the Food and Drug Administration or other Federal or State government agencies. If the study is sponsored, a representative of the Sponsor, ______, may inspect these research records.
- 7. If you have any questions or concerns regarding this study, or if any problems arise, you may call the Principal Investigator at <u>your institution</u>,. You may also ask questions or state concerns regarding your rights as a research subject to s Human Studies Committee, at <u>your institution</u>.
- 8. Investigators and their colleagues who provide services at <u>your institution</u>, and facilities recognize the importance of your contribution to research studies that are trying to improve medical care. <u>your institution's</u> Investigators and their staffs will make every effort to minimize, control, and treat any complications that may arise as a result of this research. If you believe that you are injured solely as the result of the research question being asked in the study, please contact the Principal Investigator and/or the Chairman of the Human Studies Committee as stated in item 7. <u>Your institution</u> reserves the right to make decisions concerning payment for medical treatment for injuries solely and directly relating to your participation in biomedical or behavioral research.
- 9. <u>Your institution</u> will provide immediate medical treatment in the event that a physical injury results because of your participation in this project. You will be responsible for the cost of such medical care not reimbursable through your health insurance. No compensation will be provided to you for such an injury.
- 10. If you are pregnant or become pregnant while participating in this research study, it is important that you inform the principal investigator. Some research medications or procedures can cause serious injury to an unborn child.
- 11. You will be informed of any significant new findings developed during the course of participation in this research that may have a bearing on your willingness to continue in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

4-10 OHTS Procedure Manual

I have read this consent form and have been given the opportunity to ask questions. I will also be given a signed copy of this consent form for my records. I hereby consent to my participation in the research described above.

Parent or legal guardian's signature on participant's behalf if participant is less than 18 years of age or not legally competent. (Blood drawing only: Less than 17 years of age.)	Participant's Signature Date				
	Informed consent provided by:				
Relationship to Child Date	Signature of Principal Investigator or Designee	-			

Signature of Principal or Collaborating Investigator when informed consent responsibility is entrusted to a designee.

This form is valid only if the Human Studies Committee current stamp of approval is shown below.

ADDENDUM TO PARTICIPANT INFORMATION AND CONSENT FORM

SPONSOR: National Eye Institute, National Institutes of Health

PROTOCOL: The Ocular Hypertension Treatment Study

PARTICIPANT NAME:

STUDY INVESTIGATOR/DOCTOR:

STUDY SITE TELEPHONE:

The Ocular Hypertension Treatment Study is progressing very well. At this point 1637 subjects (including 409 African Americans) have enrolled in the study in centers across the country. We are gaining very important information from the study, information that will benefit you, members of your family and other individuals with elevated intraocular pressure in the future. The study has been extended beyond the original five years by the National Eye Institute. We are asking for your continued participation in the study. No significant changes in protocol are anticipated. The study will continue to be monitored by an independent oversight committee who can stop the study at any time. The study doctor and his/her staff will discuss any questions that you have about the study.

Your continued participation in the study is voluntary. You can refuse to continue in the study now or at any time in the future. You will be provided a copy of this consent form addendum.

All other elements of the original consent form are still applicable, including the potential benefits and risks.

I have read and understand this addendum to my consent and I have also reread the original attached consent form. My questions have been answered. I voluntarily consent to participate.

Signature of Participant

Date

Signature of Person Conducting Consent Discussion Date

Form date: 6/98

Summary of Revisions

Chapter 5 – Participant Entry and Randomization

Section	Date	Description				
5.3 Assignment of Participant	10/27/95	The first two digits of the identification number indicates				
ID Numbers		the clinic where the participant completes an OHTS visit.				
5.5 Qualifying Assessment	4/1/95	Only first page of QA Form needs to be sent to				
		Coordinating Center for individuals who are ineligible,				
		who decline participation or are discontinued by the				
		clinic.				
5.6 Eligibility Confirmation	9/5/95	Randomization must be completed within 6 weeks of last				
and Randomization		Qualifying Visit date.				
<u>Assignment</u>						

5. Participant Entry and Randomization

5.1	Introduction	5-3
5.2	Initial Individual Screening for Eligibility	5-3
5.3	Assignment of Participant Identification Numbers	5-3
5.4	Procedure for Informed Consent/Decline to Participate	5-4
5.5	Qualifying Assessment	5-4
5.6	Eligibility Confirmation and Randomization Assignment	5-5
5.7	Study Entry Date	5-6
5.8	Method of Computing Random Allocation	5-6

5.1 Introduction

Randomization and careful screening for eligibility protect the scientific integrity of the study by ruling out competing explanations for study results. Furthermore, eligibility criteria ensure that the participants in the study are representative of the target group of ocular hypertensives.

Informed consent is considered an eligibility criterion because it is an agreement by the participant to be randomized and to *complete* follow-up in their assigned group. The participant's random group assignment governs the treatment, follow-up and statistical analysis of the study. Once the participant is randomized to either the medication group or the close observation group, that participant's group assignment sticks and does not change during the study, even if the participant is later found to be ineligible. Thus, it is very important that study participants are truly eligible and that informed consent is truly informed.

5.2 Initial Subject Screening for Eligibility

The OHTS Telephone Screen and Chart Screening Forms provide methods of quickly screening to determine whether it is worth the individual's and the Clinical Center's time to schedule or initiate a qualifying visit. The Telephone Screen can usually be completed during a five-minute telephone conversation with the referring physician or representative. This initial screening will spare the subject and Clinical Center unnecessary disappointment. If the individual is still potentially eligible after the screening, a qualifying visit should be scheduled. The names of all individuals beginning a qualifying visit are recorded in sequential order in the Participant ID Assignment Log provided by the Coordinating Center.

5.3 Assignment of Participant Identification Numbers

Any individual scheduled for a qualifying visit and entered into the Participant ID Log is assigned a participant identification number. The clinical coordinator should fax the participant ID Assignment Log each day a name is listed. This allows the Coordinating Center to link data from the Visual Field and Optic Disc Reading Centers, as well as from the clinics. The participant identification number is constructed in the following manner: (1) the first two digits of the participant ID is the clinical center's site code; (2) the third, fourth, fifth, sixth and seventh digits represent a sequential number from the participant log at that center; i.e., 01000 to 99999; (3) the eighth, ninth and tenth digits are three letters selected from the participant's name by any system chosen by the Clinical Center that can be consistently used. The Coordinating Center is not informed as to how the three letters are selected.

- Example: John Q. Participant is the 23rd participant scheduled for a qualifying exam at Clinical Center Site Z1.
 - **Digit 1** one letter assigned by Coordinating Center to designate the Clinical Center, e.g., **Z**.

Digit 2	one number assigned by Coordinating Center to designate clinic site, e.g. 1.
Digits 3-7	five numbers representing the sequential order of participants issued ID numbers at that center, e.g., 01023 . Each clinic is assigned a range of 1,000 numbers, i.e., 1000 - 1999, 2000 - 2999, etc.
Digits 8-10	three letters from the participant's name, (usually the participant's initials) e.g., XYZ.

John Q. participant's identification number is **Z1-01023-XYZ**.

The participant's identification number (digits 3-7 and 8-10) stays with the participant for the duration of the study. If the participant transfers to another OHTS clinic, only the clinical center code (digits 1-2) changes.

5.4 Procedure for Informed Consent/Decline to Participate

During the first qualifying visit, the individual should sign an Informed Consent form or a Decline to Participate form should be completed after a discussion of ocular hypertension, glaucoma, the treatment options, the randomized clinical trial and the follow-up. If the individual is uncertain about participation, the consent procedure can be deferred to a second qualifying visit. A detailed explanation of the informed consent procedure is in Chapter 4, "Participation Education and Informed Consent." The individual retains a copy of the consent form and the original form is kept at the Clinical Center. The original signed consent forms are audited on site visits to confirm they have been signed and are in proper order. The individual's OHTS ID is recorded on the ID Assignment Log and sent to the Coordinating Center. The original Decline to Participate form is sent to the Coordinating Center and the Clinical Center retains a copy. To protect participant confidentiality, the signed consent forms are not sent to the Coordinating Center. If signed forms are accidentally sent to the Coordinating Center, they will be returned to the clinical center.

5.5 Qualifying Assessment

The qualifying assessment visits establish whether the individual satisfies OHTS eligibility criteria. Some individuals will qualify for the study with one visit, while others require two or even three visits (Qualifying Assessment (QA) form is completed and sent to the Coordinating Center). If the individual appears to be eligible, a baseline randomization visit is scheduled in four to six weeks. If an individual is found to be ineligible or the qualifying assessment is discontinued by the individual or clinic, it is necessary to send only the first page of the QA form with the subject ID and date of visit. A brief explanation for discontinuing the individual must be given.

The final determination of the individual's OHTS eligibility requires collation of information from the following sources:

- Coordinating Center After completion of the qualifying visits, the clinic coordinator sends the QA form to the Coordinating Center. The Coordinating Center Central Coordinator uses the qualifying checklist, summarizing the individual's eligibility status from previous reports, to verify eligibility status.
- Visual Field Reading Center (VFRC) Within one week after all qualifying visual fields are submitted, the VFRC notifies the Clinical Center and the Coordinating Center whether the individual satisfies OHTS visual field criteria.
- Optic Disc Reading Center (ODRC) Within one week after submission of gradable stereoscopic optic disc photographs, the ODRC notifies the Clinical Center and the Coordinating Center whether the individual satisfies OHTS optic disc criteria.

5.6 Eligibility Confirmation and Randomization Assignment

When eligibility information from the Clinical Center, VFRC and ODRC is collated, the individual's eligibility can be fully determined and the Coordinating Center does the following:

- 1. The Coordinating Center Central Coordinator notifies the clinic coordinator and/or principal investigator of the outcome of qualifying assessment. If the individual appears eligible, the individual's data from QA is reviewed by telephone with the clinic coordinator for final confirmation of eligibility. If the individual is ineligible, the clinic coordinator informs the individual by telephone and cancels any return appointments.
- 2. If the individual is not eligible, a letter of appreciation is mailed to the individual and to the referring clinician or lay person.
- 3. If the individual is eligible, the central coordinator provides the random assignment at the time of the Baseline/Randomization visit. Participants should be present at the time of randomization. Baseline/Randomization visit should be completed within 6 weeks of the last Qualifying Assessment date.
 - The clinic coordinator informs the participant about randomization assignment to the medication or observation group.
 - The random assignment for a given study participant cannot be used for any other participant. Each participant receives his/her own random assignment.
 - The Clinical Center sends a letter to the referring clinician or lay person thanking them for the referral.
- 4. Within one week of the Coordinating Center's receipt of the Baseline/Randomization Visit form, a set of randomization assignment labels and follow-up schedule is sent from the Coordinating Center to the Clinical Center.

5.7 Study Entry Date

The date of randomization serves as the official date of entry into the OHTS. The dates of scheduled follow-up visits are calculated from the date of randomization. The Coordinating Center generates the follow-up schedule for each participant from the date of randomization.

5.8 Method of Computing Random Allocation

The schedule of random assignments is generated and stored at the Coordinating Center on a central computer file that is password protected to allow access only to the Central Coordinators and the Coordinating Center director.

The allocation ratio to the medication arm and observation arm is equal so that the number of participants assigned to the medication and observation groups is approximately the same. Blocking intervals within each stratum will be small and in random order so that a reasonable balance between the two arms of the study is assured even early in the trial. Randomization is stratified by race within clinics so that in any given clinic, regardless of the number of African Americans enrolled, there will be a balanced proportion of African Americans allocated to the medication and observation groups. The stratification of randomization assures racial balance between the two arms of the study and does not impose a minimum number to be enrolled in each racial strata. The randomization assignment is constructed using the Moses-Oakford algorithm and a computer pseudo-random number generator.

Summary of Revisions

Chapter 6 - Schedule of Visits and Form Completion

Sectio	n	Date	Description
<u>6.2</u>	Qualifying Visits	4/1/95	For ineligible individuals, only first page of QA form
			needs to be sent to Coordinating Center.
		2/16/95	QA IOP's must be consecutive.
		10/27/94	Two week washout for topical CAI's.
6.5	Follow-Up Visits	1/21/94	Annual and semi-annual follow-up visits ± 3 months of
			target are acceptable. Follow-up visits should be 60 days
			apart.
6.5.1	Semi-Annual Follow-	1/31/94	ETDRS V/A added to semi-annual exam.
	<u>Up Visit</u>		
<u>6.5.2</u>	Annual Follow-Up Visit	10/25/96	SF-36 completed only on annual visits.
<u>6.6</u>	Visual Field	6/1/97	Steering Committee approves confirmation of visual
	<u>Abnormality</u>		field abnormality by three consecutive visual fields with
	Confirmation Visit		a defect of the same character in the same location.
			Previously, this number was two.
<u>6.8</u>	Unscheduled Visits	9/5/95	Unscheduled Visit form (UN) should be used for changes
			in medication by telephone.
<u>6.9</u>	Adverse Event	1/99	Adverse Event reporting clarified.
	Reporting		
<u>6.10</u>	Participant Retention	9/5/95	If participant moves, etc., use site code where participant
			completes visit.
<u>6.11</u>	Participant Transfer	1/99	Participant Transfer procedures clarified.
<u>6.12</u>	Participant Death	1/99	Participant Death reporting clarified.
<u>6.13</u>	Missed Visit	1/99	Missed visit reporting clarified.
<u>6.14</u>	Inactive Participants	1/99	Inactive Participant reporting clarified.
<u>6.16</u>	Forms Requested by	1/99	Forms required are clarified.
	Type		
<u>6.17</u>	Forms Requested by	1/99	Forms required are clarified.
	Event		
6.18	OHTS Form List	1/99	Current forms are listed.

6. Schedule of Visits and Form Completion

6.1	Introduction	
6.2	Qualifying Visits	
6.3	Baseline/Randomization Visit	
6.4	IOP Confirmation Visit	
6.5	Follow-up Visits	
6.5.1	Semi-Annual Follow-up Visit	
6.5.2	Annual Follow-up Visit	
6.6	Visual Field Abnormality Confirmation Visit	6-9
6.7	Optic Disc Progression Confirmation Visit	6-9
6.8	Unscheduled visits	6-10
6.9	Adverse Events (AE)	
6.10	Participant Retention	6-10
6.11	Participant Transfer	6-11
6.12	Participant Death	6-11
6.13	Missed Visit	
6.14	Inactive Participants	
6.15	Schedule of Examinations	6-14
6.16	Forms Required by Visit Type	
6.17	Forms Required by Event	6-16
6.18	OHTS Forms and Current Version Number	6-17

6.1 Introduction

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

6.2 **Qualifying Visits**

A minimum of one and a maximum of three qualifying visits are required. All qualifying visits must be completed within 12 weeks to determine whether an individual is eligible for the trial and to provide baseline data.

Data and procedures required to determine eligibility:

- Detailed medical and ocular history, including medication use
- Refraction
- Best corrected visual acuity
- External and slit-lamp examination
- Humphrey program 30-2

Two out of a maximum of three visual fields must meet entry criteria in each eye. A second visual field can be performed on the same visit if spaced one hour after the previous visual field. One set of Humphrey visual fields performed within 12 weeks of the first qualifying visit that meets all study criteria can be used to determine eligibility. The prestudy visual field can be performed on an individual who is not washed out.

• Applanation tonometry

All qualifying IOP readings are performed after appropriate washout of prestudy topical ocular medications — one week for standard miotics, two weeks for alpha 2 agonists and topical carbonic anhydrase inhibitors and four weeks for beta blockers and epinephrine/dipivefrin.

Two separate consecutive determinations of IOP taken at least two hours, but not greater than 12 weeks apart are required. A determination consists of either the mean of two IOP measurements or the median of three IOP measurements.

- Dilated ophthalmoscopy, including peripheral retinal examination and optic disc examination.
- Stereoscopic optic disc photography

Prestudy optic disc photographs performed within 12 weeks of the first qualifying visit that meet all study criteria can be used to determine eligibility. Do not perform optic disc photography after gonioscopy. Photos are likely to be very poor.

• Gonioscopy

Perform after optic disc photography. A separate visit is not necessary to complete the gonioscopy.

- Participant education program covering ocular hypertension, glaucoma, treatment options and OHTS. Participant education includes one-on-one discussion, viewing of the participant education videotape, reading the participant education booklet and question-and-answer periods as needed.
- Informed consent for determination of eligibility, participation in the study and randomization.
- Completion of Qualifying Assessment form (QA).
- If an individual appears eligible, schedule a Baseline/Randomization visit in 4 ± 2 weeks at approximately the same time of the day as the Qualifying Visit.
- If an individual is found to be ineligible or the individual or clinic discontinues the Qualifying Assessment, it is only necessary to send the first page of the QA. The ID, date of visit and a brief explanation for discontinuing the individual must be given.

Following review of all qualifying information, the Central Coordinator notifies the Clinical Center of the individual's eligibility and if eligible, the randomization assignment is issued at the time of the baseline visit.

6.3 Baseline/Randomization Visit

Eligible individuals return and are informed that they are eligible for the study and receive their random assignment (medication vs. close observation). Ineligible individuals are informed by telephone prior to this visit so it can be canceled.

Data collected and procedures required during a randomization visit:

- Prior to examination, the individual completes form SF-36 for Quality-of-Life Assessment form (QL).
- Prior to examination, all individuals, regardless of randomization assignment, complete a baseline Symptom Checklist form (SY).
- IOP is measured.
- The clinic coordinator completes the Patient Tracking form (TR).
- Completion of Baseline/Randomization form (BR) which records randomization assignment from the Coordinating Center issued by telephone during this visit. Randomization defines participation in the study.

Participants assigned to the medication group are prescribed medication in an one-eyed trial. He/she is scheduled to return at approximately the same time of the day in 4 ± 2 weeks for an IOP Confirmation Visit (CF). Participants assigned to the close observation group are scheduled to return for routine follow-up in six months at approximately the same time of the day.

6.4 **IOP Confirmation Visit**

An IOP Confirmation visit is scheduled in 4 ± 2 weeks at approximately the same time of the day for participants randomized to the medication group:

- a) after the Baseline/Randomization visit
- b) after any change in medical therapy including adding a drug, substituting a drug, increasing a drug concentration, decreasing a drug concentration or the number of daily doses
- c) after the participant in the medication group does not meet IOP treatment goals to confirm that IOP goals are still not met. The visit should be scheduled at about the same time of day as the qualifying and follow-up visits to minimize diurnal fluctuation of IOP
- d) after drug-induced side effects require a change in treatment, the participant returns for IOP Confirmation visit in 4 ± 2 weeks

The IOP Confirmation visits continue until therapeutic goals are met or until the participant is uncontrolled despite maximum tolerated topical therapy. The participant then returns to the standard follow-up visit schedule.

Data collected and procedures required during an IOP Confirmation visit:

- Prior to examination, participant completes Symptom Checklist form (SY)
- Visual acuity using the most recent refraction
- Brief eye examination (external examination of lids, lashes and conjunctiva; slit-lamp examination; direct ophthalmoscopy)
- Applanation tonometry
- Dispensing of medication
- Completion of IOP Confirmation Form (CF)

The IOP treatment goal on the IOP Confirmation visit is IOP ≤ 24 mm Hg and a 20% reduction from the average of the Qualifying IOP and Baseline IOP. The 20% reduction in IOP is not required if IOP ≤ 18 mm Hg.

If the IOP treatment goal is reached, medication is continued and the participant should be scheduled to return for the next regularly scheduled follow-up visit at approximately the same time of the day.

If the IOP treatment goal is reached in an eye following a one-eyed trial, medication is prescribed for both eyes, if appropriate, and the participant is scheduled to return for the next regularly scheduled follow-up visit at approximately the same time of day.

If the IOP treatment goals are not reached at this IOP Confirmation visit, there are two options:

1) If the time since the last medication dosage exceeds limits (> 8 hrs. miotic, > 10 hrs. alpha 2 agonists and topical carbonic anhydrase inhibitors, > 12 hrs. adrenergic agonist, > 14 hrs. beta-blocker, > 24 hrs. daily beta blocker and prostaglandin), another IOP determination

can be performed on the same day one hour after instillation of drops (complete an IOP Confirmation (IP) form and send with the Confirmation Visit (CF) form), or another IOP Confirmation visit scheduled in 4 ± 2 weeks at approximately the same time of the day.

2) If time limits have <u>not</u> been exceeded, medical therapy should be altered as outlined in the stepped medical regimen. The participant should be scheduled for an IOP Confirmation visit in 4 ± 2 weeks at approximately the same time of the day to determine if IOP treatment goal is reached.

6.5 Follow-up Visits

Scheduled follow-up visits occur at six-month intervals from the date of the Baseline/Randomization visit.

Ideally, follow-up visits should occur \pm one month of the scheduled target date. However, follow-up visits \pm three months of the target date are acceptable. Regularly scheduled follow-up visits should be at least 60 days apart. If a regularly scheduled visit is not completed within \pm three months of the target date, the visit is defined as a "missed visit." A Missed Visit form (MV) is completed. Participants who miss a visit resume the regular follow-up schedule defined at baseline.

All tests and measures should be completed prior to sending the Follow-Up Visit Form (FV) to Coordinating Center. This includes fields for every follow-up visit and photos for annual visits.

Follow-up appointments should be scheduled early in the time period so that rescheduled or repeated tests (i.e., for an ungradable optic disc photograph or unreadable visual field) can occur within the time windows. Follow-up visits should be scheduled at approximately the same time of day as the qualifying and randomization visits to minimize diurnal fluctuation of IOP. There are two types of regularly scheduled follow-up visits — the six-month follow-up visit, and the 12-month follow-up visit.

6.5.1 Semi-Annual Follow-up Visit

Semi-Annual Follow-up Visit The first 6-month follow-up visit occurs six months after randomization and is repeated every 12 months thereafter — i.e., at 18, 30, 42, 54, 66, etc. months after randomization.

Data collected and procedures required at 6-month follow-up visits:

- Prior to examination, all participants, regardless of randomization assignment, complete the Symptom Checklist form (SY)
- Update Patient Tracking (TR) form. The TR form is kept at the Clinical Center. Do not send TR form to the Coordinating Center.

- Review of medications (all participants should bring with them bottles from all prescription medications used since the last follow-up visit)
- Updated medical and ocular history
- Refraction
- Best corrected visual acuity (Snellen & ETDRS)
- Humphrey 30-2 visual fields
- Complete eye examination (external examination of lids, lashes and conjunctiva; slit-lamp examination; direct ophthalmoscopy)
- Applanation tonometry
- Ophthalmoscopy
- Completion of Follow-up Visit form (FV form)
- Dispensing of medication to treated subjects
- Gonioscopy is performed once every two years at non-photography visits

All tests and measures should be completed within six weeks of initial follow-up visit and prior to sending Follow-Up Visit form (FV) to Coordinating Center.

If the IOP treatment goals for a participant randomized to the medication group are not reached on this visit, there are three options:

- If the time since the last medication dosage exceeds limits (> 8 hrs. miotic, > 10 hrs. alpha 2 agonists and topical carbonic anhydrase inhibitors, > 12 hrs. adrenergic agonist, > 14 hrs. beta-blocker, > 24 hrs. daily beta blocker and prostaglandin), another IOP determination can be performed on the same day one hour after instillation of drops. (If second IOP is performed, complete an IOP Determination (IP) form and send with the Follow-up Visit (FV) form.)
- 2) Schedule an IOP Confirmation visit in 4 ± 2 weeks to determine if IOP is still higher than the IOP treatment goal.
- 3) If it is unlikely that a participant with marked elevation in IOP will reach IOP treatment goals on a second visit, therapy should be altered. An IOP Confirmation visit should be scheduled in 4 ± 2 weeks to assess effectiveness of the change in therapy.

6.5.2 Annual Follow-up Visit

Annual Follow-up Visit The first 12-month follow-up visit occurs 12 months after randomization and is repeated every 12 months thereafter; i.e., 24, 36, 48, 60, 72, etc. months after randomization.

Ideally, follow-up visits should occur \pm one month of the scheduled target date. However, follow-up visits \pm three months of the target date are acceptable. Regularly scheduled follow-up visits should be at least 60 days apart. If a regularly scheduled visit is not completed within \pm three months of the target date, the visit is defined as a "missed visit." A Missed Visit form (MV) is completed. Participants who miss a visit resume the regular follow-up schedule defined at baseline. Data collected and procedures required at 12-month follow-up visits:

- Prior to examination, all participants regardless of randomization assignment, complete the SF-36 form (QL) and Symptom Checklist form (SY)
- Update Patient Tracking (TR) form. The TR form is kept at the Clinical Center. Do not send TR form to the Coordinating Center.
- Review of medications (all participants should bring with them bottles from all prescription medications used since the last follow-up visit)
- Updated medical and ocular history
- Visual Acuity with most recent refraction
- Humphrey 30-2 visual fields
- Complete eye examination (external examination of lids, lashes, and conjunctiva; slit-lamp examination; direct ophthalmoscopy)
- Applanation tonometry
- Ophthalmoscopy
- Dilated fundus examination
- Stereoscopic optic disc photographs
- Completion of Follow-up Visit form (FV)
- Dispensing of medication to treated participants

If the IOP treatment goals for a participant randomized to the medication group are not reached on this visit, there are three options:

- If the time since the last medication dosage exceeds limits (> 8 hrs. miotic, > 10 hrs. alpha 2 agonists and topical carbonic anhydrase inhibitors, > 12 hrs. adrenergic agonist, > 14 hrs. beta-blocker, > 24 hrs. daily beta blocker), another IOP determination can be performed on the same day one hour after instillation of drops. (If second IOP is performed, complete an IOP Determination (IP) form and send with the Follow-up Visit (FV) form.)
- 2) Schedule an IOP Confirmation visit in 4 ± 2 weeks to determine if IOP is still higher than the IOP treatment goal.
- 3) If it is unlikely that a participant with marked elevation in IOP will reach IOP treatment goals on a second visit, therapy should be altered. An IOP Confirmation visit should be scheduled in 4 ± 2 weeks to assess effectiveness of the change in therapy.

6.6 Visual Field Abnormality Confirmation Visit

A single isolated abnormal visual field does not generally warrant accelerated retesting. The next (second) visual field should be performed at the next regularly scheduled follow-up visit.

If the Visual Field Reading Center (VFRC) considers the second field abnormal, the VFRC calls the Clinical Center to make sure a repeat (third) visual field for a primary endpoint is obtained in 4 ± 2 weeks. If the participant has already developed POAG in one or both eyes, then the confirming (third) visual field is obtained at the next regularly scheduled follow-up visit.

In most cases, the visual field abnormality will have been detected by the investigator or other clinical center personnel, who will schedule the return appointment. (If the VFRC determines that the second visual field test is reliable and <u>normal</u>, the third confirming visual field test is canceled.)

Data collected and procedures required during the third visual field confirmation visit:

- Completion of the Unscheduled Visit form (UN)
- Refraction using DRVS protocol (see MOP section Chapter 7, section 7.8)
- Best corrected visual acuity
- Brief eye examination (external examination; slit-lamp examination; direct ophthalmoscopy)
- Humphrey 30-2 visual field of suspected eye(s)

The VFRC reviews the confirmatory set of visual fields. If the VFRC confirms the abnormality, the VFRC contacts the Coordinating Center, which convenes the Endpoint Committee, which will make a determination as to cause. If the abnormality is not confirmed by the confirming visual field test, the participant returns to the routine schedule of follow-up.

6.7 Optic Disc Progression Confirmation Visit

If the Optic Disc Reading Center (ODRC) detects optic disc progression, the ODRC requests a confirming set of photographs in the suspected eye to be taken 4 ± 2 weeks. In some cases, the optic disc change will have been detected by the principal investigator or other clinical center personnel, who will schedule the return appointment. In other cases, the change may be detected only by the ODRC, which will contact the clinical center to request that a confirmatory set of photos be scheduled within 4 ± 2 weeks. If the participant has already developed POAG in one or both eyes, the ODRC requests the confirming set of photographs be taken at the next regularly scheduled follow-up visit.

Data collected and procedures required during an optic disc change confirming visit:

• Completion of the Unscheduled Visit form (UN)

• Stereoscopic optic disc photographs of suspected eye only

The ODRC reviews the confirming set of photographs. If the ODRC confirms the abnormality, the ODRC contacts the Coordinating Center, which convenes the Endpoint Committee, which will make a determination as to cause. If the abnormality is not confirmed by the confirming photographs, the ODRC sends the clinical center a letter of their decision. The participant returns to the routine schedule of follow-up.

6.8 Unscheduled visits

Participants may return for a variety of reasons, including eye problems not related to the trial (i.e., conjunctivitis), to repeat unreliable fields or to confirm a suspected visual field abnormality, to repeat ungradable optic photographs, to confirm suspected progressive optic disc damage, to dispense medications, and subject initiated visits.

• This form may be used for changes in medication by telephone. If the change in medication is due to intolerance, an Adverse Event form (AE) should also be completed. The participant should return in 4 ± 2 weeks for an IOP Confirmation Visit.

The content of these visits will vary with the circumstances. Complete the Unscheduled Visit form (UN) for such visits. Each page must have the participant ID and date.

6.9 Adverse Events (AE)

The investigator completes an Adverse Event form (AE) when a participant reports ocular or systemic symptoms, medication side effects, is hospitalized, experiences a condition requiring medical or surgical intervention, experiences a permanent or substantial disability or dies. The form includes the nature of the medical problem, its seriousness, and whether the problem was caused by the drug. An Adverse Event (AE) form must be completed <u>for each</u> symptom complex. It is important to complete adverse event forms without bias for both the medication and close observation populations.

6.10 Participant Retention

It is crucial to retain 100% of the enrolled participants in OHTS for the full duration of the trial. The quality of the data and the estimates of the incidence of glaucoma are greatly affected by loss to follow-up.

Approximately one month before scheduled visits, the clinic coordinator will contact the participant to remind the participant of the upcoming examination. If the participant cannot attend the scheduled appointment, another appointment within the time window is arranged. Approximately one week before the scheduled appointment, the participant receives a letter or phone reminder from the clinic coordinator. Some participants may require additional calls or assistance to arrange transportation. Following a visit, a brief letter to the participant can be mailed summarizing the results of the examination and results from the Visual Field Reading Center and Optic Disc Reading Center.

If participants are moving to another geographic area, it is important to arrange return visits to the original Clinical Center or to transfer the participant to another more convenient Clinical Center. When completing the forms for these visits, use the site code (first two digits) where the participant is being seen and participant's ID number and initials (five numbers and three initials).

The most important factor in participant satisfaction and retention in the trial is the participant's perception that all study personnel are concerned with his or her well-being. All participants must be treated courteously, and waiting time in the clinical centers should be reduced to the minimum by careful scheduling. The clinical centers may offer appointments on selected evenings and Saturdays to accommodate the participant's work schedule. There will be a continuing education program for enrollees, including a newsletter with information about ocular hypertension, glaucoma, OHTS, general and ocular health. The study chairman and the recruitment and retention consultant will develop a recognition program for continued participation in the trial.

As part of the effort to maintain contact with participants, coordinators should review the information on the Patient Tracking form (TR) at each follow-up visit. The participant should be asked if their name, address, phone number, place of employment, or any of the information for contact persons have changed or will change before their next planned visit. The Patient Tracking form (TR) should be kept at the clinic site, these forms should not be sent to the Coordinating Center.

6.11 Participant Transfer

If a participant moves from one OHTS clinic area and wishes to be seen at another OHTS clinic, the top half of the Patient Transfer form (PX) is completed by the original clinic. The PX form is then faxed to the new clinic and the original PX form is mailed to the Coordinating Center with copies to the VFRC and ODRC. A complete copy of the participant's OHTS file is sent to the new clinic. The original clinic continues responsibility for the participant until the participant is seen at the new clinic.

Once the participant has been seen at the receiving clinic, that clinic completes the bottom portion of the Patient Tracking form (PX) and opens a study file for the participant. The receiving clinic sends the completed PX form to the Coordinating Center with copies to the VFRC, ODRC and the transferring clinic.

The participant will retain their original five-digit study code and abbreviated suffix, but will use the treating site code as the prefix.

6.12 Participant Death

In the event of a participant death, the clinic coordinator should call the Coordinating Center to report the death. This call should be followed with an Adverse Event form (AE) and a

Patient Death form (DT). All identifying information such as name, address and social security number should be blacked out prior to sending to the Coordinating Center.

6.13 Missed Visit

A visit is considered missed if the follow-up window has closed without the participant completing their follow-up visit. In the event of a missed visit, a Missed Visit form (MV) should be completed and sent to the Coordinating Center after the visit window is closed.

6.14 Inactive Participants

A participant is considered inactive if two consecutive follow-up visits are missed. An Inactive form (IN) should be completed and sent to the Coordinating Center. An inactive form does not eliminate future paperwork for the participant. The next missed visit will require another Missed Visit form (MV). The sequence of forms is two Missed Visit forms (MV), and then an Inactive Form (IN) until the participant is seen again.

6.15 Schedule of Examinations

	Qualifying Assessment	Random- ization	Semi-Annual Follow-up*	Annual Follow-up*	IOP Confirming Visit	Visual Field Confirming Visit	Optic Disc Confirming Visit	Patient Initiated UN
SF-36 Quality of Life		Х		Х				
Symptom Checklist		Х	Х	Х	Х			Х
Refraction	Х		Х			X drvs		
ETDRS Best Corrected Visual Acuity	Х		Х			Х		
Snellen Visual Acuity	Х		Х					
with most recent refraction				Х	Х			
Humphrey 30-2	Х		Х	Х		Х		
Eye Examination (complete)**	Х			Х				
Eye Examination (brief)***			Х		Х	Х		
Ocular and Medical History (full)	Х							
Ocular and Medical History (update)			Х	Х				
Applanation Tonometry	Х	Х	Х	Х	Х			
Gonioscopy****	Х		Х					
Stereoscopic Disc Photographs	Х			Х			Х	
Subject Education	Х							
Informed Consent	Х							
Continuing Education		Х	Х	Х	Х	Х	Х	
Dispense Medications		Х	Х	Х	Х			
Update Patient Tracking Information			Х	Х				

* Semi-annual follow-up visits occur at 6, 18, 30, 42, 54, 66' months, etc. Annual follow-up visits occur at 12, 24, 36, 48, 60, 72 months etc.

** A complete eye examination includes external examination of lids, lashes, and conjunctiva; slit-lamp examination; direct ophthalmoscopy; and dilated fundus exam

*** A brief eye examination includes external examination of lids, lashes, and conjunctiva; slit-lamp examination; and direct ophthalmoscopy.

**** Gonioscopy performed once every two years at non-photography visits.

6.16 Forms Required by Visit Type

Forms and Documents Required	Semi-Annual Follow-up	Annual Follow-up	Confirming Visit	Unscheduled Visit	Unscheduled Visit – Meds Only	Unscheduled Visit – Repeat Fields or Photos	First Ancillary Study Visit	One-Time
AC Ancillary Study Consent							Х	
AM Additional Measures								Х
CF Confirmation Visit			Х					
FV Follow-up Visit	Х	Х						
IP IOP Determination	X if applicable	X if applicable	X if applicable	X if applicable				
QL Quality of Life		Х						
SY Symptom Checklist	Х	Х	Х	X if applicable				
TL Transmittal Log	Х	Х	Х	Х	Х	Х	Х	
TR Patient Tracking (Keep at Clinic)	Х	Х						
UN Unscheduled Visit				Х	Х	Х		
VQ NEI VFQ								Х

6.17 Forms Required by Event

Forms	and Documents Required	Report of Adverse Event	Report of Inpatient Hospitalization	Missed Visit	2 Consecutive Missed Visits	Death	Treatment Change	Patient Transfer
AE	Adverse Event	Х	Х			Х		
DS	Discharge Summary		Х					
DT	Patient Death					Х		
IN	Inactive Patient Record				Х			
MV	Missed Visit			Х				
РХ	Patient Transfer							Х
ST	Discharge Summary Tracking (Use as worksheet at clinic. Do not send to Coordinating Center.)		Х					
TC	Treatment Change (Form completed by Medical Monitor)						Х	
TL	Transmittal Log	Х	Х	Х	Х	Х	Х	Х
Hos	pital Discharge Summary	(copy of Page 1 of corresponding AE)	Х					

Current as of 8/22/01								
FORM	FORM NAME	VERSION	FORM DATE					
AC	Ancillary Study Consent	V.4	6/1/99					
AE	Adverse Event	V.8	2/1/99					
AM	Additional Measures	V.2	4/1/01					
AV	Ancillary Study Visit Report	V.3	3/26/96 No Longer in Use					
BR	Baseline Randomization	V.2	2/28/95 No Longer in Use					
CF	Confirmation Visit	V.8	10/1/01					
CS	Chart Screen	V.1	2/11/94 No Longer in Use					
DC	Decline to Participate	V.1	2/11/94 No Longer in Use					
DG	Decline to Participate-Genetics	V.1	7/27/01					
DR	Personnel Directory	V.2	6/1/95					
DS	Discharge Summary	V.3	3/1/00					
DT	Death	V.2	6/1/95					
EN	Endpoint	V.7	4/16/98 VRCC only					
EW	Endpoint Worksheet	V.5	4/16/98 VRCC only					
GC	Genetics Consent	V.1	7/27/01					
FR	Form Requisition	V.1	2/11/94					
FV	Follow-up Visit	V.11	10/1/01					
ID	ID Assignment Log	V.2	(varies) No Longer in Use					
IN	Inactive Patient Record	V.4	7/12/99					
IP	IOP Determination	V.1	2/1/00					
MV	Missed Visit	V.5	1/1/00					
PC	Probable Cause	V.3	1/8/97 No Longer in Use					
PR	Problem Report	V.2	12/5/94 VRCC only					
PS	Patient Search	V.3	6/1/95					
РХ	Patient Transfer	V.4	6/3/98					
PY	Pachymetry	V.1	1/11/99					
QA	Qualifying Assessment	V.5	10/12/94 No Longer in Use					
QL	Quality of Life	V.2	6/1/95					
SPQL	Spanish Quality of Life	V.2	6/1/95					
RA	Randomization Phone Call	V.2	6/1/95 No Longer in Use					
RC	Reconsent	V.1	(varies)					
ST	Discharge Summary Tracking	V.3	3/1/00 Coordinator Use					
SY	Symptom Checklist	V.6	2/1/00					
SPSY	Spanish Symptom Checklist	V.5	2/1/99					
TC	Treatment Change	V.8	10/9/00 VRCC only					
TL	Transmittal Log	V.5	3/13/00					
TR	Patient Tracking	V.4	3/1/00					
TS	Telephone Screen	V.1	2/11/94 No Longer in Use					
UN	Unscheduled Visit	V.11	10/1/01					
VQ	NEI VFQ	V.1	4/1/01					
VR	ETDRS V/A Worksheet	V.2	10/4/94					

6.18 OHTS Forms and Current Version Number

When revised forms are sent, discard older version. Original forms, completed in ink, should be sent to the Coordinating Center. If corrections are needed, please strike through error, insert correction and date and sign correction. White-out should not be used for correcting forms.

Summary of Revisions

Chapter 7 - Clinical Tests and Examinations

Section		Date	Description
7.3.2	Snellen Visual Acuity	10/14/94	If Snellen V/A is worse than 20/200 then ETDRS V/A
	Scoring		does not have to be done.
7.3.3	ETDRS Visual Acuity	1/31/94	ETDRS V/A testing added to semi-annual visits.
	<u>Technique</u>		
7.10	Pachymetry	1/1/99	One-time measurement of central corneal thickness is
			performed.
7.11	Additional Measures	4/1/01	One-time form is added.
7.12	Vision Function	4/1/01	One-time, participant completed form is added.
	<u>Questionnaire</u>		
7.13	Genetics	5/1/01	One-time blood draw is performed on all participants.
7. Clinical Tests and Examinations

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7.1 Introduction

Participants evaluated for and enrolled in OHTS are examined using standardized techniques. All Clinical Center personnel must be familiar with these techniques and must follow them faithfully.

7.2 Refraction

Refraction is required semiannually for visual field testing. Standard procedures for refraction employed at the clinical center are acceptable for Qualifying Assessment and routine follow-up exams. Refraction may be performed by any certified OHTS Clinical Center personnel.

Because refraction is particularly important to visual field testing, refraction should be performed for confirmatory visual field tests using the Diabetic Retinopathy Vitrectomy Study/refraction protocol.

7.2.1 Refraction technique

The following technique is required for confirmatory visual fields. Any standard visual acuity chart, such as Refraction Chart R or a Projecto-chart, may be used for determining the best lens correction in each eye. The right eye is refracted first, then the left 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 any lenses in an effort to bring acuity to 20/100 or better. The lens corrections obtained are used as the beginning approximate refraction in the procedure outlined below for determination of best corrected visual acuity.
- If the participant's visual acuity is 20/100 or better with the participant 's present distance glasses, the glasses are measured with a lensometer and these measurements are used as the beginning approximate refraction.

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

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

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

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

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

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

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

- If it is not improved, the +0.50 sphere is tried again to see if the participant will accept still more plus.
- If vision is improved, 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 adding 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 is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder is moved 5 to 15 degrees toward the positive axis of the cross-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 subject 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.

7.3 Visual Acuity

Visual acuity is measured before pupil dilation, tonometry, gonioscopy, or any other technique that would affect vision. Visual acuity is measured using two different techniques - Snellen and ETDRS visual acuity. On all visits Snellen visual acuity is measured using a standard wall or projection chart. If the participant is moved closer to the ETDRS chart to be able to read the chart, over refract on the ETDRS chart. Any OHTS certified personnel can perform Snellen visual acuity. At Qualifying Assessment, at the 6 month visit and annually thereafter, e.g.18 months, 30 months, 42 months, etc., visual acuity is also measured using the ETDRS logmar chart. Personnel must be certified to perform ETDRS visual acuity (See "ETDRS visual acuity Certification", section 7.3.6).

7.3.1 Snellen visual acuity technique

Snellen visual acuity is measured at all regularly scheduled visits using a standard wall or projection chart. The same chart must be used for the duration of OHTS. 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.

7.3.2 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 subject 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.

7.3.3 ETDRS visual acuity technique

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. ETDRS visual acuity is measured at Qualifying Assessment, at the 6 month visit and annually thereafter, e.g. 18 months, 30 months, 42 months, 54 months, 66 months, etc. after refraction.

The room illumination should be between 80 and 320 cd/m². 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, and that the participant's eyes remain at the same distance. 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

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letter-a-second pace by reciting "A, B, C,..." If, at any point, the participant reads quickly, he or she should be asked to stop and read slowly. If the participant loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the examiner should ask the participant to go back to the line where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test.

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

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

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

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

7.3.4 ETDRS visual acuity scoring

The ETDRS visual acuity worksheets are for clinic use only and should not be sent 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 subject makes no guesses with an "x" or a line. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. The total score for each eye and the distance used for testing is recorded on the OHTS form for that visit.

7.3.5 ETDRS visual acuity testing discontinuation

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

7.3.6 ETDRS visual acuity certification

All study personnel performing a ETDRS visual acuity test must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief written test. The test must be judged as satisfactorily completed by the Central Coordinator. Certification for ETDRS visual acuity testing remains in effect as long as performance is satisfactory.

7.4 Slit-Lamp Examination

Slit-lamp examination is performed by a study-certified clinician.

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. During qualifying visits, undilated and dilated slit-lamp examinations will be performed to rule out secondary causes of elevated IOP such as the following: pigmentary dispersion (Krukenberg spindle, mid-peripheral iris transillumination, pigment deposition on the iris surface and zonules), exfoliation syndrome (deposition of material on the anterior lens surface or corneal endothelium and peripupillary iris transillumination) iridocyclitis (cell, flare, keratic precipitates), trauma (deeper anterior chamber, iris sphincter ruptures), iris or ciliary body cysts or tumors, ICE syndrome, neovascularization, congenital malformations (iris hypoplasia, adhesions to Schwalbe's line, thickening and displacement of Schwalbe's line). During follow-up examinations it is important to detect drug reactions such as allergic blepharoconjunctivitis, conjunctival hyperemia and follicular conjunctival reaction.

7.5 Tonometry

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

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

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

- At <u>least one but not more than 12 hours</u> after the last glaucoma medication prescribed to be taken twice a day.
- At <u>least one but not more than 24 hours</u> after the last glaucoma medication prescribed to be taken once a day.
- At <u>least four but not more than 24 hours</u> after use of pilocarpine 4% ointment.
- At least 10 hours but not more than 6 days after change of a pilocarpine Ocusert.

7.5.1 Tonometry technique

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a determination of intraocular pressure.

A single measurement is made as follows:

- The reader adjusts the force on 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 (Fluress, Barnes Hind) may be instilled. The examiner 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. Tightfitting neckwear is loosened. The participant is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the operator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The participant is cautioned not to hold his breath.
- The investigator looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so 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.

7.6 Gonioscopy

Gonioscopy is performed by a study-certified clinician.

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 singleor three-mirror lens or the Zeiss four-mirror lens or equivalent) is applied to the cornea with appropriate coupling fluid.

The angle is graded according to the standard Shaffer system:

- Grade IV angle between peripheral iris and trabecular meshwork is greater than 45%
- Grade III angle 30-45°
- Grade II angle 20-29°
- **Grade I** angle 10-19°
- slit angle less than 10°
- **closed** no trabecular meshwork seen without pressure on the lens.

At least 75% of the angle must be grade II or more for the subject to be eligible for the study.

It is important to rule out secondary causes of elevated IOP during qualifying examinations, e.g., post-traumatic recession of the angle, inflammatory deposits in the angle, exfoliation material, peripheral anterior synechiae, neovascularization.

7.7 Ophthalmoscopy

Ophthalmoscopy is performed by a study-certified clinician.

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The clinical morphology of the optic disc is assessed by direct ophthalmoscopy and 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 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).

During the qualifying visits these techniques are used to determine participant eligibility: The optic disc is examined carefully for signs of pre-existing glaucomatous damage (notches, hemorrhages, localized pallor or asymmetry of the cup/disc ratios in the two eyes > 0.2) or other disc abnormalities (drusen, pits, colobomas, other anomalies) that could cause visual field loss or obscure glaucomatous cupping. The clinician must also detect other diseases such as diabetic retinopathy (defined as a single microaneurysm) that are exclusion criteria and other conditions (e.g., lattice degeneration) that might affect choice of drugs in the stepped medical regimen.

During the study, the clinician performs direct ophthalmoscopy at every follow-up visit and a dilated stereoscopic examination of the disc at the 12-month examination. These examinations are done to detect glaucomatous damage (notches, localized pallor, progressive cupping) or other signs of possible future damage (e.g., disc hemorrhages). All optic disc changes are documented by photography and determined by the Optic Disc Reading Center (ODRC).

7.8 Visual Field

Visual fields are crucial for this study since they are used to determine eligibility and possible endpoints. All personnel must be familiar with the protocol for visual fields. Humphrey visual field perimeters must have an OHTS modified chip to be certified for use in the study.

See Chapter 16, the Visual Field Reading Center Manual of Procedures, for complete visual field protocol.

7.9 Stereoscopic Optic Disc Photography

Optic disc photographs are crucial for this study since they are used to determine eligibility and possible endpoints. All personnel must be familiar with the protocol for photography.

See Chapter 15, the Optic Disc Reading Center Manual of Procedures, for complete optic disc photography protocol.

7.10 Pachymetry

One-time measurement of central corneal thickness is performed for each subject.

See Chapter 17, Ancillary Studies, for complete pachymetry protocol.

7.11 Additional Measures (AM)

One-time coordinator administered questionnaire is performed for each participant that assess smoking and exercise history, updates family history of glaucoma and racial classification.

7.12 NEI Vision Function Questionnaire (VQ)

One-time participant completed questionnaire is performed for each participant.

7.13 Genetics Testing

The genetics ancillary study to the OHTS is being conducted to bank bloods for genetics studies of ocular hypertension, glaucoma and/or related conditions. The ancillary study will obtain one vacutainer (10cc) of blood from each voluntary OHTS participant. Bloods will be shipped to the University of Iowa for storage until genes have been identified for testing.

See Chapter 17, Ancillary Studies, for complete genetics protocol.

Summary of Revisions

Chapter 8 - Stepped Treatment Regimen

Section		Date	Description
8.2	Goals of Treatment	3/1/95	IOP goal is calculated from mean of QA IOP and
			Baseline IOP
8.3.1	Initial Treatment	6/1/95	Trusopt is added
8.3.2	Follow-up Treatment	9/5/95	Medication changes made by telephone to be
			recorded in Unscheduled Visit Form
8.5	Deviation from protocol		The Medical Monitor completes a Treatment Change
	of Randomization Group		form for all participants who deviate from protocol of
			their randomization assignment
<u>8.6</u>	Open Arm	9/5/95	The participant is assigned to Open-arm when
			Endpoint Committee determines that a glaucomatous
			change has occurred
<u>8.8</u>	Adverse Events	9/5/95	Adverse Events form to be completed for each
			symptom complex, not each symptom
<u>8.8.1</u>	Hospital Discharge	1/99	Procedures for reporting an inpatient hospitalization
	<u>Summaries</u>		clarified
8.8.2	Participant Death	1/99	Procedures for reporting a participant death clarified

8. Stepped Treatment Regimen

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8.1 Introduction

After completing the qualifying period, participants are assigned to either close observation or a stepped medical regimen. It is important that all personnel are familiar with the medical regimen so that treatment can be as standardized as possible. This treatment regimen was designed to reflect standard clinical practice, to reduce IOP effectively, and to minimize drug-induced side effects.

8.2 Goals of Treatment

The treatment goals for both eyes:

(1) Intraocular pressure $\leq 24 \text{ mm Hg}$

and

(2) A 20% reduction in intraocular pressure from the average of the Qualifying IOP and Baseline IOP, hereafter called treatment baseline. The 20% reduction is not necessary if IOP \leq 18 mm Hg. Medical therapy is changed and/or added until both goals are met or until the participant is receiving maximum tolerated topical medical therapy. Participants not meeting treatment goals despite maximum tolerated topical medical therapy continue to be followed in the trial. For the purposes of this trial, maximum topical medical therapy consists of a beta blocker, an adrenergic agent, a standard miotic agent, a topical carbonic anhydrase inhibitor and a prostaglandin analogue. If the IOP goal in an eye is met without treatment, it is left to the investigator's discretion whether to prescribe treatment for that eye.

8.3 Stepped Medical Regimen

Percentage reductions in IOP are computed from the "treatment baseline," which is Qualifying IOP and Baseline IOP. The average provides a better measure of the participant's true IOP than either the Qualifying or the Baseline IOP separately.

It is difficult to design a stepped medical regimen that applies to all participants. Certain general rules are followed:

• All new treatments begin with a therapeutic trial in one eye. If one eye has a higher intraocular pressure on qualifying and randomization visits, that eye receives the therapeutic trial. If intraocular pressures are symmetrical, the right eye receives the trial

- Treatment is started with a low concentration of the drug. The concentration is increased as necessary to produce the desired therapeutic effect
- If a drug is ineffective or minimally effective (IOP reduction < 10% from the treatment baseline) it is stopped and another drug substituted
- If a drug is moderately effective (IOP reduction 10%-20% from the treatment baseline) the investigator may choose to substitute or add another drug

See medical regimen flow chart in Appendix 8-A

8.3.1 Initial Treatment

Drugs used for initial one-eyed trial following randomization:

• **D**-blockers

Betagan 0.25% and 0.5% OptiPranolol 0.3% Timoptic 0.25% and 0.5% Timoptic XE 0.25% and 0.5% Ocupress 1.0% Betoptic 0.25% and 0.5%

- adrenergic agonists Epifrin 0.5%, 1.0%, and 2.0% Propine 0.1%
- miotics

Isopto Carbachol 0.75%, 1.5%, 2.25%, and 3.0% Isopto Carpine 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilagan 1.0%, 2.0%, and 4.0% Pilostat 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilopine gel 4.0%

- alpha-2 agonists Iopidine 0.5%
- topical carbonic anhydrase inhibitor Trusopt 2%

The stepped medical regimen begins in most participants with a topical beta blocker. Treatment is instituted in a therapeutic trial in the eye with the higher intraocular pressure or in the right eye if pressures are symmetrical. Participants should be given a four- to six-week supply of medication. Participants return in 4 ± 2 weeks for an IOP Confirmation visit (CF) at approximately the same time of the day. The beta blockers may have contralateral effects so it is sometimes difficult to interpret one-eyed therapeutic trials. This must be kept in mind by the investigator interpreting the results.

If the beta blocker produces the desired therapeutic goals, then both eyes are treated and the participant returns for a regular follow-up visit in approximately five months. If the beta blocker reduces IOP but not quite to the treatment goals, the concentration is increased. If the beta blocker reduces IOP to treatment goals, levobunolol or timolol can be reduced to once daily; however, the participant must be checked 24 to 26 hours after the last medication to ensure that treatment goals are still met. If the beta blocker is ineffective, it is stopped and another drug substituted in a one-eyed trial — in most cases, an adrenergic agonist. If an adrenergic agonist is contraindicated, then the participant should begin a one-eyed trial with a standard miotic, lopidine, Trusopt, Alphagan, or Xalatan.

If beta blockers are contraindicated for a participant, the participant starts a one-eyed trial with an adrenergic agonist. If both beta blockers and adrenergic agonists are contraindicated, the participant is started on a standard miotic, Iopidine, Trusopt, Alphagan, or Xalatan.

See medical regimen flow chart in Appendix 8-A

8.3.2 Follow-up Treatment

Drugs used for long-term treatment (This list is updated as new drugs become available to the study):

• **D**-blockers

Betagan 0.25% and 0.5% OptiPranolol 0.3% Timoptic 0.25% and 0.5% Timoptic XE 0.25% and 0.5% Ocupress 1.0% Betoptic 0.25% or 0.5%

- adrenergic agonists Epifrin 0.5%, 1.0%, and 2.0% Propine 0.1%
- miotics

Isopto Carbachol 0.75%, 1.5%, 2.25%, and 3.0% Isopto Carpine 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilagan 1.0%, 2.0%, and 4.0% Pilostat 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilopine gel 4.0%

• alpha-2 agonists Iopidine 0.5% Alphagan 0.2%

- topical carbonic anhydrase inhibitor Trusopt 2%
- prostaglandin analogue Xalatan 0.005% Lumigan Rescula Travatan
- combined therapy Cosopt

Systemic carbonic anhydrase inhibitors are used only in the open arm of the trial.

Acetazolomide 62.5 mg to 250 mg q.i.d. Acetazolomide sustained release 500 mg q.d. or b.i.d. Methazolamide 25 mg to 100 mg b.i.d.

During each examination, IOP is measured by two certified study personnel, an operator and recorder. If IOP meets treatment goals, medication is not altered unless the participant is experiencing annoying or serious drug-induced side effects. The participant is given a six-month supply of medication and returns for the next regularly scheduled visit in six months. At each visit, the participant completes a Symptom Checklist, and medication is altered as necessary.

If IOP does not meet treatment goals, the participant continues the same medication and returns in 4 ± 2 weeks at approximately the same time of the day. If IOP now meets treatment goals, the participant is given a six-month supply of medication and returns according to the routine schedule. If IOP does not meet treatment goals on the second visit, medication is added or altered. If IOP is sufficiently high that it seems unlikely that the treatment goal will be met on the next visit, the clinician has the option to alter treatment at this visit.

If IOP is reduced < 10% from baseline, the current drug is stopped and another substituted in a one-eyed trial. The participant returns in 4 ± 2 weeks at approximately the same time of the day to assess the response to medication. If there is a question about whether a drug is still effective, the drug can be stopped in one eye and continued for 30 days in the fellow eye in a one-eyed trial.

Example: A participant is receiving medication, but on two consecutive visits IOP is within 10% of baseline.

• If the participant is receiving a beta blocker, the beta blocker is stopped in both eyes and an adrenergic agonist is started in a one-eyed trial. If adrenergic agonists are contraindicated, the choice includes a standard miotic, Iopidine, Trusopt, Alphagan, or Xalatan.

- If the participant is receiving an adrenergic agonist, it is stopped in both eyes and a beta blocker is started in a one-eyed trial. If beta blockers are contraindicated, the choice includes a standard miotic, Iopidine, Trusopt, Alphagan, or Xalatan.
- If the participant is receiving a standard miotic, it is stopped in both eyes and a beta blocker is started in a one-eyed trial. If beta blockers are contraindicated, the choice includes an adrenergic agonist, Iopidine, Trusopt, Alphagan, or Xalatan.

If a participant is receiving a drug and treatment goals are not met, but the drug is moderately effective (IOP reduction between 10% and 20% from baseline), the clinician may choose to substitute or add another drug.

Example: A participant is receiving medication, but on two consecutive visits IOP does not meet treatment goals. The IOP reduction from baseline is between 10% and 20%.

- If the participant is receiving a beta blocker and the clinician wishes to add a second drug, add a standard miotic in a one-eyed therapeutic trial. (If the patient is receiving betaxolol, the clinician may choose to add an adrenergic agonist.) If standard miotics are contraindicated, add Iopidine, Trusopt, Alphagan, or Xalatan.
- If a participant is receiving an adrenergic agonist and the clinician wishes to add a second drug, the choice includes a standard miotic, a beta blocker, Trusopt, Alphagan, or Xalatan.
- If a participant is receiving a standard miotic and the clinician wishes to add a second drug, add a beta blocker in a one-eyed therapeutic trial. If beta blockers are contraindicated, add epinephrine/dipivefrin, Iopidine, Trusopt, Alphagan, or Xalatan.

Participants with marked elevation in IOP who are unlikely to reach treatment goals on a second visit may forego the second IOP confirmation visit and the clinician may alter medication on the first visit.

Clinicians may alter medication by telephone. Changes in medication by telephone must be reported using the Unscheduled Visit form (UN). If the change in medication is necessitated by intolerance, an Adverse Event form (AE) must be completed. The participant should return in 4 ± 2 weeks for an IOP Confirmation visit.

See medical regimen flow chart in Appendix 8-A

8.4 Compliance

Clinicians and clinic coordinators take a number of steps to increase adherence to the medical regimen and to decrease possible adverse effects of the drugs:

- **Prescribe the simplest regimen that meets the therapeutic goals**, i.e., the least number of medications, the least number of administrations, and the lowest concentrations of the drugs. One way to keep the regimen simple is to change or add medications in a one-eyed therapeutic trial.
- **Choose drugs less likely to cause side effects**, i.e., avoid nonspecific beta blockers for participants with asthma, and avoid miotics for participants with posterior subcapsular cataracts.
- Clinic coordinators instruct participants in the proper technique of eyedrop administration, i.e., punctal occlusion or simple eyelid closure for two minutes. Different drugs are instilled no less than five minutes apart.
- Clinic coordinators educate participants, spouses, and significant others about elevated IOP and glaucoma, the need for medication, the purpose of the medication, and the need for proper drug administration.
- Clinic coordinators assist participants in cueing medication administration to daily activities, i.e., choosing times for medication administration that are easy to remember and linked to other daily activities such as meals, the 6 o'clock news program, bedtime, etc.
- Clinic coordinators give the participants a brochure describing the clinical trial and a chart listing medications and times of administration.
- Clinic coordinators remind participants to bring their medications to all office visits. The medication can then be checked for accuracy and proper labeling.
- Clinicians review medications at each visit and ask participants about potential side effects and problems. Treatment is altered as necessary.
- When possible, medications with participant reminder caps are used.

8.5 Deviation from Randomized Group Assignment

- IOP □ 35 mm Hg in one or both eyes on two consecutive visits in the close observation group. Medications may be started if the clinician believes it is unsafe for the participant to continue as is. The clinician must contact the Medical Monitor to discuss this decision. The Medical Monitor completes a Treatment Change form (TC).
- IOP
 35 mm Hg in one or both eyes on two consecutive visits with maximum tolerated topical medical therapy in the medication group. Medications may be increased if the clinician believes it is unsafe for the participant to continue as is. The clinician must contact the Medical Monitor to discuss the decision. The clinician has the option of prescribing systemic carbonic anhydrase inhibitors or suggesting argon laser trabeculoplasty in one or both eyes. The Medical Monitor completes a Treatment Change form (TC).

- **Patient choice.** If a participant chooses to leave the randomized assignment, the clinician should discuss the trial, ocular hypertension, glaucoma, and the available treatment options. Every effort must be made to retain the participant in the assigned group. If the participant still wishes to leave the randomized assignment, the clinician must call the Medical Monitor. If the participant is in the close observation group, the participant may elect to begin the stepped medical regimen. If the participant is in the medication group, the participant may request altered treatment or no treatment. The Medical Monitor completes a Treatment Change form (TC).
- Medication Intolerance. If a participant is not tolerating the medication prescribed, the clinician should complete an Adverse Event form (AE), as well as contact the Medical Monitor to discuss the decision to alter treatment. The Medical Monitor completes a Treatment Change form (TC).

Participants continue their regularly scheduled follow-up visits and continue to complete all routine tests and measurements, including visual fields and stereoscopic optic disc photography until the study is completed. All study data continue to be collected and reading centers continue to be masked.

Clinicians are urged to keep participants in their original randomization group. If a participant fits into one of the above categories, the clinician is encouraged to return the patient to the follow-up protocol of his/her original randomization group if possible. When a participant resumes follow-up according to their randomization group, the clinician or coordinator should contact the Central Coordinator at the Coordinating Center who will complete a Treatment Change form (TC). All study form questions are answered for the participant's randomization group as assigned at entry.

8.6 Open Arm

Participants are moved to the open arm of the trial if any of the following occur:

- Confirmed optic disc progression attributed to primary-open angle glaucoma as determined by the Endpoint Committee. The Coordinating Center notifies the clinician of the Endpoint Committee decision. If the participant is in the close observation group, the participant begins the stepped medical regimen. If the participant is in the medication group, medical therapy is altered in the affected and/or fellow eye to achieve lower IOP. If the participant is receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors or argon laser trabeculoplasty.
- Confirmed Visual field abnormality attributed to primary-open angle glaucoma as determined by the Endpoint Committee. The Coordinating Center notifies the clinician of the Endpoint Committee decision. If the participant is in the close observation group, the participant begins the stepped medical regimen in both eyes. If the participant is in the medication group, medical therapy is altered to achieve

lower IOP. If the participant is receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors or argon laser trabeculoplasty.

The Endpoint Committee may recommend continued routine follow-up testing but discontinue confirmation testing for visual fields/optic disc photos for the affected eye. Alternatively, the Endpoint Committee may request discontinued routine follow-up testing and discontinued confirmation testing for visual fields/optic disc photos for the endpoint eye. Participants continue the regularly scheduled follow-up visits and complete all routine tests and measurements until the study is completed. All study data continue to be collected and reading centers continue to be masked.

8.7 Drug Supplies

The OHTS Planning Committee determined that recruitment would be aided if there were no direct charges to participants for medication. Free study medication may also increase compliance with the treatment regimen. Study medications have been donated to the study by Alcon Laboratories, Allergan Pharmaceuticals, Merck Sharp & Dohme, Bausch and Lomb, Otsuka Pharmaceutical, and Pharmacia & Upjohn as listed in section 8.3.1 "Initial Treatment," and section 8.3.2 "Follow-up Treatment."

• **D**-blockers

Betagan 0.25% and 0.5% OptiPranolol 0.3% Timoptic 0.25% and 0.5% Timoptic XE 0.25% and 0.5% Ocupress 1.0% Betoptic 0.25% and 0.5%

- adrenergic agonists Epifrin 0.5%, 1.0%, and 2.0% Propine 0.1%
- miotics

Isopto Carbachol 0.75%, 1.5%, 2.25%, and 3.0% Isopto Carpine 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilagan 1.0%, 2.0%, and 4.0% Pilostat 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, and 6.0% Pilopine gel 4.0%

- alpha-2 agonists Iopidine 0.5% Alphagan 0.2%
- topical carbonic anhydrase inhibitors Trusopt 2%

- prostaglandin analogue Xalatan 0.005% Lumigan Rescula Travatan
- **combined therapy** Cosopt

8.7.1 Inventory and Distribution

From Chairman's Office to Clinical Centers

The clinic coordinator should make regular inspections of drug supplies and reorder promptly when supplies are low. Reorder is accomplished by faxing a completed OHTS Drug Request to the Central Pharmacy. If there is an emergency shortage of any drug, the Clinical Center supplies that drug from other supplies or from its pharmacy. The coordinator then requests an emergency reorder.

All orders are shipped by Federal Express to the attention of the clinic coordinator. If the Clinical Center does not receive the drug supplies within ten working days after transmission of the Drug Request, the clinic coordinator should contact the Central Pharmacy to ensure that the order is filled.

Upon receipt, the coordinator should immediately verify the shipment by comparing the OHTS Drug Request with the Package Inventory/Confirmation form and the package contents. After verification, the clinic coordinator faxes the completed Confirmation form to the Central Pharmacy, noting any missing or damaged items or other problems with the shipment. Damaged or incorrectly shipped items are returned with a completed Drug Return form to the Central Pharmacy.

Study drugs should be stored at an appropriate temperature in a secure environment, and stock should be rotated regularly so that drugs closest to expiration are dispensed first. Expired drugs are returned with a completed Drug Return form to the Central Pharmacy. **Do not dispose of damaged or expired study medications at the Clinical Center.**

From Clinical Centers to Participants

Distribution of study drugs to non-OHTS participants is strictly prohibited, even if the drug will later be replaced.

After logging the information required by the Monthly Drug Distribution Log (see section 8.6.2), the clinic coordinator completes an OHTS Rx label for each bottle of medication dispensed. Study medications should never be dispensed without proper labeling (i.e.,

participant name, date, and directions for use). The clinic coordinator should take special note of the expiration dates to ensure that the drugs will be fresh when used by the participant, particularly when dispensing six-month supplies.

Drugs that have been returned by participants to the Clinical Center should not be redispensed, even if the drug container appears intact. Such drugs are returned with a completed Drug Return form to the Central Pharmacy. Empty or opened bottles are disposed at the Clinical Center.

Expired or damaged study medications received by the Central Pharmacy are logged into the main database and shipped back to the supplier for disposal. Items returned as a result of clinic overstock, return by participant, or incorrect shipment are logged into the main database, carefully inspected by the Central Pharmacy and either returned to stock or shipped back to the supplier as appropriate. Proper disposition of expired, damaged, or participant-returned study medications limits the possibility of study participants receiving contaminated medications.

8.7.2 Reporting

OHTS Clinical Centers are accountable to the Chairman's Office for the appropriate use of all study medications. The Chairman's Office may be required to report on this use to the various drug manufacturers that have agreed to donate medications to the OHTS. This reporting responsibility requires an inventory and accounting system of sufficient rigor to accommodate retrieval of detailed drug distribution data.

The following reporting requirements apply to all OHTS Clinical Centers:

- a. **OHTS Drug Request:** Reorder of study drugs is accomplished by faxing the OHTS Drug Request to the Central Pharmacy. Emergency reorders are noted by a check-box and date needed.
- b. **Confirmation:** Drug shipments are accompanied by a Packing Inventory/Confirmation form. Upon receipt of an order, the coordinator verifies the shipment by comparing the OHTS Drug Request with the Package Inventory/Confirmation and the package contents. After verification, the clinic coordinator faxes the Confirmation form to the Central Pharmacy, noting any missing or damaged items or other problems with the shipment.
- c. **Drug Return Form:** Study drugs that will not be dispensed to participants are returned to the Central Pharmacy for disposal. The following information is reported on the Drug Return form:
 - Drug and concentration
 - Lot number
 - Quantity returned
 - Reason for disposal, i.e., expired, damaged, patient return, clinic overstock, incorrect shipment
 - Participant ID (in the case of participant-returned medications)

- d. **Monthly Drug Logs:** Clinical Centers report the following information to the Central Pharmacy on a monthly basis for each unit of medication dispensed:
 - Date dispensed
 - Participant identification number
 - Drug and concentration
 - Quantity dispensed
 - Lot number
 - Initials of the study-certified person dispensing the drug

Note: The reporting responsibility extends to distribution of study approved medications not supplied from the Central Pharmacy.

The Monthly Drug Log is faxed to the Central Pharmacy by the 5th of each month.

8.8 Adverse Events (AE)

The investigator completes an Adverse Event form (AE) whenever a participant experiences ocular or systemic symptoms, medication side effects, is hospitalized, experiences a condition requiring medical or surgical intervention, experiences a permanent or substantial disability or dies. The form includes the nature of the medical problem, its seriousness, and whether the problem was caused by the drug. *An Adverse Event (AE) form must be completed for each symptom complex*.

8.8.1 Hospital Discharge Summaries

A hospital discharge summary is requested for each in-patient hospitalization (> 24 hour stay) the participant reports at the six-month follow-up visit. The discharge summary should be complete with ICD-9 codes and OHTS ID numbers should be written on all pages. Any identifying information such as participant name, address and social security number should be blacked out prior to sending to the Coordinating Center. A copy of corresponding Adverse Event form (AE) page number 1 should be attached to the hospital discharge summary and sent to the Coordinating Center.

8.8.2 Participant Death

In the event of a participant death, the clinic coordinator should call the Coordinating Center to report the death. This call should be followed with an Adverse Event form (AE) and a Patient Death form (DT). All identifying information such as name, address and social security number should be blacked out prior to sending to the Coordinating Center.

8.9 New Drugs

As new drugs become available, the Executive/Steering Committee may redesign the stepped medical regimen.

8-4 OHTS Procedure Manual

Appendix A





Summary of Revisions

Chapter 9 - Training and Certification

Section	Date	Description
9.2 Site Visit Team	5/13/94	All clinics will be routinely site-visited to insure data integrity

9. Training and Certification

9.1 In	ntroduction
9.2 Si	ite Visit Team
9.3 Pi	rincipal Investigators
9.4 C	linic Coordinators
9.5 Pl	hotographers
9.6 V	isual Field Technicians
9.7 C	linical Centers
9.8 P	erformance
9.9 N	lew Personnel
9.10 C	ross-Training

9.1 Introduction

It is important that all study personnel are familiar with the protocol and proper study procedures. The initial step in this process is the proper training and certification of all study personnel. *Qualifying assessments do not begin until all Clinical Center personnel — principal investigator, clinic coordinator, technician, photographer — are certified to perform study-related tasks.*

9.2 Site Visit Team

In the first two years of the study, all participating clinics will be site-visited. In subsequent years, clinical centers will be site-visited every two years, or on an as-needed basis as determined by the Study Chairman, Coordinating Center, Optic Disc Reading Center (ODRC), Visual Field Reading Center (VFRC) and/or the National Eye Insitute.

9.3 **Principal Investigators**

The principal investigators are furnished with copies of the Manual of Procedures (MOP) and must be familiar with all aspects of the study. Coordinating Center Central Coordinators will review the protocol by telephone with the principal investigator of each Clinical Center. Prior to participant recruitment, at a meeting of all principal investigators, the study personnel review crucial aspects of the protocol, including entry and exclusion criteria, examination procedures, visual acuity measurement, refraction, IOP measurement, informed consent, the stepped medical regimen and study endpoints. The review includes participant-based examples so that the principal investigators can think through the protocol in participant-oriented terms.

Following satisfactory completion of this training program, the principal investigators are certified. Telephone certification will be performed for backup investigators. Each clinic must satisfactorily complete Qualifying Assessments on two non-study individuals prior to certification.

9.4 Clinic Coordinators

The clinic coordinators are furnished with the MOP and must be familiar with all aspects of the study. Coordinating Center Central Coordinators will review the protocol with clinic coordinators by telephone. Prior to patient recruitment, at a meeting of all clinical coordinators, study personnel will review critical aspects of the protocol, including informed consent, refraction, visual acuity, IOP measurement, scheduling of visits, and completion and correction of forms.

Following satisfactory completion of this certification program, the clinic coordinator will be certified by the Coordinating Center. Certification of the backup clinic coordinator will be completed by telephone.

9.5 Photographers

The certification of the photographers is supervised by the director of the ODRC. This process is detailed in the MOP of the ODRC. Briefly, all photographers and their backups are supplied with the MOP of the ODRC. They read this material and review the protocol with the ODRC coordinator. The educational material covers photographic technique, proper developing, and the handling, labeling and shipping of photographs.

The photographer takes a complete set of photographs on two non-study patients and submits them to the ODRC. If these photographs pass quality standards, the ODRC certifies the photographer.

9.6 Visual Field Technicians

Certification of technicians to perform visual field testing is supervised by the coordinator of the VFRC. This process is detailed in the MOP of the VFRC. Briefly, visual field technicians and their backups are supplied with the VFRC MOP. The technician reads this material and reviews the protocol with the VFRC coordinator. The technician submits visual fields from two nonstudy patients to the VFRC. If these visual fields meet quality standards, the coordinator of the VFRC certifies the technician.

9.7 Clinical Centers

The physical facilities must include waiting rooms, examination rooms, visual field 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, a fundus camera capable of taking stereoscopic disc photos and an OHTS certified Humphrey program 30-2 visual field perimeter with the modified chip and Statpac II. The make, model and serial number of the fundus camera is provided to the ODRC; and the model and serial number of the visual field perimeter is provided to the VFRC.

A fully staffed Clinical Center includes a principal investigator, a clinic coordinator, a photographer and a 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.**

9.8 Performance

The Coordinating Center constantly monitors the quality of data coming from each Clinical Center. If problems arise, the Coordinating Center contacts the clinic coordinator, the principal investigator and the Study Chairman. Most problems are solved by telephone or at the annual Full Investigative Group meetings. If problems persist, a member of the Coordinating Center (and other personnel as indicated) site visit the Clinical Center.

9.9 New Personnel

Personnel changes will occur during the course of the study. The certification process for new personnel is the same as used by the original personnel, except for the training meeting in St. Louis, Missouri. Certification of new personnel occurs on an as-needed basis.

9.10 Cross-Training

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

Chapter 10 - Study Organization

Section	Date	Description	
10.1.4 Optic Disc Reading	2/21/94	ODRC moved to Bascom Palmer Eye Institute	
Center			
10.3.1 Executive/	2/21/94	Dr. Anderson replaced Dr. Caprioli	
Steering Committee			
	10/21/94	Study Officer's Group designated	
	1/22/95	Dr. Sheddon replaced Dr. Vogel	
	9/1/95	Donald Everett replaced Dr. Mowery	
	10/1/00	Dr. Ingrid Adamsons replaced Dr. Arthur Sheddon	
10.4.1 DSMC Committee	1/22/95	Dr. Sheddon replaces Dr. Vogel	
<u>Membership</u>			
	9/1/95	Donald Everett replaced Dr. Mowery	
	10/1/00	Dr. Ingrid Adamsons replaced Dr. Arthur Sheddon	
10.7.2 Endpoint Committee	9/5/95	Patients are assigned to "Open Arm" when Endpoint	
Function		Committee decides abnormality is glaucomatous	
	4/18/97	Probable Cause form discontinued, masked copies of	
		patient follow-up examination form sent to Endpoint	
		Committee	

10. Study Organization

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10.1.3	Visual Field Reading Center (VFRC)	
10.1.4	Optic Disc Reading Center (ODRC)	
10.1.5	Study Chairman's Office	
10.1.6	NEI Program Office	
10.2	Committees and Groups	
10.3	Executive/Steering Committee	
10.3.1	Executive/Steering Committee Membership	
10.3.2	Executive/Steering Committee Functions	
10.3.3	Executive/Steering Committee Meetings	
10.4	Data and Safety Monitoring Committee (DSMC)	
10.4.1	DSMC Membership	
10.4.2	DSMC Functions	
10.4.3	DSMC Meetings	
10.5	Full Investigative Group	
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10.7	Endpoint Committee	10-11
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10.7.2	Endpoint Committee Function	10-12
10.7.3	Endpoint Committee Meetings	10-12

10.1 Introduction

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

- Clinical Centers
- Coordinating Center
- Visual Field Reading Center (VFRC)
- Optic Disc Reading Center (ODRC)
- Confocal Scanning Laser Ophthalmoscopy Reading Center (CSLO)
- Short Wave-Length Perimetry Reading Center (SWAP)
- Study Chairman's Office
- National Eye Institute (NEI) Program Office

10.1.1 Clinical Centers

Each Clinical Center is responsible for screening potential study participants, recruiting an adequate number of eligible individuals, and following them according to the protocol until the termination of the trial. Each Clinical Center has at least one OHTS certified principal investigator, one certified photographer, one certified visual field technician, and one certified clinic coordinator. Each position requires a back-up person, although an individual can serve more than one role and can back up more than one position. The Clinical Centers are funded by a separate cooperative agreement from the National Eye Institute.

10.1.2 Coordinating Center

The Coordinating Center is a joint effort of the Division of Biostatistics and the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine. It is responsible for

- overall scientific conduct of the trial
- development and implementation of the study design
- receiving, editing, processing, analyzing, and storing study data
- coordinating activities of the Clinical Centers and Resource Centers
- implementing and maintaining quality assurance procedures
- contributing to statistical and operational methodology of multi-center clinical trials
- preparing reports, presentations and publications.

The Coordinating Center personnel include a director, co-director, central coordinators, systems analysts, programmers, and a project manager.

10.1.3 Visual Field Reading Center (VFRC)

The VFRC is located jointly in the Department of Ophthalmology at University of California, Davis and Devers Eye Institute, Legacy Portland Hospitals. The VFRC is responsible for

- receiving all Humphrey visual fields
- grading the fields according to criteria described in the VFRC MOP
- determining whether fields meet entry criteria
- determining when visual fields meet criteria for confirmation of abnormality
- maintaining records of visual field data
- transmitting visual field data and grading results to the Coordinating Center
- training and certifying study technicians
- monitoring quality of the data
- contributing to the understanding and interpretation of visual fields.

The VFRC personnel include a director, co-director, reading center coordinator, research associate, readers, and a programmer analyst.

10.1.4 Optic Disc Reading Center (ODRC)

The ODRC is located in the Department of Ophthalmology at Bascom Palmer Eye Institute, University of Miami. The ODRC is responsible for

- receiving all stereoscopic disc photographs
- grading photographs according to procedures described in the ODRC MOP
- determining whether photographs meet entry criteria
- determining when disc photographs meet criteria for confirmation of progression
- determining whether disc photographs meet endpoint criteria
- maintaining records of optic disc data
- transmitting grading results to the Coordinating Center
- training and certifying study photographers
- monitoring quality of the photographs
- contributing to the understanding and interpretation of optic disc stereo photography.

The ODRC personnel include a director, co-director, programmer analyst, reading center coordinator, readers, and a research assistant.

10.1.5 Study Chairman's Office

The Study Chairman's Office is located in the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine. The Study Chairman's Office is responsible for

- overall scientific conduct of the trial
- maintaining the study organization as an effective collaborative group
- establishing committees, appointing committee members, and dissolving committees that have completed their charges
- public relations
- participant relations and education
- maintaining and monitoring study drug supplies
- quality control and troubleshooting.

The staff of the Chairman's Office consists of the Study Chairman, three vice-chairs, and a project manager.

10.1.6 NEI Program Office

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

10.2 Committees and Groups

The OHTS is supported by the following committees and groups:

- Executive/Steering Committee
- Data and Safety Monitoring Committee
- Full Investigative Group
- Clinic Coordinators Group
- Endpoint Committee.

These committees are expected to function throughout the lifetime of OHTS.

10.3 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 and the Data and Safety Monitoring Committee.

10.3.1 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 ODRC
- Mae O. Gordon*, Ph.D., Director of the CC
- John L. Keltner*, M.D., Director of the VFRC
- Douglas Anderson, M.D., Co-Director of the ODRC
- Donald Everett*, M.A., NEI Representative
- Patricia A. Morris, Central Coordinator (non-voting)
- Ingrid Adamsons, M.D., Merck Research Laboratories (non-voting)
- Ann K. Wilder, B.S.N., C.C.R.C., Central Coordinator (non-voting)
- Two members elected from Full Investigative Group, each of whom serve a twoyear term
- One member elected from the Coordinators Group, who serves a two year term (Each clinic receives one vote in the selection of the representative.)

*Also a member of the Study Officers Group

The Study Chairman may appoint other individuals to the committee for two-year terms as he deems necessary to assure the scientific quality of the deliberations. The Study Officers Group consists of individuals who are study Vice-Chairs, Directors of Resource Centers, and the National Eye Institute representative.

Any member missing two consecutive meetings of the Executive/Steering Committee is subject to replacement by the Study Chairman. All members must file statements with the Study Chairman describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of OHTS.

10.3.2 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, except for those protocol changes based on assessment of accumulating data which are the responsibility of the DSMC
- To assist the Study Chairman with the scientific administration of the study

- To notify the NEI and the DSMC of major changes to the study protocol judged necessary or desirable
- To ratify major changes to the Manual of Procedures
- To review and approve all ancillary studies
- To advise the resource centers (Study Chairman's Office, Coordinating Center, VFRC, ODRC, CSLO and SWAP) on operational matters
- To resolve problems brought to attention by the directors of the VFRC, ODRC, Coordinating Center, CSLO and SWAP, 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, and to review all ancillary studies for suitability and all publications from ancillary studies
- To appoint subcommittees as required for special study functions
- To dissolve subcommittees and technical committees when their functions have been fulfilled.

10.3.3 Executive/Steering Committee Meetings

The Executive/Steering Committee meets twice each year for the duration of OHTS. Telephone conferences will occur as needed. Additional meetings may be called by the Study Chairman.

10.4 Data and Safety Monitoring Committee (DSMC)

The DSMC monitors the ethical conduct of the trial and the accumulating data for evidence of adverse and beneficial treatment effects. This committee decides when findings from OHTS may be released to study investigators, study participants, the medical community, and the public. This committee also oversees the informed consent process and major changes to the protocol. The DSMC is responsible to Paul Sieving, M.D., as Director of the NEI.

10.4.1 DSMC Membership

The voting members of the DSMC are not otherwise involved in the conduct of the OHTS. They consist of:

- Barry Davis, M.D., Ph.D. (biostatistician), Chairperson
- Roy Beck, M.D., Ph.D. (ophthalmologist, epidemiologist)
- John Connett, Ph.D. (biostatistician)
- Claude Cowan, M.D. (ophthalmologist)
- Ronald Munson, Ph.D. (biomedical ethicist)
- Mark Sherwood, M.D. (ophthalmologist)
- Gregory Skuta, M.D. (ophthalmologist)

Voting members are appointed by the Director of the NEI, with the advice and consent of the OHTS Executive/Steering Committee, for renewable five-year terms of office. Members missing two consecutive meetings are subject to replacement by the DSMC Chairman. All members must file statements with the NEI project office describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of OHTS.

In addition to the voting members, the DSMC includes non-voting members who serve by virtue of their roles in the study. They consist of

- Michael A. Kass, M.D., Study Chairperson
- Mae O. Gordon, Ph.D., Director of the Coordinating Center
- Donald Everett, M.A., NEI representative
- Ingrid Adamsons, M.D., Merck Research Laboratories.

The chairman of the DSMC may invite other individuals to attend one or more meetings to advise on the study design and procedures when necessary for proper interpretation of the data.

10.4.2 DSMC Functions

The specific functions of the DSMC are as follows:

- To review the design of OHTS, including methods and rate of participant recruitment by race by clinic, the informed consent process, data collection procedures and protocol violations by clinic
- To review site visit reports
- To evaluate the accumulating data at regular intervals for evidence of adverse or beneficial effects in the treatment and observation groups
- To monitor participant recruitment and retention, and data quality

- To determine when a sufficient number of participants have been randomized to obtain an answer to the major questions addressed
- To review data for biostatistical and clinical significance
- To determine when the data are sufficiently convincing to answer study questions of interest
- To determine when data collected in OHTS should be released to the study investigators, study participants, the medical community, and the public
- To recommend to the Executive/Steering Committee changes in study protocol based on periodic data analysis
- To advise the Executive/Steering Committee on interpretation of study data
- To provide the primary peer review on papers addressing the primary hypotheses and specific aims of the study
- To approve all ancillary studies
- To review study publications, particularly those reporting on the primary hypotheses
- To monitor performance of clinics and to advise NEI on the continuation of their funding.

10.4.3 DSMC Meetings

The DSMC meets twice during project year 02 and thereafter. One meeting is a faceto-face meeting, and the other meeting, which may be waived following a review of the semiannual report, can be a conference call or a face-to-face meeting, as necessary. Additional meetings are scheduled as necessary.

10.5 Full Investigative Group

The Full Investigative Group is responsible for assuring that the study protocol is specific, practical, and well understood by all OHTS personnel.

10.5.1 Full Investigative Group Membership

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

- Michael A. Kass, M.D., Study 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 ODRC
- Mae O. Gordon, Ph.D., Director of the Coordinating Center
- John L. Keltner, M.D., Director of VFRC
- Donald Everett, M.A., NEI representative
- Ann Wilder, B.S.N., C.C.R.C., Central Coordinator
- Pat Morris, Central Coordinator
- Principal Investigator of each Clinic
- Coordinator of each Clinic, VFRC, and ODRC.

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

10.5.2 Full Investigative Group Functions

The OHTS Full Investigative Group is responsible for

- Implementing OHTS protocol at the local level
- Notifying the Executive/Steering Committee when changes in procedures are required
- Implementing changes in the protocol approved by the Executive/Steering Committee.

10.5.3 Full Investigative Group Meetings

The Full Investigative Group meets once a year in conjunction with the Coordinators Group. Two investigators are elected every two years by its members as voting members of the Executive/Steering Committee.

10.6 Coordinators Group

The Coordinators Group consists of the clinic coordinators who manage the day-to-day performance of the study at each site.

10.6.1 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. Recommendations from the Coordinators Group can be made to any of the standing or ad hoc committees of the study.

10.6.2 Coordinators Group Membership

The following individuals are members of the Coordinators Group:

- coordinators from each of the Clinical Centers
- coordinator of the VFRC
- coordinator of the ODRC
- central coordinators.

10.6.3 Coordinators Group Meetings

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

10.7 Endpoint Committee

When a patient develops a reproducible visual field abnormality or a reproducible optic disc progression, it is important to determine if the change was caused by POAG. The Endpoint Committee reviews the clinical data from all participants who develop a reproducible visual field abnormality or a reproducible optic disc progression to make this determination.

10.7.1 Endpoint Committee Membership

The following individuals are members of the Endpoint Committee:

- 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 ODRC
- Mae O. Gordon, Ph.D., Director of the Coordinating Center (or representative).

10.7.2 Endpoint Committee Function

The Endpoint Committee reviews all visual fields, optic disc photographs, macular photographs and red reflex photographs of both eyes to date and masked copies of any relevant Qualifying Assessment (QA) form, Follow-up Examination (FV) forms, Unscheduled Visit (UN) forms, Confirmation Visit (CF) forms, and Adverse Event (AE) forms to determine whether the detected abnormality is attributable to POAG. The Coordinating Center masks all materials so there is no reference to the IOP or randomization assignment.

Participants whose visual field abnormality or optic disc progression is determined to be POAG in etiology are assigned to the "Open-Arm" of the study.

10.7.3 Endpoint Committee Meetings

The Endpoint Committee meets by teleconference or in face-to-face meetings on an asneeded basis.

Summary of Revisions

Chapter 11 - Policy Matters

Section		Date	Description
11.2.1	Publication and Presentation Policy	11/1/98	Publication and Presentation Policy clarified
<u>11.3.1</u>	Publication of Trial Design, Methods, and Findings	10/26/94	Procedure for publication and presentations clarified
<u>11.4</u>	Ancillary Studies	10/26/94	OHTS participants cannot be enrolled in other ocular studies without authorization from DSMC and Executive/Steering Committee
<u>11.4.4</u>	<u>Procedures for</u> <u>Obtaining Ancillary</u> <u>Study Approval</u>	10/26/94	Ancillary study must be approved by DSMC in addition to Executive/Steering Committee
<u>11.4.5</u>	Funding of Ancillary Studies	10/26/94	Investigator cannot activate ancillary study until approved by DSMC in addition to Executive/Steering Committee
<u>11.7</u>	Protection of Human Subjects Certification	7/1/00	The NIH policy is explained.
Appendix	Publication and Presentation Form	10/21/94	Form for OHTS Publication and/or Presentation
Appendix	Publication and Presentation Agreement	11/6/98	Publications and Presentations Policy agreement to be completed by all investigators and coordinators on an annual basis

11. Policy Matters

11.1	Participant Consent	
11.2	Publicity	
11.2.1	Publications and Presentations Policy	
11.3	Editorial Policy	
11.3.1	Publication of Trial Design, Methods, and Findings	
11.3.2	Presentations	
11.3.3	Publications from Ancillary Studies	
11.3.4	Publications Concerning Methodology	
11.4	Ancillary Studies	
11.4.1	Definition of an Ancillary Study	
11.4.2	Reason for Requirement of Approval	
11.4.3	Preparation of a Request for Approval for Ancillary Study	
11.4.4	Procedures for Obtaining Ancillary Study Approval	
11.4.5	Funding of Ancillary Studies	
11.4.6	Publication of Ancillary Study Results	
11.4.7	Progress Reports	
11.5	Access to Study Information	
11.5.1	Study Documents	
11.5.2	Study Data	
11.6	Participation of Women and Minority Groups	
11.7	Protection of Human Subjects Certification	

11.1 Participant Consent

The Ocular Hypertension Treatment Study (OHTS) requires that written consent be obtained from each participant prior to enrollment into the study. The participant is asked to sign the consent form only after information about study goals, risks and benefits of participation, study tests and measures and randomization are provided. The signed consent form is kept with the study records in the Clinical Center and a copy is given to the participant.

Current Clinical Center IRB approval must be on file at the Coordinating Center.

The principal investigator of each Clinical Center is responsible for obtaining approval of the study and the consent form from the local Institutional Review Board. A copy of each Clinical Center's approved consent form and documentation of IRB approval must be submitted to the Coordinating Center before participants are enrolled in OHTS.

11.2 Publicity

All publicity and press releases for OHTS must have prior approval of the Executive/Steering Committee. Members of the press should be referred to the Information Office of the National Eye Institute or the Study Chairman's Office of OHTS.

When individual investigators speak to local press, they should speak as an individual and not as official representatives of OHTS. This fact should be made clear to the press; however, the information given out should be accurate and should reflect the general policy and views of the study. The Study Chairman should be informed of all local presentations to the press and provided with a copy of the material published.

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

11.2.1 Publications and Presentations Policy

All publicity/press releases, publications and presentations of unpublished data relating to the OHTS and its Ancillary Studies must have prior approval by the Executive/Steering Committee. On an annual basis a "Publications and Presentations Policy" form will be mailed to all investigators and coordinators for signature. See the Appendix for a copy of this form.

11.3 Editorial Policy

11.3.1 Publication of Trial Design, Methods, and Findings

The Executive/Steering Committee will establish writing committees for all papers from among the OHTS investigators. A representative of the Coordinating Center will be appointed to writing committees on papers or presentations requiring study data. Investigators may volunteer for writing assignments and suggest additional topics where appropriate.

The investigator should submit an abstract and a short description of the proposed paper including co-authors, data to be reported and timeline for drafts and submission (Appendix). This information should be sent to the Study Chairman. The Executive/Steering Committee is responsible for reviewing the proposed paper's merit and deciding if it should be an OHTS study publication. This review process is intended to insure the quality of study publications and may require refinement of the proposal. The Executive/Steering Committee is reponsible for determining priorities (timeline and order of preparation) of proposed papers/presentations.

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

Conflicts regarding authorship are resolved by the Executive/Steering Committee. General guidelines for authorship are: active participation in the production of the manuscript or other important contribution. Authorship rights are not available for membership on the writing committee only, use of data only, or signing the copyright form. If the timeline for a paper has expired with no substantial evidence of progress, authorship rights are assumed to have expired. The Coordinating Center will contact the primary author and leadership of the paper will be negotiated. The Executive/Steering Committee will be informed of changes in lead authorship. An individual may be given an acknowledgement for reading and providing critical comments on the manuscript. An investigator at the Coordinating Center will be added to the author list on all papers which require statistical input.

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

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

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

The Executive/Steering Committee will review all written reports prepared for publication. All reports from OHTS will list the Ocular Hypertension Treatment Study Group as an author. The primary endpoint paper and selected other major papers will list only the Ocular Hypertension Treatment Study Group as the primary author in a manner consistent with the publication policy of the selected journal. Other publications will list the primary author and co-authors and the Ocular Hypertension Treatment Study Group. All professional participants of OHTS, including those at the central units and Clinical Centers, will be listed at the end of each paper and are considered as authors or contributors. In major papers, all study personnel, past and present, will be listed with the approval of the principal investigator for whom they have worked.

Each publication must acknowledge National Eye Institute support as follows:

"This study was supported by grants from the National Eye Institute, and the Office of Research on Minority Health, National Institutes of Health, Bethesda, MD, and a grant from Merck Research Laboratories."

Copies of principal papers from OHTS are sent (before publication) to all principal investigators, to all members of the Executive/Steering Committee, and to the Data and Safety Monitoring Committee. Reprints of published papers are mailed to each Clinical Center for distribution among the staff and to outside consultants. Ten reprints of each paper are sent to the Coordinating Center for the OHTS library.

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

All major study publications and presentations must receive approval of the Data and Safety Monitoring Committee prior to submission to any professional journal or presentation at a meeting.

11.3.2 Presentations

Oral presentations must be approved in advance by the Executive/Steering Committee. Abstracts to be printed must be cleared in advance by the Executive/Steering Committee. No unpublished study results may be used for oral presentations, local or otherwise, unless a specific exception is granted by the Executive/Steering Committee and the Data and Safety Monitoring Committee (DSMC). Study results include all data collected for OHTS, whether descriptive or comparative in nature. The above restrictions do not apply to local presentations on the design

of OHTS, provided these presentations contain no unpublished study results. Such presentations are encouraged to stimulate participant recruitment.

11.3.3 Publications from Ancillary Studies

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

11.3.4 Publications Concerning Methodology

The Executive/Steering Committee encourages the investigators at the Coordinating Center, VFRC, 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 Coordinating Center is responsible for distributing copies of methodological publications to the Executive/Steering Committee and other OHTS investigators. Five reprints of such publications should be sent to the Coordinating Center for the OHTS library.

11.4 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 and the Data and Safety Monitoring Committee before their inception, whether or not they involve the need for supplementary funds. OHTS participants cannot be enrolled in other ocular studies without authorization from the DSMC and Executive/Steering Committees. Furthermore, OHTS data may not be used for any other study that has not been approved by the DSMC.

11.4.1 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 according to a predefined protocol, or
- additional work to be done by or information to be obtained from either the Coordinating Center, VFRC, or ODRC.

11.4.2 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 or recruitment
- 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.

11.4.3 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 laboratory tests, psychiatric interviews, psychological testing, etc. Mention should be made of any substances to be injected or otherwise administered to the participants. Any observations to be made or procedures to be carried out on a participant outside of the clinic should be described. Detailed discussion must be provided regarding the additional participant 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 participants, mention should be made of all procedures to be carried out on these specimens. If access to OHTS study data are 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 require approval by the Data and Safety Monitoring Committee.

11.4.4 Procedures for Obtaining Ancillary Study Approval

The investigator proposing an ancillary study should send a written request to the Study Chairman of OHTS. The Study Chairman is responsible for distributing copies to all members of the Executive/Steering Committee. Within a reasonable time the Chairman 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 Chairman 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 Chairman is responsible for submitting a recommendation to the Data and Safety Monitoring Committee which is responsible for final approval of ancillary studies.

11.4.5 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 and Data and Safety Monitoring Committee. If additional funds are needed, the investigator may prepare and submit

a research grant application to the potential sponsor for review in the same manner as any other new research grant application. Copies of the grant application are sent to the Chairman and Coordinating Center. The investigator may not submit the grant or activate the ancillary study until approval has been received from the OHTS Executive/Steering Committee and the Data and Safety Monitoring Committee.

11.4.6 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.

After publication, 50 reprints or photocopies of the ancillary study report should be sent to the Study Chairman's Office for distribution to the Executive/Steering Committee and to the Coordinating Center for the OHTS library.

11.4.7 Progress Reports

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

11.5 Access to Study Information

11.5.1 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 and the internet (www.vrcc.wustl.edu), after approval by the Executive/Steering Committee and the DSMC, 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 either the Executive/Steering Committee or the DSMC.

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

- minutes of study meetings
- performance monitoring reports for OHTS centers
- DSMC reports

11.5.2 Study Data

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

11.6 Participation of Women and Minority Groups

A goal of the study is that all groups in the population be well represented in the study sample. This is done for the sake of fairness and also to protect the validity of the study. It is generally accepted that glaucoma occurs with equal frequency in men and women. Given the age entry criteria (40-80 years) it is anticipated that women will form a slight majority of the participants. It is generally accepted that glaucoma is more common and more severe in African Americans than others. Furthermore, many Clinical Centers will likely be located in medical facilities in major metropolitan areas. Thus, it is anticipated that African Americans will be enrolled in the study in a higher percentage than in the general population. A major goal of OHTS is to enroll 400 African Americans, approximately 25% of the total sample. Participation by Spanish-speaking individuals is encouraged through the use of interpreters and Spanish language editions of the consent form, participant-completed forms and study booklet. All Clinical Centers must be accessible to handicapped people.

11.7 Protection of Human Subjects Certification

The NIH has adopted a policy entitled "Protection of Human Subjects Certification." This policy requires that all Investigators and Coordinators involved in NIH studies must be certified as having passed a course on protection of human subjects prior to the time that their clinic budgets can be resubmitted. This includes all investigators and coordinators at clinics, satellites, reading centers, and ancillary studies. Verification that study personnel have completed the certification process is done by the IRB at the local level. Chapter 11 Appendix

Publications and Presentations

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 <u>15</u> 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	/



PUBLICATIONS AND PRESENTATIONS POLICY

As recorded in Chapter 11 of the OHTS Manual of Procedures, all publicity/press releases, presentations and publications of unpublished data relating to the Ocular Hypertension Treatment Study and its Ancillary Studies must have prior approval by the Executive/Steering Committee. In cases where outcome data are discussed, approval by the Data and Safety Monitoring Committee may also be required prior to submission. This policy applies not only to national meetings, but to regional and local meetings as well. Even presentations at your medical center could result in rapid dissemination of information, which damages the study. Additionally, do not talk about unpublished data to outside sources without approval of the Executive Committee. Any material relating to OHTS that has been previously presented with prior approval may be presented again without additional review. Refer to the list of previously approved publications and presentations distributed at the Full Investigative Group meeting for material that can be presented.

Ideas for manuscripts or presentation should be referred to the Chairman who will in turn send the idea to the Executive/Steering Committee, which is responsible for determining the merit of a proposed manuscript or presentation. This review process is intended to insure the quality of study publications. Following completion of a submission ready draft, the Executive/Steering Committee will review all written reports prior to submission to a journal.

All reports from OHTS will list the Ocular Hypertension Treatment Study Group as an author and must acknowledge the support as follows:

"This study was supported by grants (insert appropriate grant #) from the National Eye Institute, and the Office of Research on Minority Health, National Institutes of Health, Bethesda, MD, a grant from Merck Research Laboratories, and unrestricted grants from Research to Prevent Blindness."

The undersigned agrees to honor the OHTS Publication and Presentation Policy described above.

Signature

Print Name

Date

Ocular Hypertension Treatment Study Manuscript Checklist for Authors To be kept with manuscript

Author		Manuscript title	Date
		Manuscript title	Date
		Manuscript title	Date
Step	Action		Date Completed
1	Contact Dr. Michael Kass, Study Chai	r, with idea for manuscript	
2	If topic deals with outcome data, Coord approval to release the data. (If topic of skip steps 2, 3, 4 and proceed to step 5	dinating Center routes to DSMC for loes not pertain to outcome data, .)	
3	DSMC approves/disapproves release of	f data	
4	If DSMC disapproves of release of dat	a, author is notified by Study Chair	
5	Executive/Steering Committee approve	es/disapproves	
6	Chair appoints writing committee		
7	Coordinating Center holds conference	call to discuss statistical needs	
8	First author circulates draft of manusci	ript to writing committee members	
9	Writing committee makes revisions		
10	Author sends draft sent to Coordinatin	g Center	
11	Coordinating Center makes revisions a	nd returns to author	
12	Author returns draft with revisions ma	de to Coordinating Center	
13	Coordinating Center routes to Executiv Review	ve/Steering Committee for Scientific	
14	Author and Coordinating Center revise Committee, or appeals revisions to Stu	es manuscript per Executive/Steering dy Chair	
15	Study Chair signs off on submission of	fmanuscript	
16	Manuscript submitted to journal/organ	ization	

Ocular Hypertension Treatment Study Abstract Checklist for Authors To be kept with abstract

Author		Abstract title	Date
		Abstract title	Date
		Abstract title	Date
Step	Action		Date Completed
1	Contact Dr. Michael Kass, Study Cha	air, with idea for abstract	
2	Executive/Steering Committee appro	ves/disapproves	
3	Chair appoints writing committee		
4	Coordinating Center holds conference	e call to discuss statistical needs	
5	First author circulates draft of abstract	et to writing committee members	
6	Writing committee makes revisions		
7	Author sends draft sent to Coordinati	ng Center	
8	Coordinating Center makes revisions and returns to author		
9	Author returns draft with revisions m	ade to Coordinating Center	
10	If topic deals with outcome data, Coordinating Center routes to DSMC for approval to release the data. (If topic does not pertain to outcome data, skip steps 2, 3 and proceed to step 5.)		
11	DSMC approves/disapproves release of data		
12	If DSMC disapproves of release of d	ata, author is notified by Study Chair	
13	Coordinating Center routes to Executive/Steering Committee for Scientific Review		
14	Author and Coordinating Center revises manuscript per Executive/Steering		

Abstract submitted to organization

15



MANUSCRIPT REVIEW FORM

Da	te Sent for Review:				
De	adline for Return of Review to	Coordinating Center:			
Pro	posed Manuscript Title:				
Pro	pposed Journal:				_
Αı	thors:				
Rŀ	ECOMMENDATION	TECHNICAL A	SPECT	TS	
			YES	NO	UNCERTAIN
	Accept as is	Writing clear and grammatical?			
	Accept after minor revisions	Methodology adequate?			
	Accept after major revisions	Number of cases and follow-up adequate?			
	(must be re-reviewed by Steering Committee)	Conclusions follow from data?			
	Reject	Literature references adequate?			
3.	Is the title adequately descrip If no, recommend title chang	otive?			
4. Re	Is the abstract adequately desviewed by:	criptive and detailed? \Box Yes \Box No			
	Sign	ature	Today'	s Date	

Return this form and typewritten comments to the Project Manger at the OHTS Coordinating Center. Fax # 314-362-0231.



Summary of Revisions

Chapter 12 - Clinical Center Procedures

Section	Date	Description	
<u>12.4.1 Scheduling Visits</u>	1/21/94	Follow-up visits \pm 3 months of the target are acceptable. Follow-up visits should be at least 60 days apart	
12.4.2 Clinic Tracking Report	1/1/96	Report is mailed to clinics to help keep track of participant visits and outstanding forms	
12.8Recording MedicationTaken by Participant	1/21/94	If the participant does not bring medications, Clinic Coordinator should complete information on medication use by telephone	
12.9 Web Access System	116/98	Web Access System for disseminating information to clinics is described.	

12. Clinical Center Procedures

12.1	Clinical Center Responsibilities
12.2	Clinical Center Personnel
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12.2.2	Responsibilities of the Clinic Coordinator
12.2.3	Responsibilities of the Technician
12.2.4	Responsibilities of the Photographer
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12.8.1	Drug List
12.9	Web Access System

12.1 Clinical Center Responsibilities

The responsibilities of OHTS Clinical Center include the following:

- To assess eligibility of individuals identified for OHTS
- To identify a minimum of 100 eligible individuals for OHTS
- To provide each identified individual with OHTS educational materials
- To enter participants in OHTS through informed consent and to ensure that appropriate randomization is followed
- To manage each participant in accord with the randomized assignment provided by the Coordinating Center and the instructions in the MOP
- To examine each participant enrolled in OHTS using the techniques and the schedule established
- To complete the proper forms and obtain visual fields and optic disc photographs required at each visit
- To transmit all forms, documents, visual fields and optic disc photographs to the Coordinating Center and Reading Centers expeditiously after each visit
- To respond promptly to requests from the Coordinating Center and the Reading Centers
- To maintain participant records for OHTS in an easily accessible but confidential manner
- To maintain complete and current residency and employment information on each OHTS participant
- To maintain current informed consent documents that meet OHTS standards and the standards of the local Institutional Review Board
- To maintain all equipment, supplies and drugs required for OHTS
- To promote participant satisfaction and commitment to the trial through reminder systems, good rapport, newsletters, recognition awards and regular reports on their examinations
- To help train new personnel as needed
- To provide representation at all meetings of the Investigators Group and Clinic Coordinators Group

12.2 Clinical Center Personnel

Each Clinical Center must employ the following certified personnel:

- Principal investigator
- Clinic coordinator
- Technician
- Photographer

For each position there must be a back-up, although this does not necessarily require eight people, i.e., the coordinator could back up the technician and the photographer if appropriately trained and certified. Certification is maintained for all certified personnel, except visual field testing, so long as performance is satisfactory and the individual is affiliated with OHTS.

12.2.1 Responsibilities of the Principal Investigator

The principal investigator's responsibilities include the following:

- To lead and direct the overall conduct of the trial in the Clinical Center
- To develop a plan in conjunction with the Study Chairman and the recruitment specialist to identify an adequate number of eligible individuals
- To provide participant education and enroll an adequate number of participants in the trial
- To supervise all Clinical Center personnel who perform tests and measures
- To examine the participants according to OHTS procedures
- To determine the therapy for each participant in the medication group as specified by the stepped medical regimen
- To attend Full Investigative Group meetings

12.2.2 Responsibilities of the Clinic Coordinator

The responsibilities of the clinic coordinator include the following:

- To coordinate the Clinical Center activities related to OHTS
- To have a thorough understanding of OHTS design and details
- To coordinate activities between the participants, Clinical Center, Reading Centers, Coordinating Center and the Chairman's Office

- To provide a resource for other Clinical Center personnel concerning the protocol
- To schedule participant visits and arrange participant transportation
- To maintain participant interest in the study by contacts during scheduled visits and by expressing concern for the participant's welfare and problems
- To maintain study documentation including a current MOP, appointment notebooks, participant log book, copies of current study forms, log books of visual fields and optic disc photographs and current addresses and employment information about participants
- To review all forms and information for accuracy and completeness before sending them to the Coordianting Center and the Reading Centers
- To photocopy all forms for Clinical Center records and to send original of forms to Coordinating Center on a timely basis
- To assure that copies of all forms are retained in the OHTS files at the Clinical Center
- To respond to queries from the Coordinating Center and the Reading Centers
- To notify the Coordinating Center concerning personnel changes
- To inform the principal investigator and the Coordinating Center of any problems evaluating, treating, or following OHTS participants
- To attend meetings of the Full Investigative Group and Clinic Coordinators Group
- To ensure that the clinic and participant have adequate supplies of study medications
- To monitor clinic use of study drugs and report to the Central Pharmacy when requested
- To perform clinical measures, including IOP, ETDRS & Snellen visual acuity and refractions, as necessary

12.2.3 Responsibilities of the Technician

The OHTS technician's responsibilities include the following:

- To learn correct OHTS procedures, including the appropriate data forms
- To perform ETDRS & Snellen visual acuity measurements (certification for visual acuity is required by the Coordinating Center)

- To perform Humphrey visual field tests (certification by the VFRC is required)
- To label Humphrey visual fields for proper transmission to the VFRC
- To perform applanation tonometry (certification for IOP is required by the Coordinating Center)
- In some centers, the technician may also perform refractions

12.2.4 Responsibilities of the Photographer

The OHTS photographer's responsibilities include the following:

- To learn correct OHTS photography procedures, including the appropriate data forms
- To take stereoscopic optic disc photographs (certification by the ODRC is required)
- To label the photographs for transmission to the ODRC

12.3 Study Documents

Each Clinical Center must have available the following:

- A current copy of the OHTS Manual of Procedures
- A current copy of the IRB approved consent form
- Copies of the OHTS study forms for data collection, clinic management and study management
- Batch edits received at the clinic requiring data corrections should be filed with the appropriate participant form in OHTS participant file.
- A log book for assigning participant ID numbers, recording treatment allocation and filing consent forms
- Log books for participant visual field tests and optic disc photographs
- An address directory of OHTS personnel in all centers
- Other clinic and participant management aids, such as participant appointment schedules and visit reminders

Master study forms are supplied by the Coordinating Center and should be photocopied at the Clinical Center. When forms are requested from the Coordinating Center, the clinic coordinator should telephone the Coordinating Center directly, use facsimile transmission, or email from the website.

Whenever study forms are revised, the clinic coordinator is responsible for seeing that all old versions are destroyed so that they will not be used by mistake. Under no circumstances should outdated forms be used. The clinic coordinator is responsible for explaining to the clinic staff any changes in procedures that are required by form revisions.

12.4 Scheduling and Coordination of Participant Visits

In most Clinical Centers, the clinic coordinator plays a major role in scheduling and data recording. Therefore, it is important that the clinic coordinator have a thorough understanding of the required procedures for each visit, the sequence in which these are best performed, and the contents of the data collection forms and other forms to be completed.

12.4.1 Schedule of Visits

The schedule of qualifying and follow-up visits is given in Chapter 6. The clinic coordinator must be familiar with this schedule to ensure timely visits. All regularly scheduled visits (semi-annual and annual) should occur one month before or one month after the target date $(\pm 1 \text{ month})$ at approximately the same time of the day. However, follow-up visits ± 3 months of the target date are acceptable. Regularly scheduled follow-up visits should be at least 60 days apart. All four-week visits should be completed within two weeks before or two weeks after the target date $(\pm 2 \text{ weeks})$. Whenever possible, visits should be scheduled at the beginning of the ideal time window so that rescheduled appointments or repeated tests can fall within the ideal window. The clinic coordinator will contact each participant approximately one month prior to regularly scheduled follow-up appointments to remind the participant of his/her visit. If the participant cannot come on that date, the participant should be rescheduled within the time window. The clinic coordinator should send a letter reminder or telephone to confirm the appointment and remind the participant to bring all medications to the exam. With certain forgetful participants the clinic coordinator should use more frequent reminders or phone calls.

12.4.2 Clinic Tracking Report

Once monthly the Coordinating Center generates the clinic tracking report to help clinics keep abreast of participant visit windows and forms that are outstanding. This report is divided into eight sections:

- Listing of participants who are due to have follow-up visits
- Listing of participants with late or missed visits
- Listing of outstanding hospital discharge summaries. This listing is based on "Inpatient Hospitalization" checked on a Follow-Up Visit form (FV)
- List of participants who need to sign a re-consent form or addendum as approved by local Institutional Review Boards
- List of participants with pending retake or confirmation photos and photos pending 21 days
- List of participants with pending retest or confirmation visual fields and visual fields not received as reported on case report forms received at the Coordinating Center
- List of participants who need pachymetry testing
- List of participants for whom "hospitalization" is checked on the Symptom Checklist form (SY), but not checked on Adverse Event form (AE)

12.5 Checking Completed Examination Forms

Before being sent to the Coordinating Center, each form should be carefully checked by the clinic coordinator. Correcting errors that have been entered in the computerized data system is far more time-consuming and expensive than taking the appropriate steps to prevent errors. **Every** answer on the form should be checked for each of the criteria discussed below.

12.5.1 Completeness

If any required item is unanswered or has a question mark for an answer, the entire form "fails edit." If there is doubt about how an item should be answered, a member of the Coordinating Center staff should be contacted by telephone.

12.5.2 Legibility

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

12.5.3 Edits and Corrections

When there is a question regarding the answer to one or more items, an edit statement is issued to the clinic coordinator. The edit statement gives OHTS identifying information about the participant, visit and form in question, and lists the item number(s) and the original answer ("old value") reported on the form. There is space for writing in a corrected response in the "corrected value" column. An explanation of the nature of the problem follows the list of items. At times the original response is correct, and the clinic coordinator should circle OK to confirm that it is, in fact, correct. All spaces in the corrected value column must be completed.

Often the answer to one item affects other items. In this case, two or more original values are given on the edit statement. All of the corresponding blank spaces should be filled in, even though certain information may be reiterated. The item is then subject to a re-edit to determine if any new inconsistencies have been created during the correction process. The clinic coordinator should be aware of the possibility of creating new inconsistencies as a result of corrections and should recheck the form to avoid further edits.

When an edit statement is received, the clinic coordinator should obtain the participant's record from the files and determine the correct answer for each item listed. After completing the edit statement, the clinic coordinator should then make each correction directly on the clinic copy of the participant's visit form and should initial and date this notation. The edit statement, fully completed, must be returned to the Coordinating Center within 10 days from the time it was received. A copy should be attached to the copy of the form retained in the clinic.

On occasion, clinic personnel may discover errors on forms in addition to those detected by the computer edit. When this occurs, Coordinating Center staff should be notified immediately in writing, so that the data can be changed. The clinic copy of the forms should be corrected as above.

Should any questions arise regarding completion of an edit message, a telephone call to the Coordinating Center is strongly encouraged.

12.6 Assuring Completeness of Follow-up

One of the most important duties of the Clinical Center is maintaining good rapport with all OHTS participants to ensure that each participant remains in the study. The clinic coordinator should be thoroughly familiar with the materials in Chapter 6 pertaining to missed visits, participant contact between visits, and procedures for inactive or transfer participants. In addition, a library should be located which subscribes to "city directories" in the catchment area of the Clinical Center. These directories are useful for identifying neighbors of the participant if the clinic coordinator loses contact with the participant and family. A commercial locator service is helpful. The internet search services may also be used.

12.7 Preparing for Return Visits

The following things should be done prior to a scheduled participant visit:

- Remind the participant of the scheduled appointment by telephone and/or by mail in advance of the date. Remind the participant to bring medications to each scheduled follow-up visit
- Retrieve the participant's OHTS file
- Place the participant's OHTS ID number and the clinic's site number on all forms pertinent to the scheduled visit
- Refer to the most recent refraction in obtaining best-corrected visual acuity. Do not refer to the visual acuity measurements from the previous examination
- Schedule appointments for Humphrey perimetry and photography
- Be sure that pertinent information received since the last participant visit is available to the principal investigator. This information could include reports from the Reading Centers

• Put the OHTS Patient Tracking Information form (TR), in the folder as a reminder to review and update the information

12.8 Recording Medication Taken by Participant

During the Qualifying Assessment visits, the clinic coordinator records whether the participant is taking ophthalmic or systemic steroids using the Drug List (12.8.1). Participants taking ophthalmic or systemic steroids are not eligible for the study, although their eligibility can be reviewed again following discontinuation of these drugs. Investigators should contact the Study Chairman regarding this question.

Use of all medications, systemic and ocular, is recorded at each regularly scheduled follow up visit (baseline, 6 month, 12 month, and so on). The participant should bring all medication prescribed to them (non-ophthalmic and ophthalmic) to the Clinic Center. The clinic coordinator records the medication and checks medication lists (12.8.1) to determine if the medication is an antidepressant, beta-adrenergic blocking agent, calcium channel blocking agent, corticosteroid (either ophthalmic or systemic), nasal or bronchial inhaled steriod, estrogen or progesterone for hormone replacement therapy. If the medication is in one of these eight categories, the clinic coordinator checks (\checkmark) which category applies on the visit form.

If the participant did not bring in medication, the coordinator should complete the information on medication use by telephone.

Drug List 12.8.1

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ANTIDEPRESSANTS BETA-ADRENERGIC BLOCKING AGENT - Beta-Blocker CALCIUM CHANNEL BLOCKING AGENTS - Ca+Ch.Blocker ESTROGEN & PROGESTERONE – Estrogen&Prog AND COMBINATION MEDICATIONS

Acebutolol
Adalat
Adalat CC
Adalat FT
Adalat P.A.
Adapin
Alora
Amen
Amitriptyline
Amlodipine
Amoxapine
Anafranil
Apo-Amitriptyline
Apo-Atenolol
Apo-Diltiaz
Apo-Imipramine
Apo-Metoprolol
Apo-Nifed
Apo-Propranolol
Apo-Timolol
Apo-Trimip
Apo-Verap
Asendin
Atenolol
Aventyl
Bepadin
Bepridil
Betaloc
Betaloc Durules
Betapace
Betaxolol
Bisoprolol
Blocadren
Bupropion
Calan
Calan SR
Cardene
Cardizem

Beta-Blocker Ca+Ch.Blocker Ch+Ch.Blocker *Ca+Ch.Blocker Ca+Ch.Blocker* Antidepressant Estrogen&Prog Estrogen&Prog *Antidepressant* Ca+Ch.Blocker *Antidepressant Antidepressant* Antidepressant Beta-Blocker *Ca+Ch.Blocker Antidepressant* Beta-Blocker *Ca+Ch.Blocker* Beta-Blocker Beta-Blocker *Antidepressant* Ca+Ch.Blocker Antidepressant Beta-Blocker Antidepressant Ca+Ch.Blocker *Ca+Ch.Blocker* Beta-Blocker **Beta-Blocker** Beta-Blocker Beta-Blocker Beta-Blocker Beta-Blocker *Antidepressant* Ca+Ch.Blocker *Ca+Ch.Blocker* Ca+Ch.Blocker Ca+Ch.Blocker

Cardizem CD Cardizem SR Carteolol Cartrol Carvedilol C.E.S.Cenestin Chlorotrianisene Cibalith-S Climara Clomipramine Coreg Corgard Corzide Covera-HS Crinone Cycrin Delestrogen DepGynogen Depo-Estradiol Depo-Provera DES Desipramine Desvrel Detensol Dienestrol Diethylstilbestrol Diethylstilbestrol Diphosphate Dilacor-XR Diltiazem Dioval 40 Dioval XX Doxepin Dura-Estrin Estrogen&Prog Estrogen&Prog Duragen-20 Duragen-40 Estrogen&Prog *DynaCirc Ca+Ch.Blocker*

Ca+Ch Blocker *Ca+Ch.Blocker* Beta-Blocker Beta-Blocker Beta-Blocker Estrogen&Prog Estrogen&Prog Estrogen&Prog Antidepressant Estrogen&Prog Antidepressant Beta-Blocker **Beta-Blocker** Beta-Blocker *Ca+Ch.Blocker* Estrogen&Prog Estrogen&Prog Estrogen&Prog Estrogen&Prog Estrogen&Prog Estrogen&Prog Estrogen&Prog Antidepressant Antidepressant Beta-Blocker Estrogen&Prog Estrogen&Prog Estrogen&Prog *Ca+Ch.Blocker* Ca+Ch.Blocker Estrogen&Prog Estrogen&Prog *Antidepressant*

E-Cypionate	Estrogen&Prog
Effexor	Antidepressant
Elavil	Antidepressant
Emitrip	Antidepressant
Endep	Antidepressant
Enovil	Antidpressant
Eskalith	Antidepressant
Eskalith CR	Antidepressant
Esmolol	Beta-Blocker
Esterified estrogens	Estrogen&Prog
Estinyl	Estrogen&Prog
Estra-L 40	Estrogen&Prog
Estrace	Estrogen&Prog
Estrace Vaginal Crea	m
C	Estrogen&Prog
Estraderm	Estrogen&Prog
Estradiol	Estrogen&Prog
Estradiol cypionate	Estrogen&Prog
Estradiol valerate	Estrogen&Prog
Estratab	Estrogen&Prog
Estratest	Estrogen&Prog
Estring	Estrogen&Prog
Estro-Cvp	Estrogen&Prog
Estrofem	Estrogen&Prog
Estrogens, conjugated	l Estrogen&Prog
Estroject-LA	Estrogen&Prog
Estrone	Estrogen&Prog
Estropipate	Estrogen&Prog
Ethinvl estradiol	Estrogen&Prog
Etrafon	Antidepressant
Felopidine	<i>Ca+Ch.Blocker</i>
Feminate	Estrogen&Prog
FemPatch	Estrogen&Prog
Femogex	Estrogen&Prog
Flunarizine	Ca+Ch.Blocker
Fluoxetine	Antidepressant
Fluvoxamine	Andidepressant
Gesterol 50	Estrogen&Prog
Gvnogen L.A.	Estrogen&Prog
Honvol	Estrogen&Prog
Imipramine	Antidepressant
Impril	Antidepressant
Inderal	Beta-Blocker
Inderal LA	Beta-Blocker
Inderide	Beta-Blocker
Inderide LA	Beta-Blocker
	-

Isocarboxazid *Antidepressant* Isoptin *Ca+Ch.Blocker* Isoptin SR *Ca+Ch.Blocker* Isradipine *Ca+Ch.Blocker* Janimine *Antidepressant* Kerlone Beta-Blocker Kestrone Estrogen&Prog Labetalol Beta-Blocker Levate *Antidepressant* Beta-Blocker Levatol Lexxel *Ca+Ch.Blocker Limbitrol DS 10-25 Antidepressant* Lithane *Antidepressant* Lithium *Antidepressant* Lithobid Antidepressant Lithonate Antidepressant Lithotabs *Antidepressant* Lopresor Beta-Blocker Lopresor SR Beta-Blocker **Beta-Blocker** Lopressor Lopressor HCT Beta-Blocker Lotrel *Ca+Ch.Blocker* Ludiomil Antidepressant Luvox Antidepressant Maprotiline Antidepressant Marplan *Antidepressant Medroxyprogesterone acetate* Estrogen&Prog Menaval Estrogen&Prog Menest Estrogen&Prog Beta-Blocker Metoprolol Mibefradil *Ca+Ch Blocker* Mirtazapine *Antidepressant* Beta-Blocker Monitan Nadolol Beta-Blocker Nardil Antidepressant Nefazodone *Antidepressant Neo-Estrone* Estrogen&Prog Nicardipine Ca+Ch.Blocker Nifedipine *Ca+Ch.Blocker* Nimodipine *Ca+Ch.Blocker* Nimotop *Ca+Ch.Blocker* Nisoldipine *Ca+Ch.Blocker* Norethindrone Estrogen&Prog Norethindrone acetate Estrogen&Prog

Norfranil Normodyne Normozide Norpramin Nortriptyline Norvasc Novo-Atenol Novo-Diltazem Novo-Doxepin Novometoprol Novo-Nifedin Novo-Pindol Novo-Timol *Novo-Tripramine* Novo-Veramil Novopramine Novopranol Novotriptyn Nu-Diltiaz Nu-Nifed Nu-Verap Ogen Ortho Dienestrol Ortho-Est Oxprenolol Pamelor Parnate Paroxetine Paxil Penbutolol Pertofrane Phenelzine Pindolol Plendil PMB-200 PMB-400 pms Propranolol Posicor Premarin Premarin Intravenous

Antidepressant Beta-Blocker Beta-Blocker Antidepressant *Antidepressant* Ca+Ch.Blocker Beta-Blocker Ca+Ch.Blocker *Antidepressant* Beta-Blocker Ca+Ch.Blocker Beta-Blocker Beta-Blocker *Antidepressant* Ca+Ch.Blocker Antidepressant Beta-Blocker *Antidepressant* Ca+Ch.Blocker Ca+Ch.Blocker *Ca+Ch.Blocker* Estrogen&Prog Estrogen&Prog Estrogen-Prog Beta-Blocker *Antidepressant* Antidepressant *Antidepressant* Antidepressant Beta-Blocker Antidepressant Antidepressant Beta-Blocker Ca+Ch.Blocker Estrogen&Prog Estrogen&Prog Beta-Blocker Ca+Ch.Blocker Estrogen&Prog Estrogen&Prog

Premphase Prempro Primogyn Depot Procardia Procardia XL Estrogen&Prog Estrogen&Prog Estrogen&Prog Estrogen&Prog Ca+Ch.Blocker Ca+Ch.Blocker Progestasert Progesterone Prometrium Propranolol *Protriptyline* Provera Prozac Remeron Renedil Rhotrimine Sectral Sertraline Serzone Sibelium Sinequan Slow-Trasicor Sotacor Sotalol Stilphostrol Sular Surmontil Syn-Diltiazem Syn-Nadolol Svn-Pindolol TACE Tarka Teczem Tenoretic Tenormin Tiazac Timolol Timolide Tipramine Tofranil Tofranil-PM *Toprol-XL* Trandate Tranylcypromine Trasicor Trazodone Trazon Triadapin Trialodine Triavil Trimipramine Triptil

Estrogen&Prog Estrogen&Prog Estrogen&Prog Beta-Blocker *Antidepressant* Estrogen&Prog *Antidepressant* Antidepressant *Ca+Ch.Blocker Antidepressant* Beta-Blocker Antidepressant Antidepressant Ca+Ch.Blocker *Antidepressant* Beta-Blocker **Beta-Blocker** Beta-Blocker Estrogen&Prog *Ca+Ch.Blocker Antidepressant Ca+Ch.Blocker* Beta-Blocker Beta-Blocker Estrogen&Prog *Ca+Ch.Blocker* Ca+Ch.Blocker Beta-Blocker **Beta-Blocker** *Ca+Ch.Blocker* Beta-Blocker Beta-Blocker Antidepressant Antidepressant Antidepressant Beta-Blocker Beta-Blocker *Antidepressant* Beta-Blocker Antidepressant Antidepressant Antidepressant Antidepressant Antidepressant Antidepressant Antidepressant

Valergen-10	Estrogen&Prog
Valergen-20	Estrogen&Prog
Valergen-40	Estrogen&Prog
Vascor	Ca+Ch.Blocker
Venlafaxine	Antidepressant
Verapamil	Ca+Ch.Blocker
Verelan	Ca+Ch.Blocker
Viskazide	Beta-Blocker
Visken	Beta-Blocker
Vivactil	Antidepressant
Vivelle	Estrogen&Prog
Wellbutrin	Antidepressant
Zebeta	Beta-Blocker
Ziac	Beta-Blocker
Zoloft	Antidepressant

CORTICOSTEROIDS

OPHTHALMIC - Ophth Steroid INTRANASAL - Nasal Steroid RESPIRATORY INHALANT - Inhaled Steroid SYSTEMIC - SystemicSteroid TOPICAL - Topical Steroid COMBINATION MEDICATIONS

AA-HC Otic	Topical Steroid	Apo-Prednisone	SystemicSteroid
Acetasol HC	Topical Steroid	Aristocort	Topical Steroid
ACTH	SystemicSteroid		SystemicSteroid
Aclovate	Topical Steroid	Aristocort A	Topical Steroid
Acthar	SystemicSteroid	Aristocort Forte	SystemicSteroid
Acthar Gel (H.P.)	SystemicSteroid	Aristocort Intralesion	nal
Acticort 100	Topical Steroid		SystemicSteroid
AeroBid	Inhaled Steroid	Aristospan Intra-artie	cular
AeroBid-M	Inhaled Steroid	-	SystemicSteroid
Aeroseb-Dex	Topical Steroid	Aristospan Intralesio	nal
Aeroseb-HC	Topical Steroid		SystemicSteroid
A-hydroCort	SystemicSteroid	Articulose-50	SystemicSteroid
AK-Cide Suspension	Ophth Steroid	Articulose-L.A.	SystemicSteroid
AK-Dex	Ophth Steroid	Atolone	SystemicSteroid
AK-Neo-Dex Solution	Ophth Steroid	Azmacort	Inhaled Steroid
AK-Pred	Ophth Steroid	Bacitracin Zinc/Neon	nycin
AK-Spore HC Opht S	uspension	Sulfate/Polymyxin B	Sulfate/Hydrocortison
	Ophth Steroid		Ophth Steroid
AK-Tate	Ophth Steroid	Bactine	Topical Steroid
AK-Trol Suspension	Ophth Steroid	Baldex	Ophth Steroid
Ala-Cort	Topical Steroid	Becloforte Inhaler	Inhaled Steroid
Ala-Scalp HP	Topical Steroid	Beclomethasone	Topical Steroid
Alclometasone	Topical Steroid	Beclomethasone Dipi	ropionate
Allercort	Topical Steroid		Nasal Steroid
Alphaderm	Topical Steroid		Inhaled Steroid
Alphatrex	Topical Steroid	Beclovent	Inhaled Steroid
Amcinonide	Topical Steroid	Beconase AQ Nasal	Nasal Steroid
Amcort	SystemicSteroid	Beconase Inhalation	Nasal Steroid
A-methaPred	SystemicSteroid	Betamethasone	Topical Steroid
Analpram-HC	Topical Steroid		Ophth Steroid
Antibiotic Ear Soln	Topical Steroid		SystemicSteroid
AntibiOtic	Topical Steroid	Betatrex	Topical Steroid
Anucort-HC	Topical Steroid	Beta-Val	Topical Steroid
Anumed HC	Topical Steroid	Betnelan	SystemicSteroid
Anusol-HC	Topical Steroid	Betnesol	SystemicSteroid

Bio-Syn	Topical Steroid	Cyclocort	Topical Steroid
Blephamide	Ophth Steroid	Dalalone	<i>SystemicSteroid</i>
Bronalide	Inhaled Steroid	Dalalone D.P.	<i>SystemicSteroid</i>
Budesonide	Topical Steroid	Dalalone L.A.	<i>SystemicSteroid</i>
CaldeCORT Anti-Itch	Topical Steroid	Decaderm	<i>Topical Steroid</i>
CaldeCORT Light	Topical Steroid	Decadrol	SystemicSteroid
Carmol-HC	Topical Steroid	Decadron	Topical Steroid
Celestone	SystemicSteroid		Ophth Steroid
<i>Celestone Phosphate</i>	SystemicSteroid		<i>SystemicSteroid</i>
Celestone Soluspan	SystemicSteroid	Decadron-LA	<i>SystemicSteroid</i>
Cel-U-Jec	SystemicSteroid	Decadron Phosphate	<i>SystemicSteroid</i>
Cenocort A-40	SystemicSteroid	Decadron Phosphate	Turbinaire
Cenocort Forte	<i>SystemicSteroid</i>	1	Nasal Steroid
Cetacort	Topical Steroid	Decadron Phosphare	Respihaler
Cetapred	Ophth Steroid	1	Inhaled Steroid
Chloromycetin-Hydro	cortisone Ophth	Decaject	SystemicSteroid
<i>, , , ,</i>	Ophth Steroid	Decaject-L.A.	<i>SystemicSteroid</i>
Cinalone 40	SystemicSteroid	Decaspray	<i>Topical Steroid</i>
Cinonide 40	SystemicSteroid	Delacort	Topical Steroid
Clobetasol	Topical Steroid	Delta-Cortef	<i>SystemicSteroid</i>
Clobetasone	Topical Steroid	Deltasone	<i>SystemicSteroid</i>
Clocortolone	Topical Steroid	Delta-Tritex	<i>Topical Steroid</i>
Cloderm	Topical Steroid	depMedalone 40	<i>SystemicSteroid</i>
Cordran	Topical Steroid	depMedalone 80	<i>SystemicSteroid</i>
Cordran SP	Topical Steroid	Depoject-40	<i>SystemicSteroid</i>
Cortaid	Topical Steroid	Depoject-80	<i>SystemicSteroid</i>
Cortamed	OphthSteroid	Depo-Medrol	<i>SystemicSteroid</i>
Cortatrigen Mod. Ear	· Topical Steroid	Depopred-40	<i>SystemicSteroid</i>
Cort-Dome	Topical Steroid	Depopred-80	<i>SystemicSteroid</i>
Cort-Dome H.P.	Topical Steroid	Depo-Predate 40	<i>SystemicSteroid</i>
Cortef	SystemicSteroid	Depo-Predate 80	<i>SystemicSteroid</i>
Cortef Feminine Itch	Topical Steroid	Dermabet	<i>Topical Steroid</i>
Cortenema	SystemicSteroid	Dermacort	Topical Steroid
Corticaine	Topical Steroid	Dermarest DriCort	Topical Steroid
Corticotropin	SystemicSteroid	DermiCort	Topical Steroid
Cortifair	Topical Steroid	Dermol HC	Topical Steroid
Cortifoam	SystemicSteroid	Dermtex HC	Topical Steroid
Cortisporin Ophth	Öphth Steroid	Deronil	<i>SystemicSteroid</i>
Cortisol	SystemicSteroid	Desonide	<i>Topical Steroid</i>
Cortisone	SystemicSteroid	Desoximetasone	Topical Steroid
Cortone	SystemicSteroid	DesOwen	Topical Steroid
Cortone Acetate	SystemicSteroid	Dexacen-4	<i>SystemicSteroid</i>
Cortril	Topical Steroid	Dexacen LA-8	<i>SystemicSteroid</i>
Cortrophin-Zinc	SystemicSteroid	Dexacidin Suspension	Ophth Steroid
Cortrosyn	SystemicSteroid	Dexair	Ophth Steroid
Cosyntropin	SystemicSteroid	Dexamethasone	Topical Steroid
Cutivate	Topical Steroid		Ophth Steroid

Clinical Center Procedures 12-17	7
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	SvstemicSteroid
Dexamethasone Inten	sol
	SystemicSteroid
Dexamethasone Sodiu	m Phosphate
	Inhaled Steroid
	Nasal Steroid
Dexameth	SystemicSteroid
Dexasone	SystemicSteroid
Dexasone-LA	SystemicSteroid
Dexasporin	Ophth Steroid
Dexone	SystemicSteroid
Dexone 0.5	SystemicSteroid
Dexone 0.75	SystemicSteroid
Dexone 1.5	SystemicSteroid
Dexone 4	SystemicSteroid
Dexone LA	SystemicSteroid
Dexotic	Ophth Steroid
Diflorasone	Topical Steroid
Diflucortolone	Topical Steroid
Diodex	Ophth Steroids
Diprolene	Topical Steroid
Diprolene AF	Topical Steroid
Diprosone	Topical Steroid
D-Med 80	SystemicSteroid
Drotic	Topical Steroid
Duralone-40	SystemicSteroid
Duralone-80	SystemicSteroid
Ear-Eze	Topical Steroid
EarSol-HC	<i>Topical Steroid</i>
Econopred	Ophth Steroid
Econopred -Plus	Ophth Steroid
Elione	Opnin Sterola
Elocon	Topical Steroid
Epijoam	Topical Sierola
Flores	Topical Storoid
Floringf	Systemie Steroid
Florence	SystemicSteroid
Florone F	Topical Steroid
Fludrocortisone acete	
	SystemicStoroid
Flumethasone	Topical Staroid
Flunisolide	Nasal Steroid
	Inhaled Storaid
Fluocet	Tonical Steroid
Fluocin	Topical Steroid
Fluocinolone	Topical Steroid
Fluocinonide	Topical Steroid
1 1001110111110	1 opical Sici 010

Fluonid	Topical Steroid
Fluorocortisone	SystemicSteroid
Fluorometholone	Ophth Steroid
Fluor-Op	Ophth Steroid
Flurandrenolide	Topical Steroid
Flurosyn	Topical Steroid
Fluticasone	Topical Steroid
Flutex	Topical Steroid
FML Forte	Ophth Steroid
FML Liquifilm	Ophth Steroid
FML-S Suspension	Ophth Steroid
FML S.O.P.	Ophth Steroid
FoilleCort	Topical Steroid
Gly-Cort	Topical Steroid
Gynecort	Topical Steroid
Halcinonide	Topical Steroid
Haldrone	SystemicSteroid
Halobetasol	Topical Steroid
Halog	Topical Steroid
Halog-E	Topical Steroid
Hemorrhoidal HC	Topical Steroid
Hexadrol	SystemicSteroid
Hexadrol Phosphate	SystemicSteroid
Hi-Cor 1.0	Topical Steroid
Hi-Cor 2.5	Topical Steroid
HMS-Liquifilm	Ophth Steroid
H.P. Acthar Gel	SystemicSteroid
Hydeltrasol	SystemicSteroid
Hydeltra T.B.A.	SystemicSteroid
Hydrocortisone	Topical Steroid
	Ophth Steroid
	SystemicSteroid
Hydrocortone	SystemicSteroid
Hydrocortone Acetate	e SystemicSteroid
Hydrocortone Phosph	nate
	SystemicSteroid
Hydro-Tex	Topical Steroid
Hytone	Topical Steroid
I-Methasone	Ophth Steroid
Inflamase Forte	Ophth Steroid
Inflamase Mild	Ophth Steroid
I-Pred	Ophth Steroid
Isopto Cetapred	Ophth Steroid
Kenac	Topical Steroid
Kenacort	SystemicSteroid
Kenacort Diacetate	SystemicSteroid
Kenaject-40	SystemicSteroid
Kenalog	Topical Steroid

Kenalog-H Topical Ster	d Neomycin/Polymyxin B
Kenalog in Orabase Topical Ster	d Sulfate/Hydrocortisone
Kenalog-10 SystemicSter	id Ophth Steroid
Kenalog-40 SystemicSter	id Neomycin Sulfate/Dexamethasone Sodium
Kenonel Topical Ster	d Phosphate Ophth Steroid
Kev-Pred 25 SystemicSter	id Neotricin HC Ophth Steroid
Kev-Pred 50 SystemicSter	id 9-1-1 Topical Steroid
Kev Pred SP SystemicSter	id Nor-Pred T.B.A. SystemicSteroid
Lacti-Care-HC Topical Ster	d Nutracort Topical Steroid
Lanacort Topical Ster	d Octicair Topical Steroid
LazerSporin-C Topical Ster	d Ocu-Dex Ophth Steroid
Lemoderm Topical Ster	d Ocu-Pred Ophth Steroid
Licon Topical Ster	d Ocu-Pred-A Ophth Steroid
Lidemol Topical Ster	d Ocu-Pred Forte Ophth Steroid
Lidex Topical Ster	d Ophthocort Ophth Steroid
Lidex-E Topical Ster	d Ophtho-Tate Ophth Steroid
Liquid Pred SystemicSter	id Optimvd Ophth Steroid
Lite-Pred Ophth Stero	Orabase-HCA Topical Steroid
Locoid Topical Ster	d Oracort Topical Steroid
Lyderm Topical Ster	d Oradexon SystemicSteroid
Maxidex Ophth Stero	Oralone Topical Steroid
Maxiflor Topical Ster	d Orasone 1 SystemicSteroid
Maxitrol Oint/Ophth Ophth Stero	Orasone 5 SystemicSteroid
Maxivate Topical Ster	d Orasone 10 SystemicSteroid
Medralone-40 SystemicSter	id Orasone 20 SystemicSteroid
Medralone-80 SystemicSter	id Orasone 50 SystemicSteroid
Medrol Topical Ster	d Otic-Care Topical Steroid
SystemicSter	id Otic Tridesilon Topical Steroid
Medrol Enpak SystemicSter	id OtiTricin Topical Steroid
Medrysone Ophth Stero	Otobiotic Otic Topical Steroid
Meprolone SystemicSter	id Otocort Topical Steroid
Methylprednisolone Topical Ster	d Otomvcin-HPN Otic Topical Steroid
SvstemicSter	id Otosporin Topical Steroid
Meticorten SystemicSter	id Panasol-S SystemicSteroid
Metimvd Ophth Oint Ophth Stero	Paramethasone SystemicSteroid
Mometasone Topical Ster	d Pediapred SystemicSteroid
M-Prednisol-40 or 80 SystemicSter	id Pediotic Topical Steroid
My Cort Topical Ster	d Penecort Topical Steroid
Mymethasone SystemicSter	id Pentacort Topical Steroid
Nasacort Nasal Steroi	Pharma-Cort Topical Steroid
Nasalide Nasal Steroi	PMS-Dexamethasone Sodium Phosphate
NeoDecadron Ophth Stero	Onhth Steroid
Neo-Dexameth Ophth Stero	PolvPred Suspension Ophth Steroid
Neomycin/Polymyxin B Sulfate/	Pramoxine HC Topical Steroid
Dexamethasone Suspension	Predair Onhth Steroid
Onhth Stero	Predair A Onhth Steroid
	Predair Forte Ophth Steroid

Predaject-50	SystemicSteroid
Predalone 50	SystemicSteroid
Predalone T.B.A.	SystemicSteroid
Predate 50	SystemicSteroid
Predate S	SystemicSteroid
Predate TBA	SystemicSteroid
Predcor-25	SystemicSteroid
Predcor-50	SystemicSteroid
Predcor-TBA	SystemicSteroid
Pred Forte	Ophth Steroid
Pred G	Ophth Steroid
Pred-G S.O.P.	Ophth Steriod
Pred Mild	Ophth Steroid
Predicort-50	SystemicSteroid
Predicort-RP	SystemicSteroid
Prednicen-M	SystemicSteroid
Prednisolone	Ophth Steroid
	SystemicSteroid
Prednisone	SystemicSteroid
Prednisone Intensol	SystemicSteroid
Prelone	SystemicSteroid
ProctoCream-HC	Topical Steroid
Proctocort	Topical Steroid
Proctofoam-HC	Topical Steroid
Psorcon	Topical Steroid
Pulmicort Turbuhaler	Topical Steroid
Rectacort	Topical Steroid
Rederm	Topical Steroid
Rep-Pred 40	SystemicSteroid
Rep-Pred 80	SystemicSteroid
Rhinocort	Topical Steroid
Rhuli cort	Topical Steroid
Rimexolone	Ophth Steroid
R.ODexasone	Ophth Steroid
Selestoject	SystemicSteroid
Solu-Cortef	SystemicSteroid
Solu-Medrol	SystemicSteroid
Solurex	SystemicSteroid
Solurex-LA	SystemicSteroid
Spersadex	Ophth Steroid
S-T Cort	Topical Steroid
Sterapred	SystemicSteroid
Sterapred DS	SystemicSteroid
Storz-Dexa	Ophth Steroid
Sulfacetamide Sodium	/Prednisolone Sodium
Phosphate	Ophth Steroid
Synacort	Topical Steroid

Synalar	Topical Steroid
Synalar-HP	Topical Steroid
Synemol	Topical Steroid
Tac-3	<i>SystemicSteroid</i>
Teladar	Topical Steroid
Temovate	Topical Steroid
Temovate Scalp App	Topical Steroid
Terra-Cortril Suspens	ion
	Ophth Steroid
Texacort Scalp Sol.	Topical Steroid
Tobradex	Ophth Steroid
Topicort	Topical Steroid
Topicort LP	Topical Steroid
Triacet	Topical Steroid
Triam-A	SystemicSteroid
Triam-Forte	SystemicSteroid
Triamcinolone	Topical Steroid
	SystemicSteroid
Triamcinolone Aceton	ide
	Nasal Steroid
	Inhaled Steroid
Triamolone 40	SystemicSteroid
Triamonide 40	SystemicSteroid
Triderm	Topical Steroid
Tridesilon	Topical Steroid
Tri-Kort	SystemicSteroid
Trilog	SystemicSteroid
Trilone	SystemicSteroid
Tristoject	SystemicSteroid
Trymex	Topical Steroid
UAD Otic	Topical Steroid
Ultra Pred	Ophth Steroid
Ultravate	Topical Steroid5
Uticort	Topical Steroid
Valisone	Topical Steroid
Valisone Reduced St.	Topical Steroid
Valnac	Topical Steroid
Vancenase AQ Nasal	Nasal Steroid
Vancenase Nasal	Nasal Steroid
Vanceril	Inhaled Steroid
Vasocidin Ophth Oint	Ophth Steroid
Vasocidin Ophth Soln	Opht Steroid
Vexol	Ophth Steroid
VoSol HC Otic	Topical Steroid
Westcort	Topical Steroid
Winpred	SystemicSteroid

12.9 Web Access System

A web access system (www.vrcc.wustl.edu) for viewing selected recurrent study reports is available to authorized personnel of the study via the world wide web. Each report is updated every 24 hours. Future upgrades will include the flexibility of real-time updates.

Only certified OHTS personnel are provided access to information available on the OHTS web access system through a unique User ID and password. To obtain a User ID, study personnel must complete an application form (appendix), co-signed by his/her clinic PI or resource center director. In the application, the user agrees to maintain the confidentiality of all information received via the web, and to not distribute any of its contents to persons other than OHTS personnel at their own clinic. Upon leaving the study, their userid and password will be deactivated.

Each authorized user of the system is provided access to only a limited set of the information available, according to their role within the study. For example, staff at a particular clinical site are only provided access to participant-specific information for their own participants, and to summary information for the study as a whole.

Contents of the Web Access System include:

- All randomized Participants
- Participant form history
- List of Case Report Forms received by type of form
- IOP report
- Quarterly report
- Staff Certifications
- Reconsent Dates
- Hospital Discharge Summaries Received
- Daily Tracking Reports
 - Follow-Up Visit Reminders
 - Late/Missed Visits
 - Reconsents Needed
 - Discharge Summaries Needed
 - Pachymetry Forms
 - Unresolved edit queries
- Follow-up Visit Schedules and close dates
- Current Participants: Gender by Race Distribution
- Administrative Items
 - OHTS Directory/Phone Numbers
 - AE Guidelines
 - OHTS Protocol Review for IOP Certification
 - OHTS Protocol for Visual Acuity Certification
 - Drug List
 - List of Current OHTS Forms

- On-Line Requests for labels or forms
- Memorandums

The OHTS Web Access System is best viewed with either Netscape version 4.0 or above, or Internet Explorer version 5.0 or above.

APPENDIX

APPLICATION AND AUTHORIZATION FOR OHTS REPORTS WEB ACCESS

Description of Web Access

The Ocular Hypertension Treatment Study (OHTS) Coordinating Center has made some administrative information accessible to authorized users through the internet. Study codes are used to protect patient anonymity. All OHTS data are privileged and confidential.

Internet access to OHTS information is restricted to certified OHTS personnel who have specifically been granted authorization for OHTS internet access by the Coordinating Center. Web access to OHTS information is restricted by a unique userid and password for each staff member. Each clinic will be able to access only its clinic's and satellites' data.

Terms of Agreement for Web Access

I agree not to release any information from the OHTS web access system to anyone outside of OHTS or to any OHTS certified personnel from other clinics or reading centers. I agree to safeguard my userid and password and not make them available to any other person. I understand that upon leaving the study or for other reasonable causes, my userid and password will be deactivated.

Full Name of Person Requ (Please Print)	lesting Access	Clinic or Reading Center	Applicant's OHTS Certification Code
Position in OHTS		Email Addr	ess
Applicant Signature	Date	Clinic PI Signat	ture Date
	For Coordinating C	Center Use Only	
Userid	Temporary Password	Date Assigned	Date Removed
Comments:			

OHTS Web address: http://www.vrcc.wustl.edu/data/ohts/

Summary of Revisions

Chapter 13 - Chairman's Office

Section	Date	Description
13.1.1 Study Chairman	12/22/94	Chairman routinely reviews all AE's
	10/98	Adverse events no longer routinely reviewed by
		Study Chairman. AE's now reviewed by an
		appointed staff member.
13.1.2 Vice-Chairs	5/13/94	Vice Chairs assist in regularly scheduled clinic site
		visits and serve on the Endpoint Committee
13.1.3 Project Manager	9/5/95	Develops and implements program for participant
		retention
13.1.4 Medical Monitor for	10/98	Chairman is unmasked to study data, Dr. Douglas
Treament Change		Gaasterland now reviews all Treatment Change
		requests

13. Chairman's Office

13.1	Introduction	
13.1.1	Study Chairman	
13.1.2	Vice-Chairs	
13.1.3	Project Manager	
13.1.4	Medical Monitor for Treatment Change	

13.1 Introduction

The Study Chairman's Office is located in the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine in St. Louis. The staff of the Chairman's Office includes:

- Michael A. Kass, M.D., Study Chairman Washington University School of Medicine
- Dale K. Heuer, M.D., Vice-Chair Medical College of Wisconsin
- Eve J. Higginbotham, M.D., Vice-Chair University of Maryland School of Medicine
- Richard K. Parrish, II, M.D., Vice-Chair University of Miami School of Medicine
- Douglas Gaasterland, M.D., Medical Monitor for Authorizing Treatment Changes — Washington OHTS Center
- Deborah Dunn, Project Manager, Central Pharmacy Washington University School of Medicine
- Ellen Long, Project Manager Washington University School of Medicine

13.1.1 Study Chairman

The study chairman is responsible for the overall scientific conduct of the trial and for maintaining the study organization as an effective collaborating group. The study chairman chairs the Executive/Steering Committee and Full Investigative Group and serves as an *ex officio* member of the Data and Safety Monitoring Committee, as well as all other study committees. The study chairman communicates regularly with the chairpersons of all standing committees. He appoints new committees as the need arises during the course of the study and dissolves committees that have completed their charges. The study chairman advises the NEI program office on data monitoring and other issues of importance in the overall conduct of the study. The study chairman deals with problems that arise at various Reading Centers and Clinical Centers as needed.

13.1.2 Vice-Chairs

Three vice-chairs assist the study chairman in the leadership of the trial. They are prominent, acknowledged leaders of the ophthalmic research community. They serve on the Executive/Steering Committee and Full Investigative Group. In the study chairman 's absence they would chair these groups. The vice-chairs communicate regularly with the study chairman and deal with problems arising in the Reading Centers and Clinical Centers if the study chairman is not available. The vice-chairs assist in the regular conduct of clinical center site visits and serve on the Endpoint Committee.

13.1.3 Project Manager

The project manager prepares the annual budget for continuation of the study chairman's grant and monitors expenditures made by the vice-chairs, Visual Field Reading Center, and Optic Disc Reading Center. The project manager attends all meetings of the Executive/Steering Committee and Full Investigative Group, pays all bills arising from these meetings, and prepares minutes of these meetings. The project manager is responsible for the preparation of informational and educational materials related to the trial, develops and implements a program of continuing participant education, develops and implements a program to encourage participant retention, and supervises the development and progress of a public relations campaign. The project manager maintains and distributes supplies of study drugs, monitors Clinical Center use of study medications, and reports to suppliers/manufacturers of study medications. The project manager acts as the study chairman's representative.

13.1.4 Medical Monitor for Treatment Change

The medical monitor for treatment change is appointed by the Study Chairman and reviews all treatment change requests as well as reviews requests for expedited visual field confirmation testing.

Summary of Revisions

Chapter 14 - Coordinating Center

Section	Date	Description
14.2 Personnel	9/5/95	Personnel updates
14.7 Quality Assurance	5/31/94	Site visits to Clinical Centers in first 18 months of the
		study and every two years thereafter.

14. Coordinating Center

14.1	Introduction	
14.2	Personnel	
14.3	Protocol Development	
14.4	Recruitment and Follow-up	
14.5	Participant Close-out	
14.6	Termination Phase	
14.7	Quality Assurance	
14.8	Data Security	
14.9	Records Flow Within the Coordinating Center	
14.10	Form Design	
14.11	Data Management	
Append	ix	

14.1 Introduction

The Coordinating Center is a joint effort of the Department of Ophthalmology and Visual Sciences and the Division of Biostatistics at Washington University School of Medicine. The Coordinating Center collaborates with the Study Chairman's Office, Executive/Steering Committee, Full Investigative Group, and the Data and Safety Monitoring Committee in the design and implementation of the Ocular Hypertension Treatment Study (OHTS). The Coordinating Center coordinates the efforts of investigators, monitors protocol adherence, manages and analyzes study data.

The staff of the Coordinating Center includes the Director, Co-Director, Project Manager, two Central Coordinators, one Project Assistant, two Statistical Data Analysts, two Research Analysts, two Research Assistants, and one Web Master.

14.2 Personnel

Director

Mae O. Gordon, Ph.D.

- Provides overall guidance on the design and implementation of the primary study and ancillary studies
- Collaborates with the study biostatistician in the analysis of data and the generation of reports. Participates actively in Executive/Steering Committee, Full Investigative Group, and all Publication Committees
- Serves as an ex-officio member of the Data and Safety Monitoring Committee
- Conducts site visits to reading centers and clinical centers
- Responsible for personnel decisions

Co-Director

J. Philip Miller, B.S.

- Contributes statistical expertise in the data analysis
- Assists in the adaptation of applications software for data analysis. Responsible for analyses for the Data Safety Monitoring Committee and Publication Committees. Attends meetings of the Executive/Steering Committee, Full Investigative Group, Publication Committee and the Data and Safety Monitoring Committee

Project Manager

Ellen Long, B.S., CCRA

- Assumes primary responsibility for the editing and production of study documents including the Manual of Procedures, all study forms, training and certification materials, study presentations and publications
- Serves as study archivist and maintains a computerized catalog and library of study documents including abstracts, reprints, slides and tapes
- Maintains a performance schedule calendar
- Coordinates the efforts of Coordinating Center staff
- Assists in organization of local and national meetings

Central Coordinators

Patricia Morris Ann Wilder, BSN, CCRC

- Each central coordinator works with specific clinical centers
- Randomizes study participants
- Reviews data received from clinical centers
- Monitors adherence to the protocol
- Trains and certifies clinic coordinators and investigator
- Trains and certifies staff for IOP determination and visual acuity
- Conducts troubleshooting calls with clinic coordinators
- Conducts site visits to clinics
- Participate in training sessions for clinic coordinators and investigators
- Liaison to Endpoint Committee and Medical Monitor for Treatment Change
- Reviews Adverse Event forms
- Non-voting members of the Executive/Steering Committee
- Verifies IRB coverage
- Conducts conference calls to each clinic with Chairman's Office as needed

Senior Statistical Data Analyst Statistical Data Analyst

- Responsible for statistical analyses for study publications/presentations and local and national meetings
- Develop data cleaning programs and data entry programs
- Develop and maintain web system for static and interactive access to study data

Julia Beiser, M.S. Mary Bednarski, M.A.S.

Joel Achtenberg, M.S.W.

Karen Clark, B.A.

Managers, **Applications, Programming and Development**

http://www.vrcc.wustl.edu/mop/mop.htm

- Responsible for management and processing of study data •
- Responsible for writing and maintaining programs for data entry, editing, management • and reporting
- Generation of recurrent reports for recruitment, data quality, protocol adherence and activity reports for resource centers
- Maintain study databases, tape archives and comprehensive documentation of ٠ variables, formats and program code used in reports
- Provide programming support to the director and co-director for statistical analyses •
- Provide oversight of computer systems and direction for future computing needs ٠

Data Control Coordinators

Denise Randant Christopher Ewing, B.A.

- Responsible for data entry, managing, filing and archiving of all case report forms • received at the Coordinating Center
- Responsible for data editing •
- Responsible for coordinating the services of the data entry subcontractor and the • courier company

Data Control Coordinator/Web Master

- Develop and maintain web system
- Develop and maintain on-line reference library of study manuscripts
- Responsible for "Free Text" data entry on case report forms for POAG Endpoint • participants

Project Assistant

- Assists Director with manuscript preparation and editing •
- Maintains archive of conflict of interest and publication/presentation agreement forms •
- Maintains archive of participant reconsents for study extension •
- Maintains OHTS directory of study personnel ٠

Carolyn Miles, M.A.

Elizabeth Hornbeck, B.S.

14.3 Protocol Development

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:

- Developing forms and procedures for data collection at clinical centers
- Design and development of computer systems for data entry/editing/management
- Developing programs to generate monthly reports to clinical centers and semi-annual reports to the Executive/Steering Committee and the Data and Safety Monitoring Committee
- Generating randomization schedules
- Completing a detailed Manual of Procedures
- Developing procedures for training and certifying clinic coordinators, technicians, photographers, principal investigators, and reading center personnel
- Distributing the Manual of Procedures and forms to clinical centers

14.4 Recruitment and Follow-up

Recruitment and follow-up is projected to take five to eight years. This phase includes the time from initial participant recruitment to completion of follow-up visits. Coordinating Center responsibilities during this phase include the following:

- Providing scientific support to clinical centers, the Visual Field Reading Center (VFRC), and the Optic Disc Reading Center (ODRC).
- Taking all necessary steps to identify and correct problems at the clinical centers, VFRC and ODRC.
- Supplying clinical centers with forms for the purpose of data collection, entry, and editing.
- Monitoring the flow of participant visits and data from the point of collection at the clinical center to deposition in a master data base at the Coordinating Center. (The Coordinating Center generates dates for scheduled participant visits from the time of randomization. Monthly monitoring reports summarize timeliness of visits and subsequent data processing.)
- Assisting clinical center staff in interpreting the Manual of Procedures and study protocol.
- Collecting, processing, and analyzing data.
- Receiving, editing, and storing data files from clinical centers, the VFRC, the ODRC, and the Endpoint Committee.

- Preparing monthly reports to clinical centers on participant recruitment and follow-up, and protocol adherence (See Appendix).
- At six-month intervals and upon request, the Coordinating Center will produce extensive monitoring reports for the Executive/Steering Committee and the Data and Safety Monitoring Committee. These reports include protocol violations by clinic, number of participants returning for follow-up within time windows, and adverse effects (See Appendix).

14.5 Participant Close-out

Participant close-out includes:

- Monitoring procedures for participant close-out.
- Assisting in the preparation of manuscripts.
- Final data editing and archival storage.
- Close-out of clinical centers, the VFRC, the ODRC, and the Coordinating Center.
- Final disposition of data files.

14.6 Termination Phase

During the termination phase, study datasets have essentially undergone final editing. This phase includes:

- Completing data analyses and writing of manuscripts.
- Archiving data files and study documents.
- Serving as OHTS communications center.

14.7 **Quality Assurance**

- The Coordinating Center will conduct training sessions for clinical center personnel on the protocol, examination procedures, forms completion, and data entry/editing.
- Coordinating Center personnel will conduct weekly/monthly telephone troubleshooting calls with clinical centers as necessary.
- Coordinating Center personnel and/or Study Vice-Chairs will site-visit the clinical centers and the Visual Field Reading Center and Optic Disc Reading Center as needed in the first 18 months of the study. Clinical Centers, Reading Centers and Ancillary Study Reading Centers are site visited every two years thereafter.

Clinic site visits are conducted to:

a) verify completion of consent and/or Decline to Participate form

- b) determine accuracy and completeness of reported eligibility and follow-up data, including but not limited to IOP, visual fields and optic disc photography. Reported data are compared to participant source documents such as participant charts and visual field directories at the clinic
- c) inventory supplies of study medication
- d) verify study equipment
- e) to help resolve other problems as necessary
- Coordinating Center will generate quality control reports on the performance of clinical centers, reading centers and the Coordinating Center (See Appendix).

14.8 Data Security

As the central repository of information for the study, the Coordinating Center has particular responsibilities towards data security. The Coordinating Center will protect the data from all hazards, including disasters and unauthorized access. The computer room in the Division of Biostatistics is locked to access except by staff and contains fire and heat sensors. The building is under guard at night and on weekends. The computer system is backed up daily and weekly, and the monthly back-ups are stored in a remote facility.

To guard against unauthorized access to the data, all shared-use computer systems are protected with passwords, which are changed frequently. Only individuals with a particular "need to know" are given access, and system privileges are carefully restricted. All of the PCs to be used in the Coordinating Center are located within a secure area, and the system is locked when not in use.

SAS, the primary software package to be used in OHTS, supports passwords for its datasets which make it more difficult to access information in an intelligible fashion. Systems connected to the ethernet are carefully controlled, and all systems without ethernet access control are insulated from the backbone by bridges or routers. The ethernet cable itself is routed only through secure passageways.

14.9 Records Flow Within the Coordinating Center

Within one working day of receipt, the Research Assistant manually checks consistency between (a) the information in the form type, participant ID, and visit date fields as recorded on the Transmittal Log and (b) the information in the form type, participant ID, and visit date fields as recorded on each case report form sent with the Transmittal Log. Unresolved discrepencies are flagged with a problem report when the Research Assistant enters Transmittal Log information, and the clinic is required to re-transmit if necessary. Additional manual checks conducted by the Research Assistant include checking for the correct number of pages, participant ID and date on each page of the form. The Central Coordinator performs a manual scan of case report forms for missing or erroneous data before they are bundled by form type for key data entry. The Research Assistant bundles case report forms by type and version, stamps a unique batch number on each page of the case report forms and stamps the batch number on a computer generated batch inventory log. Case report forms with serious problems are not sent to data entry pending resolution of the problem. Frequently, problems of protocol adherence are noted at this stage, and remedial actions are initiated. The Coordinating Center's response to problems with protocol adherence range from discussions with the clinic coordinator to a discussion with the Study Chairman and Executive/Steering Committee about possible protocol changes. Another action considered would be to schedule a special site visit to the clinical center.

Key to disk entry of data is performed off-site by a commercial data entry service. Data is picked up by courier three days per week. Data is keyed to disk by two different key operators, with the second operator performing verification. The turnaround time for data to be received on disk from the time of pick up by courier is 1 - 3 working days.

The data entry service completes a problem log by case report form type for each batch of forms processed. In this manner, the Coordinating Center is able to distinguish internal data errors that escape detection from errors that were introduced upon data entry. Each form type is a different file; the file name consists of the form code, form version and batch number.

Batch editing of data files consists of three types of edits, beginning with a check for consistency of form type within a file and the number of pages for each form. The second phase of editing consists of core edits that are conducted for all case report forms. These edit checks include identification of missing values, out-of-range values, illegal characters, verifying correctness of participant ID codes, and certifications. Form specific edits consist of edits that are unique to that case report form type. These include correctness of IOP computation, specific visit windows, i.e. IOP Confirmation Visit, and any medication decisions.

Edit checks are reported by issuing an edit message that is faxed to the clinic coordinator. The edit message states the participant ID, visit date, form type, form version, item number and the type of error detected, i.e. missing value, range check, illegal character, etc. The edit message also lists forms that pass edit. Computer generated flags are attached to the record at the Coordinating Center to document the status of the record. Records with errors or questionable items are marked and remain in a temporary file until final correction and verification. Records that pass editing are transferred to the central database on a daily basis.

14.10 Form Design

Forms for the study were designed, field tested and revised during the planning phase. The Coordinating Center distributes master forms to clinical centers and the clinic coordinator is responsible for photocopying forms as needed. The following guidelines are observed in the design of forms:

• Forms are self-contained, when possible. Their completion should not require reference to separate instruction manuals or tables of codes for completion. The instruction necessary for the completion of the form are routinely printed on the forms.

- Individual items are self-explanatory. Clarity takes precedence over compactness of forms.
- Forms are designed for direct data entry and should not require recoding of variables.
- Forms include information which is available at a given point in time. Information collected at another date is incorporated into another form.
- Each person responsible for data collection and/or data entry will be identified along with relevant dates of processing. This increases our ability to manage the data collection and to identify staffing or quality control problems.
- Forms are reviewed periodically and revised to include changes made necessary by protocol changes, corrections suggested on trouble reports, etc. Revised forms are indicated by a unique form version number and date printed on each page.

14.11 Data Management

The SAS system is used for virtually all computer processing within the Coordinating Center.

We have considerable experience with SAS on a variety of hardware platforms and have contributed to the development of SAS to meet the needs of the Coordinating Center (Miller, 1977; Roesti et. al., 1984; Achtenberg, 1989). The use of SAS software allows the use of a single software system across a broad spectrum of hardware platforms.

Over the course of the study, significant changes will occur in the cost/performance curves for computers. SAS's flexibility across hardware platforms allows balance between the stability of existing hardware systems with the economies of newly available hardware. All Coordinating Center staff have a PC available for use with the SAS software installed. Additionally, all PC's are connected to the university-wide network for rapid and reliable file transfer, the use of email, and for connecting to other computers for the execution of the SAS tasks which require a shared use computer.

In the OHTS database, all instances of each form type are grouped together as a single SAS dataset, cross-indexed by participant 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, Coordinating Center and Data and Safety Monitoring Committee develop jointly. Other programs extract analysis subsets for interim analyses and quality control monitoring.

Attached to each observation are flags indicating the stage of processing for that form. Along with these flags are the relevant dates so that aged management reports can track forms flow. When new or revised data is received from the clinical center, the database programmer runs PROC COMPARE between the old master (father) and updated dataset (son). The discrepancies form an audit trail of all changes to the database and can be utilized to back out of inadvertent changes to the database. This procedure tracks changes, whether they were intended updates or inadvertent computer processing errors.

References:

Miller JP, Moore P, Achtenberg J, Thomas LJ: Computerized information handling for long term clinical studies. *Proceedings of Computers in Cardiology*, IEEE Catalog 77-CH-1234-2C, 151, 1977.

Roesti P, Achtenberg J, Fisher DG: Managing human resources information: Using the SAS/FSP products. *Proceedings of the Ninth Annual SAS Users' Group International Conference*, SAS Institute, Cary, 1984

Achtenberg J, Casanova P: A hematology laboratory system using SAS(r)PC. *Proceedings of the 14th Annual SAS users' Group International Conference*, SAS Institute, Cary, 1472, 1989.

Appendix

All reports are routinely reviewed by Executive/Steering Committee and the Data and Safety Monitoring Committee.

A. Transaction Reports

1. Edit report - batched daily, as received Receiver: Clinic Coordinator Frequency: Daily Documents: Clinical Report Forms (CRF's)

2. Eligibility Status Report

Receiver: Clinic PI & Clinic Coordinator Frequency: When eligibility can be determined Documents: QA, VRFC daily report, ODRC daily report (The Central Coordinator reviews eligibility status for participants who are eligible and faxes the clinic coordinator a copy of the eligibility report.

3. Certification Status Report

Receiver: Clinic Coordinator, PI or person certified Frequency: When certification is completed Documents: Certification report completed by the Central Coordinator

B. Reports To Participating OHTS Clinics

1. Monthly Recruitment Report

Receiver: PI & Clinic Coordinator Frequency: Monthly Documents: QA, Randomization, FV, CF form(s)

- a. # of QA's received by clinic, for most recent month, total to date
- b. # of eligible participants by clinic, for most recent month, total to date
- c. # of participants randomized by clinic, for most recent month, total to date
- d. % of participants entering QA who are eligible (E/QA), total to date
- e. % of participants randomized who are African American, cumulative to date by month, total to date by clinic
- f. study totals by most recent month, total to date for items a through e

2. Follow-up and Retention Report

a. % of participant visits within time window by visit type (QA, BR, FV), by clinic and across clinics.

3. Data Quality of Case Report Forms

Receiver: PI & Clinic Coordinator Frequency: Semi-annually to Data and Safety Monitoring Committee and Executive Committee. Annually to Full Group Coordinating Center Edit Reports Documents:

- a. % of forms with edit queries, by quarter, total to date
- b. % of forms with outstanding edit queries, by quarter, total to date
- c. frequency distribution of time to resolution of edit query from time it is issued from Coordinating Center to the time it is resolved or closed. Reported in one week increments.

4. Adherence to Protocol

Receiver:	PI & Clinic Coordinator
	(semi-annually to Data and Safety Monitoring Committee and
	Executive Committee)
Frequency:	Semi-annually to Full Group
Documents:	Coordinating Center Edit Reports

5. **Data Quality of Optic Disc Photography**

(Generated by ODRC)

Receiver:	Clinic PI, Cl Coordinator, Cl. Photographer, semi-annually to
	Data and Safety Monitoring Committee, Executive Committee
Frequency:	Semi-annually to Full Group
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 clinics, last 6 months and total to date
- b. time for repeat photography
- c. time interval for confirmation photography
- d. #, % of slides with labeling errors
- e. % of stereo pairs that are received by ODRC within 1 week of photography protocol.

Data Quality of Visual Fields 6.

(Generated by VFRC)

Receiver: Clinic PI, Cl Coordinator, Visual Field Technician, Semi-annually to Data and Safety Monitoring Committee, Executive Committee Frequency: Annually to Full Group VFRC Grading Screen & VFRC log Documents:

- 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 technical problems
- d. duration of time for repeat fields
- e. duration of time for confirmation fields
- f. #, % of visual fields that are received by VFRC within time window

7. Clinic Site Visit Reports

Receiver:	Clinic PI, Clinic Corrdinator, Study Chairman, Study Vice-Chairs
	Coordinating Center Director, Data and Safety Monitoring
	Committee Chairman, NEI Representative, Reading Centers
Frequency:	Following initial site visit 12-18 months following study start-up
	and every two years thereafter.
Documents:	Site Visit Form

8. Clinic Tracking Report

Receiver:	Clinic Coordinator
Frequency:	Monthly
Documents:	Clinic Tracking Report

C. Semi-Annual Visual Field Reading Center Performance Report

Receiver:	VFRC, Coordinating Center, Semiannually to Data and Safety
	Monitoring Committee, Executive Committee
Frequency:	Semi-annually to Full Group
Documents:	Weekly and monthly VFRC transmissions

- a. "a" through "e" of VFRC Report to clinical centers for total study by clinics, in last reporting period, total to date.
- b. Time ticks in VFRC performance VFRC receipt of field to grading for quality VFRC receipt of field to grading for abnormality time interval for adjudication
- c. Agreement of quality
- d. Agreement on abnormality
- e. Agreement on QC set

D. Semi-Annual Optic Disc Reading Center Performance Report

- Receiver: ODRC, Coordinating Center, Semiannually to Data Safety and Monitoring Committee, Executive Committee Semiannually
- Documents: Weekly and monthly ODRC transmissions
- a. "a" through "e" of ODRC Report to clinical centers for total study by clinics in last reporting period, total to date.
- b. Time ticks:

ODRC receipt of photo to grading for quality ODRC receipt of photo to grading for abnormality Time interval for adjudication

- c. Grader Agreement on quality
- d. Grader Agreement on abnormality
- e. % adjudication on quality
- f. % adjudication on abnormality
- g. Grader Agreement on QC set

E. Semi-Annual Coordinating Center Performance Report

Receiver:	Coordinating Center, Semiannually to Data and Safety
	Monitoring Committee, Executive Committee
Frequency:	Semiannually
Documents: Directory, Forms, Edit Reports to Clinics, Transmittal Logs

- a. Certification status of clinic 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 by Coordinating Center.
- d. Time ticks in increments of days participant visit date to receipt of form at Coordinating Center edit query issued and resolved
- e. Site visit reports for resource centers and clinics
- f. Monitoring balance in study groups. Proportion of participants in Medication and Observation Groups with regard to: previous ocular hypotensive medication, race, sex, age, concurrent use of systemic beta-blockers by clinic and overall study sample.
- g. Monitoring loss to follow-up with regard to previous ocular hypotensive medication, race, sex, age, clinic by clinic and overall study sample.

Summary of Revisions

Chapter 15 - Optic Disc Photography

Section	Date	Description	
15.1.1 Personnel	2/21/94	ODRC moved from Yale University to Bascom Palmer Eye Institute: Dr. Parrish, Director, Dr. Anderson, Associate Director, Dr. Budenz, Assistant Director, Ms. Maria-Cristina Wells, Coordinator	
15.8When to take Optic DiscPhotographs	7/28/95	A red reflex photograph of each eye to document the presence of either lens or corneal opacities is to be taken of both eyes at every visit	
15.8 Macular Photos	11/24/97	A single photograph of the macula area is to be taken of each participant at every visit	
15.8.5 OHTS Cameras & Procedures	7/28/95	If replacement camera is required because the original camera cannot be repaired, the ODRC must be notified <u>in writing prior</u> to the changes in the camera.	
<u>15.9.2 Film</u>	2/21/94	Film changed to Ektachrome or Fujichrome 100	
15.9.3 Dilation	7/28/95	Participants should keep eyes closed 20-30 minutes after dilation and before photography.	
15.9.4 Photography Instructions	2/20/01	Photography instructions when using NIDEK or Topcon simultaneous stereo cameras	

15. Optic Disc Photography

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15.2.3	Logging in Photographs from Clinical Centers	
15.2.4	Storage of Optic Disc Photographs	
15.2.5	Evaluation of Stereo and Clarity	
15.2.6	Evaluation of Optic Disc Entry Criteria: Abnormality	
15.2.7	Evaluation of Optic Disc Eligibility: Symmetry of Baseline	
	Cup/Disc Ratio	
15.2.8	When Readers Disagree on Technical Quality or Eligibility	
15.2.9	Disc Endpoint Assessment: Change from Baseline	
15.2.10	Masked Rereading of Change	
15.2.11	Confirmatory Change Photographs	
15.3	Quality Control Procedures	
15.4	Communications to Clinical Center	
15.4.1	Transmission of Data from ODRC to Coordinating Center	
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15.8	When to take Optic Disc Photographs	15-12
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15.9.5	Developing Film	
15.9.6	Labeling Slides	
15.9.7	Mailing Slides to ODRC	

15.1 ODRC Objective

Optic disc stereo photography will be used to evaluate entry and endpoint criteria in OHTS. Optic disc stereo photography, required for eligibility assessment, will be performed annually after randomization to determine if glaucomatous damage has occurred. Treatment assignment is not provided to the ODRC personnel.

15.1.1 Personnel

Principal Investigator and Director	Richard K. Parrish III, M.D.
1 0	Email: rparrish@bpei.med.miami.edu
Associate Director	Douglas R. Anderson, M.D.
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Bascom Palmer Eye Institute McKnight Vision Research Ctr. 1638 NW 10th Avenue Fifth Floor Miami, FL. 33136

15.1.2 Responsibilities of ODRC

Surface and Express Mail Address

- Trains and certifies Optic Disc Readers.
- Develops performance protocol for optic disc photography at the clinical centers and for evaluation of photographs at the ODRC.
- Certifies photographers and back up photographers.

- Receives, processes, and archives all photographs and associated data.
- Assesses photograph quality and instructs photographers at Clinical Centers when photographs must be repeated.
- Determines if individuals meet optic disc entry criteria.
- Determines if progressive optic nerve damage has occurred.
- Enters and manages optic disc related data.
- Transmits data to the Coordinating Center, the Clinical Centers, and the Endpoint Committee in a timely fashion.
- Generates reports for the Steering Committee, Executive Committee, and Data and Safety Monitoring Committee. (per 15.4.3)
- Provides statistical analyses requested by the Coordinating Center.

15.2 Optic Disc Reading Center Procedures

15.2.1 Reader Pre-requisite

Candidate readers must demonstrate stereopsis at a level of 40 seconds of arc using a standard stereo acuity test.

15.2.2 Method of Training and Certification of Optic Disc Readers

The Director of the Optic Disc Reading Center will develop training and test sets for reader certification for eligibility and for progression. Certification has 3 parts (I, II, and III). Certification for eligibility reading has two parts: the first for recognition of exclusion identities, and the second for recognition of asymmetry and quantifying cup/disc ratio; and certification for reading progression has one part.

Part I: Recognition of exclusion entities (eg., giant drusen of the disc).

Training: A teaching set will contain at least one example of the entities that constitute exclusion: 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: Testing will consist of two test sets. The test set would include at least one example of each of the exclusion entities. Localized thinning of the neuroretinal rim would be

one of the entities included. For testing, an equal number of eligible discs (with a variety of cupdisc ratios) would be mixed with them. Competent readers will have no trouble picking up the clear-cut entities like drusen, not likely to be submitted by the investigators. The real test will be if the prospective reader can recognize the example of thinned neuro-retinal rim. Two sets will be available so that if the prospective reader fails the test (100% expected), there would be a second set to use for another test after further training. If the prospective reader passes on the first try, he should look at the second set anyway for the additional experience it would provide.

Part II: Recognition of asymmetry and quantifying the cup/disc ratio.

Training: The Director, Associate Director, or Assistant Director of the ODRC will read slides with the trainees. Looking at the slides side by side with a certified reader has been demonstrated to be the best way to train.

Testing: When the supervisor/trainer feels the trainee is ready, the trainee will no longer read the slides together with a teacher, but independently. The trainee's results will not be official, but will be compared with the readings of the two independent official readers. <u>On 50 consecutive sets</u>, the C/D ratio must be within 0.1 of at least one of the official readers. <u>More importantly, the amount of asymmetry must be within 0.1 of the consensus of the two official readers.</u> More importantly, the amount of asymmetry must be within 0.1 of the consensus of the two official readers (adjudicated consensus, if necessary). Thus, the candidate reader may designate 0.3 in one eye and 0.5 in the other. This would be a perfect match with 0.4 and 0.6 readings of the official readers, but would not be a match with 0.4 and 0.8 readings of the official readers, nor a 0.2 and 0.6 reading of the official readers. <u>If on any participant the candidate reader fails before reaching 50 consecutive correct readings, the count for 50 consecutive correct readings begins again.</u>

The individual is certified to be a reader to judge eligibility after completing parts I and II.

Part III. Judgement of progression

Training: In the future, the ODRC will receive duplicate sets to judge progression. The candidate readers will look at pairs side by side with the Director, Associate Director or Assistant Director until the candidate readers (already certified to judge eligibility) are deemed ready to be tested.

Testing: As in part II, successful match with the official readers in 50 consecutive sets of discs read, provided that at least 3 indeed had shown progression, will be required for certification of judging progression. One instance of false positive call of progression in the set of 50 would be permitted. If the set of 50 had not contained 3 true positive cases, the series continues until it happens to include 3 positive cases and there had been correct recognition of all progressive cases and no more than 1 false call of progression in non-progressive case.

Upon completion of phase III, the reader is certified both for reading for eligibility and reading for progression.

15.2.3 Logging in Photographs from Clinical Centers

- Upon receipt, the Research Assistant compares package contents to the Photography Checklist and telephones the Clinical Center when inconsistencies in the checklist occur.
- The Research Assistant assigns a unique tracking number (two alpha and three numeric characters) to the set of slides for the right eye and another tracking number for the left eye, and completes report on adequacy of labeling and identifies slides that are grossly unreadable.
- The Research Assistant masks the readers to the information on the slides by placing an opaque label on the plastic slide sheet or the side frame itself.
- The Research Assistant validates photographer ID, visit code, participant ID and camera model and serial number.
- The Research Assistant logs in the computerized "Daily Photo Receipt Logbook".

15.2.4 Storage of Optic Disc Photographs

All photos are stored in a single 8 $1/2 \ge 11^{\circ}$ plastic sheet filed by clinic and participant ID number. Ungraded slides are stored in separate plastic sheets in the same participant file.

15.2.5 Evaluation of Stereo and Clarity

- Only technically acceptable photographs will be evaluated for eligibility and change.
- The Center Coordinator or Research Assistant will select the best stereo pair and arrange the slides in grading sheets.
- Two masked readers will independently evaluate the best slides for stereo and clarity (one stereo pair for the right eye and one stereo pair for the left eye) (See Appendix A, Figure 1).
- If there is disagreement of greater than one point on clarity or stereo, or between "poor" and "unacceptable," the reading will be adjudicated by the Director, Associate Director, or Assistant Director.
- If one reader grades an "unacceptable," retake photos will automatically be requested. The reader does no further grading of a stereo pair graded as "unacceptable."
- A final adjudicated grade of "poor" for clarity or stereo demands retake if adjudication between grade "fair" and "poor" had occurred; however, the reader completes the grading form for eligibility or change.

• If the best set is graded "poor" or "unacceptable" for either clarity or stereo, both sets are returned to the photographer with the report explaining the reason and request for retake. The ODRC coordinator telephones the Clinical Center coordinator to request that repeat photographs be performed within four weeks and discusses the reason for retake.

15.2.6 Evaluation of Optic Disc Entry Criteria: Abnormality

Eligibility photos will be read independently by two readers. If either or both readers judge a disqualifying abnormality to be present, The Director, Associate Director, or Assistant Director will make a reading and adjudicate eligibility within one week after receipt of photographs and a report generated to the clinic within two working days.

As a general principle, an individual is ineligible if (1) There is evidence of glaucomatous optic nerve damage already present, or (2) There is evidence of a non-glaucomatous optic nerve or retinal disease that might produce confounding visual field defects. Determination by either of the masked readers of any of the following disc abnormalities will render an individual ineligible, if confirmed by the Director, Associate Director or Assistant Director:

- loss of rim tissue to disc edge
- diffuse thinning of the rim
- localized thinning of the rim
- disc hemorrhage
- notch in the rim
- localized or diffuse parlor
- disc drusen
- congenital pit
- optic nerve coloboma
- evidence of non-glaucomatous atrophy
- other conditions that might lead to a confounding non-glaucomatous visual field defect
- cup/disc asymmetry per section 15.2.7

Retinal nerve fiber layer dropout is not an exclusion

A sloping or tilted disc is not an exclusion (Visual fields must be okay).

15.2.7 Evaluation of Optic Disc Eligibility: Symmetry of Baseline Cup/Disc Ratio

Two readers will independently record the horizontal (3:00-9:00 meridian) cup to disc ratio to the nearest 0.1 unit.

If the two readers both describe a C/D ratio difference of >0.2, the pair will be read in a masked fashion by either the Director, Associate Director, or Assistant Director. If their reading confirms a C/D difference of >0.2 the individual is judged ineligible.

Disagreement >0.2 on C/D ratio will require masked adjudication by the Director or Associate Director.

The ODRC Coordinator will issue a report to the Clinical Center coordinator within two working days of an eligibility determination. The report to the clinic will consist of the following: participant ID, eligibility status of participant, and date eligibility status determined.

15.2.8 When Readers Disagree on Technical Quality or Eligibility

When masked readers disagree, the Director, Associate Director, or Assistant Director will reread the set remaining masked as to first round of results. This process is called adjudication.

When adjudicator agrees with one of the previous readers, those results will represent the ODRC results.

When the adjudicator disagrees with both readers, the set is discussed in conference with graders and ODRC result is determined by the Director, Associate Director, or Assistant Director.

15.2.9 Disc Endpoint Assessment: Change from Baseline

The Research Assistant will place baseline and follow-up photos in masked plastic sheets in alphabetical order by tracking number.

The reader will determine if the two sets are different, and identify which pair of photos is baseline and which is follow-up. The reading is positive only if the order is judged correctly.

Progressive optic nerve damage is defined for the OHTS, a visually detectable decrease in neural rim surface, as either generalized or localized thinning of the optic disc rim. Excavation of localized areas of rim tissue, a change in position of the vessels, or development of a notch, are evidence of this change.

The ODRC Coordinator will email the Coordinating Center within one working day of confirmation of progression.

15.2.10 Masked Rereading of Change

To minimize false positives and to monitor endpoint results, the Director, Associate Director, or Assistant Director will reread any set in which either reader reports a change.

15.2.11 Confirmatory Change Photographs

ODRC Coordinator will call the Clinical Center coordinator to schedule a confirmatory photograph to be taken within four weeks of the ODRC request, when a change finding is confirmed in writing by the ODRC Director/Associate. Confirmatory photographs may be obtained at the participant's next regularly scheduled study visit if the participant has previously reached a photographic or visual field POAG endpoint. The ophthalmologist and clinic coordinator are informed in writing within two working days, of a suspected change in the optic nerve and the need for a second photograph. A copy of the letter is sent to the Coordinating Center.

The masked reading of confirmatory photographs is conducted in an identical fashion to all other photographs, and are not identified as "confirmatory" photographs.

If the confirmatory photographs show change, the ODRC Coordinator will notify the Coordinating Center who in turn notifies the Endpoint Committee. The ODRC then prepares four copies of all the photos in the participant file; three copies for the Endpoint Committee members and one for the Coordinating Center file.

If the confirmatory photos do not show change, the PI, clinic coordinator, and the Coordinating Center are notified in writing. The participant is to continue the regular follow-up visit schedule.

15.3 Quality Control Procedures

On an annual basis, reading reports will consist of the number of stereo sets received, photographic time windows and the number of photo requests by the Clinical Center.

15.4 Communications to Clinical Center

Reports will be sent to clinical centers within two working days of eligibility declaration or suspicion of change detailing technical quality, eligibility, and for follow-up photographs, the occurrence of change. An annual report will be sent to Clinical Centers summarizing labeling errors, technical quality for photographs, turn around time from receipt by the ODRC to issuing a report.

15.4.1 Transmission of Data from ODRC to Coordinating Center

Data will be transmitted by E-mail or File Transfer Protocol (FTP).

Daily:

- eligibility/ineligibility
- reason for ineligibility
- suspected confirmation of progression
- request for confirmation photos
- confirmed endpoint

Weekly:

- Data logs including: participant ID, photographer ID, visit code, photo date, date of visit (1st QA or follow-up), and date photos received at ODRC.
- Participant data entry files.

Ad hoc basis:

- Any problem with clinic with regard to labeling, eligibility status, photo quality, retakes, timeliness of photos.

15.4.2 Data Entry

Personnel will be trained to do data entry and verification. They will enter data to computer files from paper forms which have been completed by the two ODRC readers. The data will be re-keyed by another person to ensure accurate entry. The date of entry and the certification number of the persons doing the entry and verification will be included in the data files.

15.4.3 Report Generation

The ODRC will produce reports for Steering Committee and Data and Safety Monitoring Committee meetings. These reports may include the following information:

- I. Summary of Reading Center Activity
 - 1. Certification

- a. Number of photographers certified by month and total.
- b. Number of photographers per site, equipment etc.
- 2. Number of units/participants:
 - a. logged in by month, total to date
 - b. under review
 - c. completed review
 - d. proportion of eligibility photos that are pre-study

(The balance of the report is based on units that have completed review)

- II. Technical Quality/Performance at Clinic
 - 1. Number and percentage (n,%) failing technical criteria for clarity & stereo and required re-photography?
 - 2. Tabulation according to clinic/photographer with regard to ranking of photos for clarity, stereo, percentage re-take required, and protocol violations.
- III. Technical Quality at Reading Center
 - 1. Intergrader Agreement
- IV. Eligibility Outcome
 - 1. Number and Percentage requiring adjudication? (n,%)
 - 2. Percentage of participants eligible photographically? ineligible?
 - 3. Breakdown reasons for ineligibility
- V. Timeliness
 - 1. Number of days from date of photos to receipt at reading center.
 - 2. Number of days from receipt at reading center to an eligibility declaration.
 - 3. Number of days from date of photos to transmission of data to Coordinating Center.

15.5 Transmission of Data from Coordinating Center to ODRC

- Method of transmission occurs by E-mail or File Transfer Protocol
- Valid participant ID numbers
- Follow-up visit schedule for each randomized participant
- Semiannual ODRC performance report to Data and Safety Monitoring Committee

15.6 Optic Disc Eligibility Criteria

- Intact disc rim (no areas of loss of rim to edge)
- Sufficiently clear media adequate for optic disc photography
- Absence of all the following conditions:
 - diffuse thinning of the rim
 - localized thinning of the rim
 - disc hemorrhage
 - notch in the rim
 - localized or diffuse pallor
 - disc drusen
 - congenital pit
 - optic nerve coloboma
 - evidence of non-glaucomatous atrophy
 - other conditions that might lead to a confounding non-glaucomatous visual field defect
 - cup/disc asymmetry between both eyes greater than .2 disc diameter.

15.7 Optic Disc Eligibility Ascertainment

Eligibility is determined:

- by an OHTS certified ophthalmologist during Qualifying Assessment and;
- by Optic Disc Reading Center (ODRC) evaluation of stereo optic disc photographs

15.8 When to take Optic Disc Photographs

• QA: Pre-Study:

Stereo optic disc photographs taken within 12 weeks of the first Qualifying Assessment Visit (Pre-Study photos) and in compliance with OHTS protocol may be used for eligibility. Photographs must be mailed to the ODRC within 2 weeks of the first Qualifying Assessment visit.

• QA:

Optic disc photographs taken within the 12 weeks allotted for the Qualifying Assessment visit. Photos must be mailed to the ODRC within 2 weeks of the date of the photographs.

• Follow-up:

12 month intervals following randomization, (12, 24-, 36-, 48-, 60- months, etc.) Photographs must be mailed to the ODRC within 2 weeks of the date of the photos.

• Retakes:

When technical quality is poor, "retakes" may be requested by the ODRC. Repeat photos must be taken within 28 days of the ODRC request and must be mailed to the ODRC within 2 weeks of the date of the photographs. Retakes completed 3 weeks after the end of the QA window will not be evaluated for eligibility. A protocol violation will be issued.

• Confirmation of Progression:

To confirm progressive optic nerve damage, confirming photos will be requested by ODRC. Confirming photos must be taken within 28 days of the ODRC request and must be mailed to the ODRC within 2 weeks of the date of the photographs.

• Fundus Red Reflex Photograph:

A red reflex photograph of each eye to document the presence of either lens or corneal opacities is to be taken of both eyes at every visit. Pull the fundus camera back away from the participant, centering the iris, with the focusing knob at the maximum plus position. If necessary, the joystick or the focusing knob may be used at this point to ensure that the focus is crisp. An exposure is made at the same camera power setting used for fundus photographs. The iris should fill a 30° field.

• Macula Photos:

A single photograph of the macula area (the camera should be at its lowest magnification) is to be taken of each participant yearly, when photos are required. Center the macula at the intersection of the cross hairs in the ocular. In practice, to keep the central gray artifact created by some cameras from obscuring the center of the macula, the intersection of the cross hairs may be placed approximately 1/8 - 1/4DD nasal of the center of macula.

• Unscheduled Photos:

At the PI's discretion, a participant may have an extra set of photos taken in a year in addition to the mandated set taken at the annual visit.

All photos taken of a participant for OHTS or non-OHTS visits (excluding fluorescien angiograms) must be mailed to the ODRC for review and/or filing. Should the participant ever be determined to show progression, then all the photos in the participant's file will be forwarded to the Endpoint Committee.

15.8.1 Who must be certified for Photography

Stereoscopic optic disc photographs must be taken by certified OHTS photographers. Participating Clinical Centers are not permitted to initiate Qualifying Assessment visits until the photographer is certified for optic disc photography. Photographs used for photographer certification may not be used for official participant study visits.

15.8.2 Certification for Photography

- Clinic Coordinator notifies ODRC Coordinator that a photographer needs certification.
- Photographer completes two full stereo sets, both right and left eyes, of two participants (16 slides all together), (See Appendix A, Figure 2) completes the photography checklist, labels slides and sends them to ODRC. Once received by the ODRC, the slides become official study property and cannot be returned to the clinic.
- Model and serial number of fundus camera designated for OHTS is reported to the ODRC.
- ODRC Photographer Consultant determines if photography checklist, labeling and technical quality of photographs are adequate and notifies the Coordinating Center of the photographer's name, initials, clinic, and date of certification.
- ODRC Photographer Consultant contacts the photographer and notifies him/her of certification. If the photographs are acceptable, the photographer is asked for his/her initials to be used as certification code number (see section 15.8.4 below). If the photographs are not acceptable, the reason is discussed with the photographer and additional sets of photos are requested. The review process continues until the photographs are accepted and the photographer is certified.
- ODRC contacts the Coordinating Center with the new photographer certification information including photographer initials.

15.8.3 Certification Code

Certification code consists of a two digit site code and a three character name code, the first, middle and last initial; for example site code = 99, name, John A. Doe, certification would be 99-JAD.

15.8.4 Staying Certified as OHTS Photographer

- Once certified, a photographer remains certified if performance, and the quality of the disc photographs, is judged acceptable by the ophthalmology photographer consultant at the ODRC.
- Certification may be rescinded if the ODRC determines that the photographer's performance is unacceptable.

15.8.5 OHTS Cameras & Procedures

- Each study center will designate one camera for OHTS. Acceptable fundus cameras include Zeiss, Topcon, Nidek, Nikon, and Kowa.
- Those using a Zeiss fundus camera should use a 2X or 1.6X magnification lens.
- For all other fundus cameras, the highest magnification available should be used.
- Report make, model and serial number of OHTS camera to ODRC.
- Only the camera designated for OHTS should be used throughout the study.

If a replacement camera is required because the original camera cannot be repaired, the ODRC must be notified <u>in writing **prior**</u> to the changes in the camera (whenever possible) advising the reason for the change in addition to the replacement camera's make, model, and serial number.

If a camera is being replaced for better quality but the original camera is useable, the original camera should be kept for participants already randomized into the study for use on follow-up visits.

Whenever possible, the original camera should be kept until all participants entered into the study with that camera have had the next annual visit requiring photos. At that visit, participants should be photographed both with the original and the replacement cameras. If the photos taken with the replacement camera are of acceptable quality and the photos show no change from the QA visit then the new photos will become the baseline photos to which all future follow-up photos will be compared. If the replacement camera is a different make from the original camera, all study photographers must be certified on the new camera following the procedures set in section 15.8.2.

Once certified, photographers may begin using the new camera to photograph participants beginning the qualifying assessment process. This will then be the participant's camera for the remainder of the Study.

15.9 Optic Disc Photography Protocol

15.9.1 Determine Eyepiece Setting

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

15.9.2 Film

All photographs must be taken on Ektachrome or Fujichrome 100. Use one roll of film (24 exposure) per study participant. Take at least four (4) stereo pairs of each eye in order to ensure the required two (2) good stereo pairs for each eye.

15.9.3 Dilation

Pupils should be dilated prior to photography. Participants should be instructed to remain with eyes closed at least 20 - 30 minutes prior to photography to ensure best possible medium through which to photograph.

15.9.4 Photography Instruction

- 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. Describe the procedure to the participant.

- If a Zeiss fundus camera is used, set the 2X or 1.6X magnification lens, or set the highest magnification for any other camera used.
- 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.
- At the first exposure, photograph the participant ID.
- The ODRC strongly recommends that the clinical center photographer maintain a photography logbook for study participants. Suggested notes for each participant may include pupil size, flash setting and comments on participants photophobia status, and media clarity.
- Photograph the right eye first, then the left.
- Instruct the participant to follow the fixation light until the optic nerve is centered on the cross-hairs.
- Tilt the joystick right to the 3 o'clock position just outside the pupillary crescent and take the first right stereo photograph, focusing at the junction of the RPE and the rim. After taking this photograph, tilt the joystick left to the 9 o'clock position outside the pupillary crescent, focusing at the junction of the RPE and the rim.
- Repeat this technique to obtain two good stereo pairs of the right eye.
- Use this technique to obtain two stereo pairs of the left eye.
- When a Nidek or Topcon simultaneous stereo cameris is used set at the highest magnification available.
- Set the appropriate flash settings, and use the same settings, which give the best results each time the participant is photographed.
- Positioning the participant's head in the chin-rest, focusing on the participant's eye and pressing the shutter completes stereo fundus photography. It is possible to position the optic disc accurately by having the participant monitor the internal red LED directly.
- For clinical center records, additional photographs must be taken. When the slides are returned from developing, the photographer selects the best stereo combination of each eye for submission to the ODRC (two stereo sets per eye).

15.9.5 Developing Film

Send film for processing within two working days from exposure. It is advisable for clinics to develop film after participant visit. Waiting until the end of a roll could cause the clinic to miss the two-week submission deadline.

15.9.6 Labeling Slides

Follow labeling instructions (see Appendix). Cardboard slide mounts are preferable to plastic slide mounts. If plastic slide mounts are used, use a permanent ink black pen (e.g. Pilot extra fine point permanent marker) for labeling slides.

15.9.7 Mailing Slides to ODRC

- All study slides must be mailed within 2 weeks of the date taken.
- Place slides in side-loading $8 \frac{1}{2} \times 11^{"}$ clear plastic sheets. Do not use frosted sheets.
- Place right eye stereo pair on left side of sheet and left stereo pair on right side of sheet (See Appendix).
- Mail slides to ODRC Coordinator with the Photography Checklist to the following address:

OHTS Optic Disc Reading Center McKnight Vision Research Center 1638 N.W. 10th Avenue Fifth Floor Miami, FL 33136 Appendix

Summary of Revisions

Chapter 16 - Visual Field Reading Center

Section	Date	Description
16.3.1 VF Shipments	10/28/94	All abnormal or unreliable follow-up fields, as well as the corresponding retests, must be faxed as well as mailed to the VFRC.
<u>16.3.4 VF Eligibility</u>	9/22/95	An individual who is ineligible because of abnormal fields is permanently ineligible for the study. However, if an individual is ineligible because of unreliable fields, the clinical center may test the individual again for eligibility after a twelve-week wait. Also documented in OHTS Memorandum #4.
<u>16.3.5 VF Endpoint</u>	9/1/95	If the P.I. at a clinical center believes a follow-up field is abnormal simply because the participant performed poorly on the test, the participant may be retested the same day rather than between two and six weeks later; however, if the second test on the same day is also abnormal, a confirming VF must be done two to six weeks later.
	11/1/97	Before a visual field abnormality is considered as a potential endpoint, it must appear on three consecutive visual fields in the same location for the same eye.

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16.1 Organization

The Visual Field Reading Center (VFRC) is a unit of the Department of Ophthalmology in the School of Medicine at the University of California, Davis. It is located at the UC Davis Medical Center at 4860 Y Street, Suite 2400, Sacramento, California. The staff of the VFRC consists of the following personnel: a Director, an Associate Director, a Coordinator, two Assistants to the Coordinator, a part-time Computer Programmer, and a part-time Visual Field Technician.

16.1.1 Personnel

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16.1.2 Responsibilities of VFRC Personnel

John L. Keltner, M.D., serves as the Principal Investigator and Director of the VFRC. He is responsible for overseeing all aspects of the research, which include the following: (a) guiding the development of the VFRC for the OHTS, (b) ensuring that the data received by the VFRC are handled in the appropriate manner, (c) ensuring that data processing is carried out according to schedule, (d) submitting reports on visual field issues, (e) setting up the protocol for visual field technician training and certification procedures, (f) determining the eligibility of individuals from the initial visual fields, and (g) determining when visual field change signifying glaucomatous damage has occurred.

<u>Chris A. Johnson, Ph.D.</u>, serves as Co-investigator and Associate Director of the Visual Field Reading Center. He is responsible for: (a) assisting with the development of the VFRC for the OHTS, (b) guiding the development of the computer programs used by the VFRC, (c) monitoring the quality of the visual field information, (d) helping to provide direction for technician training and certification, (e) determining the eligibility of individuals from the initial visual fields, and (f) determining when visual field change signifying glaucomatous damage has occurred.

<u>Kimberly E. Cello</u> serves as the Coordinator of the Visual Field Reading Center. She is responsible for: (a) communicating with the other centers involved in the study, (b) ensuring that VFRC quality control procedures are being carried out properly, (c) ensuring that the visual field data are being processed appropriately and forwarded in a timely manner to the OHTS Coordinating Center, (d) reviewing the qualifying assessment and follow-up visual fields, (e) developing a visual field database for the study, (f) performing visual field data analyses, (g) preparing reports on visual field issues, (h) contributing to the development of manuscripts, (i) preparing manuscripts for publication and, (j) supervising the work of the VFRC Assistants.

<u>Shannan Bandermann</u> serves as an Assistant to the VFRC. She is responsible for the daily activities in the center. Her responsibilities are: (a) receiving and processing of visual field data, (b) tracking and updating the VFRC abnormality/unreliability log, (c) monitors abnormality and unreliability faxes for the 3 clinical sites, and (d) certifying the visual field technicians of each clinical center. She has officially been certified as a VFRC Reader and Personnel.

<u>Mary Edwards</u> serves as an Assistant to the VFRC. She is mainly responsible for assisting in manuscript writing and preparation. She also contributes to the daily activities at the center: (a) receiving and processing of visual field data, (b) tracking and updating the VFRC abnormality/unreliability log, and (c) monitors abnormality and unreliability faxes for the 3 clinical sites. She has officially been certified as VFRC personnel.

<u>Marilyn Sponzo, Visual Field Technician,</u> the VFRC Visual Field Technician, is responsible for retrieving requested visual field data from participants who have reached reproducible Optic Disc progression and sending the data to the OHTS Coordinating Center.

Bhupinder S. Dhillon, the Computer Programmer, is responsible for: (a) programming the VFRC computers so that reports are produced for the Coordinating Center which indicate the status of the visual fields the VFRC has received, (b) revising the HUMPHREY.COM computer program (see section 16.3.3.2) for the OHTS so that the Humphrey data records are written to a data file in the appropriate format for analysis, and (c) providing programming support on an ongoing basis to assist in the processing and analysis of the visual field data.

16.2 VFRC Objectives

The objectives of the VFRC with respect to the OHTS are:

- (1) to establish standard test conditions for the performance of automated, static Humphrey visual fields, including coordinating the development and distribution to the clinical centers of the Humphrey chip sets modified for the OHTS;
- (2) to determine the eligibility of individuals who are candidates for entry into the study based on the normality and reliability of their Humphrey visual fields (see section 16.3.4);

- (3) to perform the following quality control functions (section 16.4):
 - (a) establishing visual field reliability criteria for the clinical centers,
 - (b) reporting on the adherence to the OHTS protocol in the performance of visual fields,
 - (c) reporting on the turnaround time for transmission of fields and data from clinical centers to VFRC to Coordinating Center,
 - (d) maintaining an internal quality control system,
 - (e) responding to an external quality control system,
 - (f) maintaining perimetry certification at the clinical centers with the assistance of VFRC visual field technicians;
- (4) to process all visual field data from the Humphrey tests performed on OHTS participants using the VFRC computers, to convert the visual field data into the appropriate format, and to transmit the resulting data files to the Coordinating Center;
- (5) to determine if there has been deterioration in the visual fields of the participants, which is one of the primary criterion for assessing the onset of glaucomatous damage in the OHTS (see section 16.3.5);
- (6) to provide training and certification of technicians who will be performing the Humphrey visual field examinations for the OHTS (see section 16.5);
- (7) to store and archive all visual field information associated with the OHTS (see section 16.6).

16.3 VFRC Daily Operations and Procedures

The VFRC will receive all of the visual fields from the OHTS clinical centers, process the data, and prepare the data files for the Coordinating Center in a form suitable for analysis. There will be over 40,000 Humphrey visual fields processed over the span of the study from the 1,636 participants entered into the study as well as roughly an additional 7,256 Humphrey fields performed on ineligible individuals.

16.3.1 Visual Field Shipments from the Clinical Centers

Although the OHTS clinical centers will send all of their visual fields to the VFRC by regular mail (see below), they must also fax to the VFRC <u>all</u> visual fields from qualifying assessment visits <u>immediately</u> after each testing session to allow for a timely determination of an individual's eligibility for the OHTS (see section 16.3.4). If the clinical center wishes to use prestudy visual fields as the first set, these fields should be faxed along with the first set of fields performed at the clinical center. The VFRC will notify the clinical center of its decision regarding the eligibility status of these fields within one working day, when possible. In addition, all abnormal or unreliable follow-up fields, as well as the required retests for these fields, must also be immediately faxed to the VFRC.

Each clinical center should send its OHTS visual fields by regular mail to the VFRC by the end of the week (i.e., Friday) in which they were performed. The visual fields must be packaged according to the instructions in the *OHTS Perimetry Protocol*. The clinical center should include in the shipment all visual fields for that week, including fields that are obviously abnormal or unreliable, unless it has already been determined that the individual is ineligible for the study. The clinical center must keep copies of everything in the shipment. A shipment should include:

- (1) one Humphrey disk containing all of the visual field files for that week (the clinical center must save or copy the visual field data files onto a total of three disks and keep two),
- (2) a Humphrey disk directory listing the visual field files on the disk,
- (3) a printout of each visual field on the disk (the printouts should correspond exactly to the fields listed on the disk directory, and they should be checked off on the directory).

16.3.2 Filing, Back-up, and Review Systems

The VFRC performs the following procedures, and the completion of each procedure is tracked by the VFRC:

- (1) VFRC staff inspects each shipment of visual fields received. If there are any problems, the clinical center is contacted.
- (2) Copies of the original Humphrey disk files are made for back-up purposes, and copies of the visual field data are stored in the VFRC office as well as in Davis, twenty miles away, to ensure the safety of the data.
- (3) Quality Control Reports are produced for each visual field received (see section 16.3.3.5). Copies of these reports are then sent to the clinical centers as feedback regarding the performance of the technician in following the OHTS visual field protocol. A computer program, HUMPHREY.COM, which was modified for the OHTS, is used to expedite this process because of the large volume of fields received. The materials are reviewed for the following:
 - (a) accuracy and completeness of information
 - (b) adherence to study protocol

- (c) proper packaging for shipment to the VFRC
- (4) All qualifying assessment visual fields are reviewed by the VFRC staff, and all questionable qualifying assessment fields are reviewed by the Director and/or Associate Director of the VFRC (see section 16.3.4). The Director and Associate Director also review all follow-up visual fields that may show a conversion indicating possible glaucomatous damage (see section 16.3.5). They record their comments regarding the fields on OHTS Visual Field Review Sheets. These observations form the basis for discussions at the VFRC and with other study centers regarding the fields, and they serve as a record of the reviewers evaluations.

16.3.3 Management of Humphrey Field Data

The procedures involved in handling the data from the Humphrey fields are described below.

16.3.3.1 Humphrey Field Data Files

The fields recorded by the Humphrey Field Analyzer are stored on double-sided, doubledensity, $5^{1/4}$ " floppy disks in a specialized format derived by Humphrey Instruments. The data files are not compatible with any database software packages. It is therefore necessary to convert the data files on the Humphrey disks into a format which can be imported into database programs.

16.3.3.2 Conversion of the Humphrey Disk Format

The data conversion software program called HUMPHREY.COM was developed for transferring data from the Humphrey Field Analyzer format to a DOS-compatible text file that can be imported into commercially available software packages. At the present time, this program is being successfully used by individuals at approximately 30 eye centers throughout the world. HUMPHREY.COM has been revised for use in the OHTS.

The following steps are followed in the management of the Humphrey field data:

(1) The OHTS HUMPHREY.COM program performs an automatic inspection of all fields to see that all test parameters have been followed, that participant data have been entered in the proper format, that all information is within the proper range of options for the various fields of participant data or visual field data, and that there are no erroneous or corrupted pieces of data contained in the Humphrey data file. Data records that contain improper, suspect, or missing data are noted and

this information is included in the quality control evaluation (see section 16.3.3.5).

- (2) A Humphrey data file is automatically converted by the OHTS HUMPHREY.COM program into a DIF (data interchange format) text file. Participant information that is not needed for the OHTS is deleted.
- (3) In a multiple-step procedure, the DIF file is translated into the comma-delimited text format in which it is transmitted to the Coordinating Center. During this process, the visual field data records are double-checked for accuracy.

16.3.3.3 Handling of Missing or "Not Tested" Data

When a Humphrey test is not performed, this is considered missing data. The Coordinating Center will provide a regular report to the VFRC containing information on the most recent visit for each study participant.

16.3.3.4 Conversion of Data into a Format for Analysis

The Humphrey visual field results include a total of 76 threshold values. It is not practical to evaluate the 76 values separately; therefore, summary data are produced which reduce the amount of information to a more manageable form for analysis.

The <u>global indices</u> are the summary statistics on the Humphrey test data provided by STATPAC 2, a validated software package developed by taking the data from the visual field tests on a large number of normals. They include the mean deviation, pattern standard deviation, short-term fluctuation, corrected pattern standard deviation, and the glaucoma hemifield test. Definitions for these indices are given below:

- (1) <u>Mean Deviation (MD)</u> is the mean elevation or depression in a participant's overall field compared to a normal reference field. If the deviation is significantly outside population norms, a *p* value is given. A significant mean deviation may indicate that the participant has an overall depression and/or that there is a loss in one part of the field and not in another.
- (2) <u>Pattern Standard Deviation (PSD)</u> is a measurement of the degree to which the shape of the participant's measured field departs from the normal, age-corrected reference visual field. A low pattern standard deviation indicates an irregular "hill of vision" and may be due to either variability in participant response or actual visual field irregularities. The statistical significance for the pattern standard deviation is indicated with a *p* value as it is for the mean deviation.

- (3) <u>Short-term Fluctuation (SF)</u> is an index of the consistency of the participant's answers during the test and is obtained by testing twice at ten preselected points.
- (4) <u>Corrected Pattern Standard Deviation (CPSD)</u> refers to the measure of how much the total shape of the participant's hill of vision deviates from the shape of the normal hill of vision for the participant's age, corrected for intra-test variability. The hill of vision may be irregular in shape because of unreliable participant responses, actual field loss, or a combination of the two factors. In calculating the corrected pattern standard deviation, STATPAC 2 attempts to remove the effects of participant variability and to present only the irregularity caused by actual field loss. Corrected pattern standard deviation, therefore, depends on both the pattern standard deviation and the short-term fluctuation.
- (5) <u>Glaucoma Hemifield Test (GHT)</u>, a new index introduced with STATPAC 2, gives a measure of the evidence in a single Humphrey 30-2 Visual Field of a pattern of glaucomatous field loss. This test evaluates five zones in the superior visual field and compares these zones to their counterparts in the lower visual field (see Figure 1). Using information about normal performance at each point in the visual field, STATPAC 2 evaluates the severity of deficit at each point within these zones and prints out one of three messages: WITHIN NORMAL LIMITS, OUTSIDE NORMAL LIMITS, or BORDERLINE. The probability of a visual field from a normal subject falling in the borderline category is 3%; the probability of being outside normal limits is 1%. This test has been developed to reveal a particular pattern of localized visual field loss; however, if a field shows a significant reduction or increase in general sensitivity (at levels shown in fewer than 0.5% of the normal population), an additional message to this effect is printed.

16.3.3.5 Visual Field Quality Control Data

The reliability of the Humphrey visual fields is assessed in several ways. This information is included in each data record sent to the Coordinating Center.

- (1) The <u>reliability indices</u> are automatically produced on the printout of the test on the Humphrey Field Analyzer as indicators of the reliability of the test. Unreliable tests must be repeated in an attempt to obtain reliable test results (see the *Perimetry Protocol*). For the OHTS, STATPAC 2 will place the "xx" indicating unreliability by any of these indices when there are 33% or more occurrences. These indices include the following:
 - (a) <u>Fixation losses</u>. A light is periodically presented in the physiologic blind spot, and the number of times the participant responds as seeing the stimulus is recorded.

- (b) <u>False positive errors</u>. The noise associated with the stimulus presentation is produced without a light being presented, and the number of times the participant responds is recorded.
- (c) <u>False negative errors</u>. A suprathreshold stimulus is presented in a location for which the threshold has been previously determined, and the number of times the participant does not respond as seeing the light is recorded.
- (2) <u>Quality Control Reports</u> will be produced by the OHTS HUMPHREY.COM program. These reports will be sent to the clinical centers regularly as feedback about their performance. The test data are examined for the following:
 - (a) use of Humphrey program 30-2
 - (b) use of the STATPAC 2 program
 - (c) use of the central fixation target
 - (d) use of target size III
 - (e) use of blind spot check size III, II, or I
 - (f) use of the short-term fluctuation test
 - (g) use of the foveal threshold test
 - (h) verification of pupil diameter of 3 mm or larger
 - (i) inclusion of visual acuity
 - (j) appropriateness of the central lens correction
 - (k) correctness of the participant data
 - (1) threshold values of 42 dB or greater for any of the 76 points tested (No threshold value should be as large as 42 dB. Therefore, the presence of such a threshold indicates an inappropriate participant response.)
 - (m) in addition, it records the actual ratios for fixation losses, false positives, and false negatives

16.3.3.6 Data File Transfers to the Coordinating Center

On a monthly basis, the VFRC will send its visual field data files in comma-delimited text format to the Coordinating Center via FTP (File Transfer Protocol). In every shipment but the first, the VFRC will send: (1) the data from the preceding calendar quarter and (2) summary data (specifically, the means for two numeric fields) for the entire visual field database up to that point. The summary data will serve as a check of the VFRC's database against the Coordinating Center's corresponding database.

16.3.4 Visual Field Eligibility

An individual is considered eligible for the study from the standpoint of visual fields if, for each eye, two visual fields out of a maximum of three performed within a three-month period (pre-study fields have more latitude -- see below) and according to OHTS protocol are within

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normal limits for the global indices (p < 5% will be considered abnormal), the glaucoma hemifield test (see section 16.3.3.4), and the reliability indices (see section 16.3.3.5). In addition, the fields must be considered normal by the VFRC.

The P.I. at a clinical center may elect to have an individual retested the same day if he or she wishes. One or both eyes may be retested; however, if the decision is made to retest on the same day, there must be at least an hour break between test sessions.

In addition, the first set of visual fields may be ones that were performed at a regular clinical (i.e., pre-study) visit the individual has had, as long as the fields were performed according to the OHTS protocol and were performed no more than three months prior to the first qualifying assessment visit (thus, in this case alone, three eligibility fields may be from a period greater than three months). In such cases, the clinical center coordinator must complete a brief Pre-Study Visual Field Data Form for each field. The information on it should be used in editing the visual field data for OHTS purposes, and then it must be attached to the field when it is sent to the VFRC (see the *Perimetry Protocol*).

If an individual is ineligible for OHTS because of abnormal visual fields, the participant is permanently ineligible for the study. However, if an individual is ineligible because of unreliable visual fields, the clinical center may elect to begin the qualifying assessment process over again with the individual after a period of twelve weeks has passed.

The VFRC will report its decision regarding an individual's eligibility for the OHTS to both the clinical center and the Coordinating Center by fax.

16.3.5 Visual Field POAG Endpoint

An eye is considered to have reached a visual field POAG endpoint if the visual fields indicate the development of either glaucomatous field damage or a non-glaucomatous abnormality that would obscure the possible subsequent development of glaucomatous field damage. To meet the basic visual field POAG endpoint criteria, the eye must have either a glaucoma hemifield test (GHT) result of Outside Normal Limits or General Reduction of Sensitivity or a corrected pattern standard deviation (CPSD) with a *p* value <5%, and these results must be reproducible. Specifically, before a visual field is considered as a potential endpoint, it must appear on three consecutive visual fields in the same location and the same index for the same eye.

The first two of these abnormal visual fields should be two consecutive regular follow-up fields. If they both show abnormalities in the same location that involve the same index(es), the GHT and/or CPSD, an additional field should be performed to confirm the abnormality. Effective January 2000: For participants already at POAG endpoint in one or both eyes, the visual fields and/or optic disc photos completed at regularly scheduled follow-up visit will be used to confirm subsequent abnormalities. Expedited confirmation visits will not be required to confirm subsequent abnormalities for these subjects. This confirmation field should be
performed from one day to eight weeks after the last test. If, once again, there is an abnormality in the same location that involves the same index(es), the participant's fields will be independently reviewed by the VFRC Director and Associate Director. They must concur that, from a clinical standpoint, the visual field loss is not artifactual and that it has recurred in the same location on all three fields.

If the VFRC Director and Associate Director confirm the development of a visual field abnormality, the participant's visual fields are sent to the OHTS Coordinating Center for review by the Endpoint Committee. The Endpoint Committee decides if the visual field loss is glaucomatous or non-glaucomatous. If they decide it is glaucomatous, then the eye is considered to have reached a visual field POAG endpoint. If they decide it is non-glaucomatous, then they must also decide, based on the severity of the abnormality, if the eye has reached a visual field POAG endpoint or not. If the visual field loss would obscure the possible subsequent development of glaucomatous field damage, then the eye is considered to have reached a visual field POAG endpoint. Regular follow-up fields will continue to be performed every six months on all eyes, except for the most severe cases of visual field loss, regardless of endpoint status. However, additional confirmation fields will not be performed for any reason on eyes after they have reached a visual field POAG endpoint.

On fields showing relatively minor non-glaucomatous abnormalities, the possible subsequent development of glaucomatous field damage might still be observable. If the Endpoint Committee decides this is the case, the eye is considered not to have reached a visual field POAG endpoint, and it is "thrown back in the pool" with the normal eyes. However, because of the abnormal GHT and/or CPSD on these fields, a request for a confirmation field by the VFRC is now based on whether, in the judgment of the VFRC, the visual field has worsened and a "new" abnormality has developed in an area of the visual field that was previously normal. This abnormality would have to be confirmed in the prescribed manner, i.e., with three consecutive visual fields showing the same "new" abnormality.

16.3.6 Additional Visual Field Data Considerations

Follow-up visual fields must be repeated when they are unreliable as well as when they are abnormal. In contrast to the retesting of abnormal eyes, an unreliable field may be repeated as soon as one hour after the last test (or as much as eight weeks later) if the clinical center elects to do so. The test should be repeated only once regardless of the result. If the visual field is again unreliable, no action is taken, and the participant will simply be tested again at the next regularly scheduled visit. When a follow-up visual field test is repeated because the first test was either unreliable or abnormal, the data from only one of the tests will be considered the "official" data for that visit, although the data from the "unofficial" test will also be kept. The table below shows which test will be considered official in various circumstances (N = normal, A = abnormal, R = reliable, and U = unreliable):

Status of 1st VF

Status of Retest

Decision

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NU	NR	Use Retest
NU	NU	Adjudicate
NU	AR or AU	Use 1st VF*
AR or AU	NR	Use Retest
AR or AU	NU	Adjudicate
AR or AU	AU	Adjudicate
AR	AR	Adjudicate
AU	AR	Adjudicate

*Although the retest is abnormal in this case (following a normal first test), the eye will not be retested again for the following reasons: (1) it is our position that, in the first test, the reliability indices are less important than the finding that the field is normal; (2) the only purpose of the retest is to try to obtain a reliable field so the data are as accurate as possible, not to double-check whether the field is truly normal, and we wish to avoid a test-retest spiral; and (3) the sixmonth wait until the next regularly scheduled test is short enough to protect the participant's safety, even if the visual field has started to convert.

16.4 Quality Control Functions

The VFRC is responsible for a series of quality control functions which are described below.

16.4.1 Visual Field Quality Control

The guidelines established to assess the quality of the Humphrey fields performed at the clinical centers are described in section 16.3.3.5. Visual Field Quality Control Reports will be produced by the OHTS HUMPHREY.COM program for all visual fields received (see section 16.3.3.5). Copies of these reports will be sent to the clinical centers on a regular basis to provide feedback regarding their performing and handling of visual fields. A summary of the quality control results will be distributed on a regular basis to the VFRC Director and Associate Director, the Coordinating Center, and the respective clinical centers for their review and information.

16.4.2 Turnaround Time Reporting System

Information on the turnaround time of the visual field data are included in the files transmitted to the Coordinating Center. Specifically, there is information regarding the following: the test date, the date of processing by the VFRC, and the date the files were sent to the Coordinating Center.

16.4.3 Internal Quality Control System

Controls have been established at the VFRC to ensure that high standards are maintained in processing data. Review systems are in place so that an absolute minimum number of errors are allowed in the completed data files. To automate these controls as much as possible, several checks are built into the computer programs used in processing the visual field data.

The following internal quality control checks are performed on a regular basis:

- (1) The OHTS HUMPHREY.COM program provides several automatic checks on the quality of the data (see section 16.3.3.5). Messages are produced on the computer screen and printed out which alert the operator to data problems.
- (2) The VFRC Coordinator reviews the quality control information obtained from the OHTS HUMPHREY.COM program and prepares periodic summaries of the information for the Director and Associate Director of the VFRC. This provides an opportunity to double-check the visual field evaluation performed by the OHTS HUMPHREY.COM program.
- (3) After the processing of each data file, the information is double-checked before it is translated into the format for the Coordinating Center (see section 16.3.3.2).

16.4.4 External Quality Control System

To check the reliability of the VFRC, the Coordinating Center will arrange to have 10% of the total number of visual fields sent to the VFRC twice. Thus, 10% of the Humphrey fields will be processed twice by the VFRC in a masked fashion. These results will be analyzed by the Coordinating Center to assess the reliability of the VFRC. There will be a tolerance limit of 95% accuracy for the processing of the fields; however, the causes for any discrepancies will be determined.

16.4.5 Certification of Visual Field Technicians

The VFRC will conduct perimetry certification of the OHTS visual field technicians by telephone and mail (see section 16.5). Each clinical center must have at least two technicians certified for OHTS visual field testing before it is allowed to enroll individuals in the study, and any technicians joining the study after it is in progress must also be certified.

The certification process will serve to promote a high level of competency among the OHTS visual field technicians for following the OHTS perimetry protocol. In addition, when site visits of the OHTS clinical centers are carried out, the visual field technicians will be

checked for their understanding of the protocol. The VFRC will assist in this process by reviewing the fields performed for this certification check.

16.5 Training and Certification of Technicians

All technicians performing visual field testing must be certified for automated static perimetry using the Humphrey Field Analyzer program 30-2. For instruction in OHTS perimetry, each clinical center is provided with the *OHTS Perimetry Protocol* and the *OHTS Perimetry Procedures* videotape as well as this MOP chapter. These materials describe the test procedures and data recording methods used in the OHTS. The Principal Investigator at each clinical center is responsible for ensuring that the appropriate personnel are competent in the OHTS perimetry protocol.

16.5.1 Training on the Humphrey Field Analyzer

All clinical center technicians must study the materials provided by the VFRC that describe the visual field protocol. Visual field testing should be practiced according to OHTS protocol before an appointment is requested for a telephone certification session with the VFRC. Prior to testing for certification, technicians should be familiar with or experienced in the following:

- (1) routine maintenance and repair procedures for the Humphrey Field Analyzer, including changing light sources, cleaning disk drives and other key components, formatting new disks, and performing other related tasks;
- (2) the methods for giving instructions to the participant, selecting an appropriate lens correction, occluding the nontested eye, aligning the participant to the perimeter, and making any other preparations for the visual field testing;
- (3) the entry of participant data according to protocol;
- (4) the criteria for pausing during a test due to participant fatigue, misalignment, or the necessity of providing additional instructions to the participant;
- (5) the methods for storing data, determining that all relevant information has been obtained, and verifying that the test conditions required by the protocol have been provided;
- (6) the procedures for making back-up copies of Humphrey disks, storing disks properly, and sending the materials to the VFRC.

16.5.2 Certification Procedures

In a telephone session with a VFRC visual field technician, each candidate for certification must demonstrate a complete understanding of the proper techniques for OHTS visual field testing. Subsequently, the technician will need to perform visual fields according to the OHTS protocol on both eyes of two participants and submit them to the VFRC (see the *Perimetry Protocol*). If these fields are satisfactory, the technician will be certified for OHTS visual field testing.

The technician must satisfactorily demonstrate the following:

- (1) calibration of the Humphrey perimeter and formatting of a floppy disk;
- (2) adjustment of comfort features for the participant, such as the chin rest and chair;
- (3) calculation of the proper lens power from the distance Rx;
- (4) adjustment of the lens to minimize lens rim artifact;
- (5) adjustment of the fixation monitor and resetting of the fixation monitor later during the test;
- (6) entering of the participant data;
- (7) running of the Demo program and Program 30-2;
- (8) sensitivity to participant fatigue -- allowing the participant to rest during the test;
- (9) running of the STATPAC 2 program and printing of the data;
- (10) making of back-up disks.

All certified technicians will need to maintain their certification by performing visual field tests according to OHTS protocol on a regular basis. Certification will lapse for any technician who does not perform an OHTS visual field for a period of six months. If a technician's certification lapses, he or she will need to submit to the VFRC one practice field performed according to OHTS protocol along with a memo attesting that he or she has re-read the *Perimetry Protocol*.

16.6 Archival Function of the VFRC

The VFRC is responsible for storing the visual field information generated by the OHTS. The original visual field printouts are kept in filing cabinets located in the VFRC office. The files are kept in order by participant ID. All data processed by the VFRC are stored on the hard

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disk of the VFRC computer with back-up files on removable cartridges. A copy of all the visual field data is stored twenty miles away in Davis. Only VFRC personnel have access to the OHTS files. Thus, the VFRC manages a growing database of visual field information and will maintain the database for the duration of the OHTS. Effective 6/00, the VFRC has implemented an additional backup system of converting the 5.25 inch disks to 3.5 inch disks due to the discontinuation of the HFA I perimeters.

Superior field zones used in the glaucoma hemifield test (GHT)



These zones are compared with their "mirror images" in the inferior field to obtain the GHT

result

VISUAL FIELD READING CENTER

PERIMETRY PROTOCOL for the OCULAR HYPERTENSION TREATMENT STUDY

March, 1999

Department of Ophthalmology

School of Medicine

University of California, Davis

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Visual Field Reading Center PERIMETRY PROTOCOL for the OCULAR HYPERTENSION TREATMENT STUDY

I. INTRODUCTION

In ocular hypertension, changes in the visual field can take place which indicate possible glaucomatous damage. Often these changes affect some parts of the visual field while other parts remain relatively unaffected. Visual field changes will be a major factor in assessing whether a difference in outcome develops between the two treatment groups in the Ocular Hypertension Treatment Study (OHTS). Since the difference between the two groups may not be large, small changes in the visual field may be quite important. To analyze the participants' visual fields, automated static perimetry will be employed using the Humphrey Field Analyzer.

Participant Visit Timetable

The visual field testing will consist of Humphrey tests of the central 30° field of both eyes. These tests will be performed at two or three eligibility testing sessions, depending on the results of the tests at the first two sessions, and they will be performed at six-month intervals thereafter for the duration of the study.

II. VISUAL FIELD TEST PROCEDURES

General Test Guidelines

Reduce the lighting in the room to a moderate level or the Humphrey will display a message that it cannot adapt to the background luminance. Perform the visual field test on each eye of a participant using threshold program 30-2 of the Humphrey Field Analyzer, and test the participant's right eye first. Use the following test parameters:

Threshold strategy	Full threshold
Fixation target	Central
 Blind spot check size 	III
Stimulus size	III
Stimulus color	White
• Test speed	Normal
• Foveal threshold	On
Fluctuation	On
• FASTPAC	Off

Page 4 OHTS Perimetry Protocol

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

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

GOLDMANN'S TABLE

Age	Add
40 - 44	1.50 DS
45 - 49	2.00 DS
50 - 54	2.50 DS
55 and older	
or cyclopleged	3.00 DS

Examples:

1.	Best-corrected distance Rx (41-year-old):	OD OS	-2.00 +2.00 x 120 -3.25 +0.75 x 090
	Use:	OD OS	-0.50 +2.00 x 120 -1.50 DS
2.	Best-corrected distance Rx (53-year-old):	OD OS	+1.00 DS Plano +1.50 x 090
	Use:	OD OS	+3.50 DS +2.50 +1.50 x 090

Preparing the Participant

Measure the participant's pupils (to the nearest 0.5 mm). If they are less than 3 mm in diameter, dilate them with 2.5% Neosynephrine drops, unless contraindicated. If this is ineffective, dilate with a cycloplegic and wait a full 20 minutes before starting the test. In the case of a cycloplegic, the full near correction should be used (see Determining the Appropriate Refraction). In addition, enter the letter N (for Neosynephrine) or C (for a cycloplegic) into the ID field after the Visit Code in the participant data screen (see Entering Participant Data below). If a participant is taking Pilocarpine, he or she should discontinue its use 24 hours before the test. If this causes a significant increase in IOP, it will be necessary to set an additional, separate appointment for the pressure check.

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

HUMPHREY PARTICIPANT INSTRUCTIONS

- keep at your perimeter -

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

Figure 1

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 band 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 2) and by aligning the pupil in the center of the lens (see Figure 3).

Performing the Over-Refraction Procedure

Perform the following over-refraction procedure at the perimeter bowl for each visual field test on an eye with visual acuity of 20/40 or better; however, do not perform it on eyes with worse visual acuity. By placing lenses in the lens holder, offer the participant a choice of half Diopter PLUS or half Diopter MINUS over the calculated spherical correction. Ask the participant to look at the fixation hole in the center of the bowl and report which is better: (1) a +0.50 DS over-correction, (2) a -0.50 DS over-correction, or (3) no over-correction. From the participant's responses, determine the proper lens correction.



Proper Trial Lens Position





Participant Alignment

Figure 3

Entering Participant Data

Load pre-formatted floppy disks into drives A and B. If you have only one floppy drive, you will have to save the test data on the floppy disks one at a time. Enter participant data as follows (see Figure 4):

Humphrey Screen	Information Entered
ID	¹ Site Code, Tech Initials, Visit Code, Dilation
BIRTHDATE	. MM-DD-YY
PUPIL DIAMETER	RE: e.g., <u>4</u> mm LE:
NAME ²	Participant ID, Best-corrected Distance Rx
VISUAL ACUITY	RE: ³ e.g., <u>20/20</u> LE:
RX USED RE: LE:	$^{4}(+ \text{ or } -)$ $_{-}$ $_$

¹ The following 3 pieces of information should be entered in the ID section when using the HFA I instrument and in the **comments** section when using the HFA II instrument. Your Site Code has two characters. It should be followed immediately by your (i.e., the technician's) initials and the code for the participant's visit. For your initials, enter three initials and three only. If you have no middle name, enter the letter X. The Visit Code is a three-digit number which represents the target month of the visit. The code for the eligibility visits is 000, the six-month visit code is 006, the twelve-month visit code is 012, etc. Be sure to enter zeros where they belong rather than letter O's. Finally, if Neosynephrine was used to dilate the pupil, enter the letter N into the ID field after the Visit Code; if a cycloplegic was used, enter the letter C. *Example:* The entry G1DKB018 would be entered at clinical center G1 by technician Doreen K. Beam at the participant's 18-month visit.

- ² Be sure to distinguish between zeros and letter O's appropriately. The Participant ID has eight characters: the first five are a unique number given by your clinical center to each potential study participant and the other three are the participant's initials (as for the technician's initials, three and three only). The Participant ID should be followed by the best-corrected distance Rx for the eye being tested. Enter three digits each for the sphere, cylinder, and axis, with decimals for the first two. Enter the letter X for a sphere of 10 Diopters, E for 11 D, and T for 12 D. Use the letter P for the plus sign, and enter the letter X before the axis. Enter <u>P0.00</u> for plano. 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 Data (unless it is the same as for the right eye). *Example:* 06007KEC-1.50P1.25X075
- ³ If a participant's visual acuity is worse than 20/400, enter nothing on the screen. Instead, write the visual acuity on the printout.
- ⁴ Enter three digits for each, 0.00 for plano.



Enter Participant Data Menu

Figure 4

Proceeding with the Test

Follow the instructions shown on the Humphrey's screen under "Operator Assistance," EXCEPT omit the reference to holding the button down to rest. It is permissible for you (i.e., the technician) to encourage the participant occasionally if the participant seems to be fatigued or 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 subject's criteria for response during the course of the test but to remain alert to problems that develop.

At a participant's first visit, use the DEMO program to ensure the participant's understanding of the test and proper use of the response button. The first DEMO demonstrates the foveal threshold test. The small diamond fixation target automatically illuminates in the bowl, and a message telling you to instruct the participant to fixate at a point in the center of the four lights appears on the screen. You will hear a beep at the conclusion of this portion, and another message will remind you to tell the participant to fixate on the central fixation target. The visual field test will automatically follow the DEMO program. At a participant's subsequent visits, the DEMO program should be used at your discretion.

If the blind spot is not detected during the blind spot location phase of the test (see Figure 5), explain the procedure to the participant once more and try again to locate the blind spot. If you are using a HFA I instrument and still cannot locate the blind spot, change to <u>blind spot</u> check size II and try again. If, in the unlikely event, that does not work either, change to <u>blind spot</u> check size I. If you are using a HFA II instrument, there is NO option to change the blind spot check size. You are only allowed to re-locate the blind spot.



Change Blind Spot Check Size Menu

Figure 5

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. If excessive fixation losses are again detected after the second try to locate the blind spot, just allow the participant to continue through to the end of the testing program. Again, 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 Humphrey Field Analyzer. The second (i.e., left) eye should be tested in a fashion similar to the above. **DO NOT forget to edit the best-corrected distance Rx in the Name field of the patient data before the start of the second test.**

Saving the Results

The test results must be saved on three floppy disks after each test. Send one disk to the Visual Field Reading Center (VFRC), and keep copies of each visual field on two disks at your clinical center. In addition, print out the STATPAC 2 test results at the completion of each test, and make a copy of each printout.

Repeating Visual Field Tests

After you print out the STATPAC 2 hard copy, check the reliability indices (i.e., fixation losses, false positive errors, and false negative errors) to see if the test results are reliable. If the "xx" indicating unreliability appears by one or more of the indices, the eye must be re-tested. If the fields for both eyes are unreliable, then both must be re-tested.

The participant may be re-tested the same day; however, there must be at least one hour between test sessions. For unreliable follow-up fields, the test must be repeated within eight weeks. An unreliable follow-up field should be repeated only once, though, even if the re-test is also unreliable. If the re-test is abnormal when the first test was normal but unreliable, it will not officially be considered an abnormal field, and you should not repeat the test again (see below). With results such as these, simply test the participant again at the next regularly scheduled visit.

To be eligible for the OHTS, a participant must have two sets of normal, reliable fields performed within a three-month period. A total of three fields may be performed on each eye to obtain the two sets of good eligibility fields, and the first set of fields may be from a pre-study visit (pre-study fields may be from a date as much as three months prior to the first qualifying assessment visit). To be considered normal for eligibility purposes, a field must be within normal limits for the STATPAC 2 global indices (mean

deviation [MD], pattern standard deviation [PSD], short term fluctuation [SF], and corrected pattern standard deviation [CPSD]) and glaucoma hemifield test (GHT). It also must be considered normal by the VFRC. The VFRC will inform the clinical center by fax of the status of each eligibility visual field it receives.

If an eligibility visual field is abnormal, the abnormal eye must be re-tested at another session. Although it is preferred that you repeat the test at a separate visit between two and six weeks after the original session, it may be repeated sooner or even the same day if you wait at least one hour.

If a follow-up visual field is abnormal, the eye will be monitored to see if the visual field is abnormal at the next regular follow-up visit. If this second consecutive follow-up field is abnormal in the same location and on the same index(es), the GHT and/or CPSD (the other indices are not used as endpoint criteria), the eye must be retested at another visit between one day and eight weeks later. If this retest and the two previous visual fields all show an abnormality in the same location and on the same index(es), and the VFRC Director and Associate Director agree that the visual field loss is not artifactual, all of the visual fields for this eye are sent to the OHTS Endpoint Committee for review. The committee decides if the abnormality is glaucomatous or non-glaucomatous and if the eye has reached a visual field POAG endpoint. If so, the eye is transferred to the open arm of the study.

III. TRANSMISSION OF THE VISUAL FIELDS TO THE VFRC

All OHTS visual fields, including abnormal and unreliable ones, must be mailed to the VFRC, unless the participant has been declared ineligible for the study. You should mail them by the end of the week (i.e., Friday); however, if you mail a shipment late, please add a note of explanation. In a shipment, you should include one Humphrey disk with the corresponding STATPAC 2 printouts for all fields performed that week. In addition, you should include a disk directory you have printed out (use the Humphrey Field Analyzer Disk Functions/Recall Functions menu). Before mailing the shipment, compare the printouts you are including against the fields listed on the directory and check them off (literally) on the directory to ensure you are sending all of the correct printouts. Be sure to double-check the contents of a shipment before mailing it!

If you wish to use pre-study visual fields for a participant's initial eligibility test session, you must use the fields for both eyes, You should mail them to the VFRC with the fields from the participant's first qualifying assessment visit, and you should copy all of the Humphrey disk files for these fields onto one disk for this purpose. You must complete a Pre-Study Visual Field Data Form (see Figure 6) provided by the VFRC for each pre-study field. Use it to edit the information in the Name and ID fields in the Humphrey data, and print out new hard copy fields to send to the VFRC. Attach the appropriate Pre-Study Form to each printout before mailing. Please do not attach these forms to regular study fields.

OCULAR HYPERTENSION TREATMENT STUDY PRE-STUDY VISUAL FIELD DATA FORM				
Enrolling Clinical Center:	Patient ID:			
Test Date://	Еуе:			
Technician Initials:				
Best-corrected Distance Rx:	DSDCX			
Pupil Dilation: (N = Neosynephrine, C = Cycloplegic)				

Figure 6

Be sure to attach a label to each Humphrey disk you send to the VFRC (see Figure 7). The VFRC will provide some labels and a label master sheet from which you can make more as needed. On the label, enter your clinical center ID code and the mailing date. In addition, you should write the mailing date on each STATPAC 2 printout that you keep on file (see below).

Humphrey Disk Label



Figure 7

The Humphrey disk must be enclosed in a protective disk mailer. Although the VFRC will periodically return disks and disk mailers to you, you will need to purchase an initial supply of them. You may enclose all of the visual field materials in the disk mailer; however, if you prefer, you may enclose all of the materials in a manila envelope, as long as you add a label to it stating "Floppy Disk Inside -- Handle With Care." With this approach, you would not have to seal the protective disk mailer, and it would remain

in good condition for repeated use. For your convenience, the VFRC will provide some VFRC address labels.

In <u>addition</u> to the above, you must <u>immediately</u> fax the printouts from each participant's qualifying assessment visits to the VFRC. The VFRC fax number is (916) 734-6550. Please double-check the data entries on all visual fields before faxing them! The VFRC will notify you of its decision regarding the eligibility status of these fields usually within one working day. If the fields faxed represent the final fields required for an eligibility decision, the VFRC will notify you by fax of the participant's eligibility for the OHTS from the standpoint of visual fields.

You must also immediately fax all abnormal or unreliable follow-up fields to the VFRC, as well as the required retests for these fields.

Finally, you need to keep your copies of the OHTS visual fields (i.e., two sets of floppy disks and one set of STATPAC 2 printouts) in an organized and secure manner. Furthermore, the two sets of floppy disks should be kept in separate rooms as a safeguard against accidents. To minimize disk storage problems, you may consolidate the Humphrey disk files on master disks.

IV. CERTIFICATION PROCEDURES

Each clinical center must have at least two visual field technicians certified for OHTS perimetry. It is the responsibility of the P.I. at each clinical center 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 (see Figures 8a and 8b). The certification process involves a telephone session with a VFRC visual field technician after which the candidate must submit a set of practice visual fields to the VFRC. The candidate for certification should study this manual and the *OHTS Perimetry Procedures* videotape before making an appointment for a telephone session. To make an appointment, the candidate or clinical center coordinator should call the VFRC at (916) 734-6076.

For the telephone session, the candidate should use a telephone directly by a Humphrey Field Analyzer, and the candidate will initiate the call to the VFRC visual field technician. After a satisfactory telephone session, the candidate must submit visual fields performed on both eyes of two subjects according to OHTS protocol. These fields should be faxed to the VFRC. 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 read this protocol again and fax a memo to the VFRC stating he or she has re-read it. In addition, the technician must perform a single practice visual field according to protocol, and it should be faxed to the VFRC with the memo.

To become certified for OHTS visual field testing, a technician must demonstrate competency in the following:

- calibrating the Humphrey perimeter and formatting a floppy disk;
- measuring the pupil size;
- adjusting the comfort features for the participant, such as the 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;
- running the Demo program;
- running Program 30-2;
- being sensitive to participant fatigue -- allowing the participant to rest during the test;
- saving the test data, running the STATPAC 2 program, and printing the data;
- making a back-up disk and copying visual field files onto another disk.

HUMPHREY FIELD ANALYZER

OHTS CERTIFICATION EXAM

TEC	HNICIAN NAME:		
CLN	NICAL CENTER:CODE:		
1.	Initialize disks in upper and lower drives	YES	NO
2.	Measure pupil size		
3.	Adjust lens holder properly and align participant		
4.	Calculate lens correction		
5.	Perform refraction at the bowl		
6.	Select proper test parameters and enter participant data		
7.	Run Demo and 30-2 program with foveal threshold		
8.	Change fixation monitor		
9.	Edit distance Rx in Name field between tests		
10.	Save test data on disk		
11.	Printout STATPAC 2 results		
12.	Copy test data onto disk #3		
13.	Solve lens correction problems (Figure 6b)		

Figure 8a

HUMPHREY FIELD ANALYZER

OHTS CERTIFICATION EXAM

LENS CORRECTION CALCULATIONS

TECHNICIAN NAME:	
	CODE
CLINICAL CENTER:	CODE:

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

OD	-2.25 +0.50 x 180

OS -2.00 +2.00 x 090

Calculated correction:

OD:			

OS: _____

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

- OD +1.25 DS
- OS -0.75 +1.00 x 070

Calculated correction:

OD:	

OS: _____

Figure 8b

17. Ancillary studies

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17.2	Short Wavelength Automated Perimetry (SWAP)	
17.3	Pachymetry Measurements in the OHTS	
17.4	Genetics	

Note: Sections in this chapter are revised and maintained by the individual reading centers.

Confocal Scanning Laser Ophthalmoscope Reading Center

Heidelberg Retina Tomograph Manual of Procedures for the Ocular Hypertension Treatment Study

Version 3.1

AUGUST 15, 2001

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1.0 INTRODUCTION

Confocal Scanning Laser Ophthalmoscopy is a technique, which can reliably measure the topography of the optic nerve. Since changes in the optic nerve can indicate possible glaucomatous progression, this technique is being included in this clinical study.

Since small changes in the optic nerve may be important, proper acquisition of the images is the essential prerequisite for obtaining reliable measurements of topography. Mistakes occurred during image acquisition can never be compensated by subsequent image processing software. Therefore it is necessary that each study site strictly observe the image acquisition procedures and study protocol described in this manual.

This manual contains specific information regarding image acquisition and processing for the OHTS Study. This manual is based on sections of Heidelberg Retina Tomograph (HRT) Operation Manual (Software Version 2.01) that are relevant to image acquisition, archiving, back-up, exporting and transfer only. This manual should be used in conjunction with the HRT Operation Manual and Operation Software Release Updates, but should not replace it. All certified operators should be familiar with all aspects of the HRT Operation Manual provided with the HRT by Heidelberg Engineering.

2.0 USE OF TOPOGRAPHIC INFORMATION

It is essential that each participating center ensure that this ancillary study will not exhibit an adverse impact on the OHTS trial by jeopardizing recruitment, implementation of the primary trial or assessment of the primary findings. This is a new technology that does not have established clinical criteria of efficacy demonstrated to date. Patients can be shown their optic disc images on the video monitor, if they are interested. However, no editorial comments or opinions about the condition of the disc will be rendered. Personnel at the participating study sites are not to review the images or data collected for this study, or allow themselves to be influenced by this information. **The HRT image information is NOT to be used for patient management decisions.** All Principal Investigators and treating clinicians participating in OHTS already should have signed and returned the statement (located in Appendix B of this manual) indicating their agreement that HRT image information will not

be used for patient management decisions. Any clinician that has not signed such an agreement must do so in order for your Center to participate. To reinforce this policy, the study sites will not receive any form of feedback concerning the results or analysis of topographic data obtained for the OHTS Study other than information on image quality or other technical issues.

3.0 INFORMED CONSENT AT THE RANDOMIZATION VISIT

It must be clearly indicated to all OHTS patients, both in written form and verbally, that the HRT procedures are entirely voluntary and are independent of the decision to participate in the OHTS. To insure that there is no confusion between agreeing to participate in OHTS and agreeing to participate in the ancillary testing, informed consent for HRT imaging it to be obtained at the randomization visit after subjects have provided informed consent for OHTS at the qualifying assessment examination. Each participating center must use the consent form for the HRT ancillary study, which has been approved by their University Human Subjects Committee. Participants should understand that participation in the ancillary study is voluntary, does not affect their participation in OHTS, does not affect their treatment or quality of care, and that they can withdraw from the ancillary study at any time without risk to their participation in OHTS.

Since this ancillary study was initiated after recruitment for OHTS had begun, not all participants will have their first image obtained at the randomization visit. If HRT imaging cannot be completed at randomization, obtain images at the next possible visit.

4.0 PATIENT VISIT TIMETABLE

The first image will be obtained without dilation at the randomization visit (or at the next possible visit). Annual examinations will be completed with pupil dilation at the same 1 year, 2 year, 3 year, 4 year and 5 year visits when stereophotographs are taken.

5.0 INSTALLATION OF SOFTWARE VERSION 2.01

All OHTS Study images will be processed using HRT Operation Software Release 2.01/OHTS Study or higher. A separate OHTS Study database in its own directory

(C:>\OHTS) will be created to facilitate maintenance of the integrity of the images and data. An OHTS specific config.sys file will be created upon installation of Operation Software Release 2.01/OHTS Study to ensure that the investigator identification and patient data codes are identical at each site. Follow the instructions for installation of the software that accompany the diskette. After installation, enter the OHTS Study database by double clicking the OHTS HRT icon located on your desktop (at UCSD the icon is named HRTo). For DOS based users type C:>OHTS.

6.0 OVERVIEW OF HRT OHTS STUDY IMAGE ACQUISITION PROTOCOL

- 1. All examinations must be completed by certified personnel.
- 2. Image right eye first, then left eye.
- 3. Make sure far point fixation target is in place.
- 4. Ensure that template of pupil sizes is attached to forehead rest. (See item 7.1.3)
- 5. Reduce the lighting in the room to a minimal level.
- 6. Turn on the HRT at least 30 minutes prior to examination.
- Obtain k-values (keratometry readings) at the Baseline visit. If the patient undergoes intraocular surgery, then a new "baseline" k-value should be obtained three months post-operatively.
- Corrective lenses should be removed for HRT examination, unless the patient has astigmatism > 1.0 diopter or <-1 diopter. Contact lenses can be worn. If astigmatism > 1.0 diopter or <-1 diopter use corrective lenses for Baseline and all follow-up images. (See Section 7.1.2)
- Obtain all OHTS images in the separate OHTS database/directory by double clicking the OHTS HRT icon on your desktop (at UCSD the icon is named HRTo). For DOS based users type C:>OHTS.

- 10. Enter patient information accurately. (See Section 7.2)
- 11. Obtain 3 images using a 15 degree field for the right eye only. Then obtain images of both eyes using a 10 degree field (for a total of 9 images per visit).(See below)
- 12. Set field of view to 15 degrees for imaging of right eye.
- 13. Set intensity to maximum.
- 14. Prepare the patient. (See Section 7.1.2)
- 15. Record pupil size while laser is focused on pupil.
- 16. Obtain image. (See Section 7.3)
- 17. Review 32 optical sections for quality.
- 18. Review movie for eye movement.
- 19. Save image.
- 20. Complete OHTS HRT Image Acquisition Log.
- 21. Repeat Steps 16 to 20 to obtain 3 good quality images at 15 degrees (at the same scan depth) of the right eye only.
- 22. Set field of view to 10 degrees.
- 23. Repeat Steps 16 to 20 to obtain 3 good quality images at 10 degrees (at the same scan depth) of the right eye.
- 24. Repeat Steps 15 to 20 to obtain 3 good quality images at 10 degrees (at the same scan depth) of the left eye (at 10 degrees only).
- 25. Archive image Series on optical diskette.
- 26. At the end of the quarter (January 1, April 1, July 1, October 1), send data ("HRT Print List" disk) of eligible, randomized patients, using the "Print List" command, to the CSLORC

27. Upon CSLORC request, export images of eligible, randomized patients onto an optical diskette for sending (overnight express) to the CSLORC.

7.0 IMAGE ACQUISITION PROTOCOL

7.1 **PREPARATION**

A few items concerning the preparation of the patient and of the HRT should be observed prior to image acquisition.

7.1.1 PREPARING THE SYSTEM

The procedure for switching on the instrument is described in Chapter 3 (General Information on Operating the Instrument) of the HRT Operation Manual Software Version 2.01 or higher. The instrument should be turned on at least 30 minutes before the start of the examination.

In order to achieve stable patient fixation during the examination, a fixation target is required. Good results are achieved with a clearly visible mark, which is positioned five to ten feet away from the patient, for example on a wall facing the patient. For myopic patients, the fixation light integrated into the headrest can be used.

7.1.2 PREPARING THE PATIENT

No special preparation of the patient is required for an examination with the Heidelberg Retina Tomograph. Spherical refraction errors are compensated for during the image acquisition by shifting the instrument's focal plane (See Section 7.2.3, Step 4). If the eye to be examined has astigmatism between 1 diopter and -1 diopter, the patient should not wear glasses during the examination. With astigmatism of greater than (>) 1 diopter or less than (<) -1 diopter, glasses or trial lenses placed in the HRT lens holder are required for the examination. Contact lenses may be worn during an examination with the Heidelberg Retina Tomograph.

Note: If the first (baseline) examination of a patient is conducted with glasses or contact lenses, all subsequent examinations of this patient (for follow-up) should be conducted in the same manner.

7.1.3 THE INFLUENCE OF PUPIL SIZE

Under normal circumstances, the pupil of the eye under examination will close to a diameter of approximately 2 to 3 mm when the laser beam of the laser scanning camera enters the eye. As a general rule, the image acquisition is accomplished without pupil dilation. However, the signal-to-noise ratio, and therefore the image quality, will improve if the pupil is dilated. With opaque media, therefore, a dilation of the pupil is recommended -- insofar as it is possible.

For this study, all images will be obtained with pharmacologically dilated pupils of > 3 mm in diameter. However, when recording images through a dilated pupil, the adjustment of the laser scanning camera to the center of the pupil can be more difficult. Baseline images will be obtained at the study Baseline visit. Follow-up images will be obtained at Months 12, 24, 36 and 48, etc. and at the visit where the study medication is discontinued. Pupil size will be recorded at each imaging session using the provided pupil size card. Pupil size will be recorded while the laser is focused on the pupil.

7.2 CREATION OF A DATABASE ENTRY AND INPUT OF PATIENT DATA

Prior to acquiring the first images of an OHTS Study patient, it is necessary to create a new database entry by entering the data for a new patient and eye. This is performed by using the sub-menu Database of the Main Menu as described below. As soon as a three-dimensional image is acquired and stored under a specific database entry, no further images can be acquired under that entry.

7.2.1 CREATING A NEW DATABASE ENTRY WITH NEW PATIENT DATA

For all OHTS Study patients, creation of a new database entry is required, even if the patient has been imaged previously for clinical purposes. This is important so that the OHTS Study Patient Identification Number will be entered appropriately, as the Patient Last Name.

- (1) In the software Main Menu, select the menu item 'Acquisition'. A selection field is displayed. Choose 'Examine new patient' if you want to examine a patient for the first time, then continue with Step 2. If you want to perform a follow-up examination of a patient, select 'Re-examine patient' and continue at Section 7.2.2. To exit the menu without image acquisition, select 'Cancel'.
- (2) Before examining a new patient, you must first fill in a form with information about the patient (top part) and the eye examined (bottom part). For this study, patient data must be entered according to the standard protocol. Enter "#" and OHTS patient ID (5 digit numerical patient ID and 3 character patient initials e.g. #12345ABC) in the space for Last Name; patient initials (first, middle, last; if no middle initial use an "X") in the space for First name; date of birth and sex (See Figure 1).
- (3) Then select the right eye ('right' fields). The bottom part of the form is pre-set with standard values. The standard information can be optionally modified. If you are examining a structure other than the optic nerve head, it is important that you indicate this in the 'examined structure' field. Moreover, it is important for the absolute scaling of the data to enter the corneal radius of curvature of the examined eye. In the 'classification' field, enter the OHTS study visit code. Then select 'OK'.

If the default parameters are applicable to the second eye, select 'Yes' to applying default parameters. If different parameters are needed, select 'No', select Left eye accordingly, then input the appropriate parameters. When all of the information is correct for the second eye, select 'OK'.

- (4) If you select 'OK' before all the necessary information for the two eyes has been given, you will receive a message to this effect. For Example: "Patient Name Incomplete" will appear if the field for patient's first name (patient initials) or last name (OHTS Study patient ID) (or both) was not specified. "Invalid Date" will appear if the date of birth of the patient was incorrect or was omitted.
- (5) After the input of the patient data is completed, the instrument is ready to acquire images. The patient's ID Number will be displayed on the screen. In the OD/OS selection field at the top right, the red backing shows which eye is undergoing image acquisition. You can

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switch over between the right and left eye at any time by selecting 'OD' or 'OS'. Below the selection field, you are shown the number of image series of the respective eye which have been acquired and stored. In the lower area of the screen, you are told how much space is still available on the hard drive to store images. Approximately 2 MB of space is needed for each image series.

Figure 1:

Enter patient information as follows:

HRT Patient Data Screen	Information Entered
Last Name:	Enter "#" then OHTS Patient ID ¹
First Name:	Patient initials (3 required) ²
Patient Number:	Enter OHTS Patient ID (8 digits: 4 digit investigator #, 4 digit pt ID#)
Date of Birth:	mm. dd. yyyy
Sex:MF	Click on appropriate box
Ancestry: $\Delta \nabla$	Scroll for appropriate response ³
Operator:	Enter your 3 initials ⁴ .
Eye Examined:RightLeft	Click on appropriate box
Cornea Curv.:	Enter mean k-value (in millimeters)
Vis Fld Mean:	Leave blank
Vis Fld Var.:	Leave blank
Refraction:0. dpt	Enter value for last test refraction ⁵
Cylinder:0. dpt.	Enter value for last test refraction ⁵
Axis:	Enter value for last test refraction ⁵
Pupil Ø (Size):	Record to nearest millimeter ⁶
Corrective Lenses: $\Delta \nabla$	Scroll for appropriate response ⁷
Classification:	Enter Code for Patient's Visit ⁸
Remarks:	Leave Blank

- 1. The OHTS Study Patient ID ("#" and 5 digits, 3 letters): The five digit patient ID number assigned by OHTS, followed by the patients initials if there is no middle name, use an "X" (e.g. #12345ABC).
- 2. Patient initials: 3 are required. If there is no middle name, use an "X".
- 3. Appropriate Responses are limited to the following: Asian/Pacific Islander, American Indian/Alaskan, African Origin, Hispanic, White, and Other.
- 4. Operator initials: 3 are required. If there is no middle name, use an "X".
- 5. Obtain refraction from current OHTS Study visit this will usually be at the 000, 012, 024, 036, and 048 visits. Enter a '+' or "-" and three digits for each, 0.00 for plano (e.g. -1.25 Sphere Refraction, +0.50 cylinder, 180 Axis).
- 6. Pupil size is recorded. Record pupil size to the nearest millimeter diameter that most closely matches pupil gauge size on template attached to forehead rest.
- 7. Contact lenses can be worn during image acquisition. Corrective lenses worn during image acquisition due to astigmatism only (when cylinder is greater than 1 diopter or less than -1 diopter). Responses are limited to: None, Glasses, Hard Contact Lenses, Soft Contact Lenses, trial lens-astigmatism.
- 8. Visit Code: The 2 digit number which represents the OHTS visit code of the visit. The Baseline visit code is 0, month 12 visit code is 12, month 24 visit code is 24, etc.
7.2.2 DUPLICATING AN EXISTING DATABASE ENTRY FOR ALL OHTS STUDY FOLLOW-UP VISITS

If the patient has been examined before for the OHTS study, a database entry already exists. In this case, creation of the new database entry can be very much simplified by loading and duplicating the existing database entry instead of entering all data once again.

- (1) If you want to examine a patient who has already been examined with the Heidelberg Retina Tomograph, it is not necessary to enter the patient data again. After selecting the acquisition menu, select the 'Re-examine Patient' menu item.
- (2) First, you will be shown a loading mask. In the 'Patient' field, enter the OHTS Patient ID number, and select the 'Search' field. A list of patients will be shown whose Patient ID numbers correspond to your information.
- (3) From this list, select the line with the name of the desired patient. A new list will then be displayed, with all the examinations of this patient which have already been conducted.
- (4) From this list, select one examination of the right eye and one examination of the left eye. As a general rule, it is favorable to select the last examinations of the patient in each case. The data of the selected previous examinations will be automatically transferred to the new examination.
- (5) If necessary, the patient data can be modified. The data in the various items of the data sheet must now be changed as required to match with the new examination planned. The new study visit code (refer to table below), refraction, corneal curvature, and pupil size must be changed to reflect the latest information. After doing this, select 'OK'.
- (6) After completion of the patient data input, the instrument is ready to acquire images. The screen will display the name of the patient and the settings on the Operations Panel of the patient's previous examination. It is recommended to pre-set the Operations Panel with these values for the new examination. In the lower area of the screen, you are told how much space is still available to store images on the hard drive. In the OD/OS selection field at the top right, the red backing shows which eye is undergoing image acquisition. You can switch over between the right and left eye at any time by selecting 'OD' or 'OS'.

Below the selection field, you are shown the number of image series of the respective eye which have been acquired and stored.

7.2.3 ADJUSTING THE CAMERA TO THE EYE BEING EXAMINED

- (1) Now, the Operation Panel can be used to control the image acquisition (See Chapter 3 of the HRT Operation Manual). If information about the image acquisition parameters is displayed on the screen (as is the case with a follow-up examination), set the focal plane, the scan depth, and the size of the scanning field to these values. Otherwise, select the following settings: focal plane to the refraction of the examined eye (spherical equivalent), and scan depth to 2.5 mm. Set the size of the field of view to 15 degrees to obtain image of right eye only, then reset field of view to 10 degrees to obtain images of both eyes (right eye, then left eye). The laser intensity is always set to maximum. The detector sensitivity should be at approximately the 1 o'clock position.
- (2) Ask the patient to position their head and chin firmly against the head rest and chin rest. The height of the chin rest should be adjusted so that the eye being examined is located at the height of the mark on the headrest. Ask the patient to stare at the fixation target with the eye that is not being examined.
- (3) On the Operation Panel, press the 'Freeze' button. The camera and the laser will be switched on. Move the camera (upwards, downwards, right, and left) so that the red laser beam enters the pupil of the eye to be examined. The distance between the front edge of the objective tube and the examined eye must be approximately 15 mm. As soon as the laser beam enters the pupil, you will see an image of the fundus of the eye on the screen. Now move the camera so that the structure to be examined is visible on the screen. Remember to record pupil size while the laser is focused on the pupil. Often, too large a distance between the HRT lens and the pupil causes framing. Framing is the result of misalignment between the HRT laser and the pupil, resulting in dark shaded borders around each of the 32 image series. The HRT quality control software does not assess framing, therefore it is imperative that the operator is familiar with this problem. See the "CSLO Reading Center HRT Image Quality Control Guidelines" for further details.

- (4) Move the focal plane until the image appears brightest, and then set the detector sensitivity so that a bright, but not overexposed image is visible. You can detect overexposure by white areas with read and blue dots inside the image.
- (5) For the fine adjustment of the image, move the camera so that the structure to be examined is located precisely in the center of the image. Move the camera slightly up and down, and sideways, until the image appears brightest. This is the point at which the laser beam falls directly into the center of the pupil of the eye under examination. Carry out a visual check to ensure that this is the case. Then move the focal plane (quarter-diopter switch) until the image is brightest, and if necessary, set the detector sensitivity again so that you see a bright, but not overexposed picture.

7.3 IMAGE ACQUISITION AND MONITORING

- (7.3.1) Ask the patient not to blink any more, and not to move, and then press the series acquisition button 'Record' on the Operation Panel. A series of 32 confocal images is acquired. This process lasts 1.6 seconds. After the acquisition, the 32 images are shown on the screen in small format.
- (7.3.2) The acquired series of images is automatically monitored for quality. If the position of the focal plane, the scan depth, or the detector sensitivity need to be modified, you will be given messages to this effect. In this case, re-set the relevant parameters on the Operation Panel and acquire another image (continue at Section 7.2.3, Step 3). It is very important that you follow the automatic quality monitoring messages. Instructions on how to inspect images for brightness, axial location and scan depth are included in Appendix A. Also see the "CSLO Reading Center HRT Image Quality Control Guidelines" for further image quality details.
- (7.3.3) If the quality of the image series is perfect, you will receive the quality control message, 'Settings of acquisition parameters OK. Inspect series for eye movements.' If this message does not appear, after re-setting the relevant parameters as suggested, please note your attempts to obtain a good quality image on the "OHTS Image Acquisition Log Sheet".

Note: As rather complex decisions are necessary for the automatic inspection of an acquired image series, it might occur under some circumstances, that the result of the quality control is inappropriate. Therefore, the operator should still observe the guidelines for inspection of the images described in Appendix A and in the "CSLO Reading Center HRT Image Quality Control Guidelines". Of course, even if the quality control software indicated inadequate settings of the acquisition parameters, this image series can be stored on the hard drive.

- (7.3.4) In order to examine the images for eye movements, select the 'Display' sub-menu and 'Movie' menu item. All 32 images will be displaced cyclically one after the other, and it is possible to detect very slight eye movements by the patient during image acquisition. Quite small eye movements of up to one quarter of the image size are acceptable. (These will be automatically corrected during the subsequent processing of the images). If larger eye movements, or many eye movements are present, you should repeat the image acquisition (continue at Section 7.2.3, Step 3). Halt the display of the images by pressing any key.
- (7.3.5) If the quality of the image series is perfect and no excessive eye movements are present either, store the series on the computer's hard drive. To do this, select the 'Save Series' menu item. Continue at Step 2.3 until you have stored at least three image series per eye.
- (7.3.6) To examine the patient's second eye, select the second eye in the 'OS/OD selection' field on the screen, and continue with Section 7.2.3, Step 1.

8.0 ARCHIVING

All image series that have been saved to the hard drive of the HRT computer must be archived to a designated OHTS optical disk. Each study site should have at least 3 optical disks: two for archiving images and database backup and a third for exporting and mailing images to the CSLORC. The disks for archiving images and database back-up will remain at the study site for the duration of the study. Archiving and database backup should take place each day after image acquisition is completed. Only after image series have been archived on optical disks should they be deleted from the hard drive to make room for image files from future examinations. This procedure is described in Chapter 6 of the Heidelberg Retina Tomograph Operation Manual (version 2.01). It is recommended that all HRT operators review these sections of the HRT operation manual.

8.1 ARCHIVING MEDIA

Optical disks are used to archive data with the HRT. Magneto-optical (MO) disks can be written on multiple times, and currently have a capacity of 1.3 GB (650 MB per side), 2.3 GB (1.15 GB per side), 2.6 GB (1.3 GB per side), or 5.2 GB (2.6 GB per side).

Before using a new optical disk to archive data, it must first be prepared with the operation software of the Heidelberg Retina Tomograph. Magneto-optical disks in some cases require a so-called High-Level Formatting, which is undertaken in the DOS level according to the manufacturer's instructions.

To prepare an optical disk for use with the HRT, proceed as follows:

- (1) In the Main Menu, select the 'Database' menu and the 'Prepare Optical Disk' menu item.
- (2) You are asked to insert an optical disk into the disk drive. Confirm by selecting the 'OK' field. The preparation process will start.
- (3) During the preparation, the relevant side of the optical disk will be assigned a number that is displayed on the screen after the preparation has been completed. The numbering of the disks is carried out automatically. It starts with HRT0001 when the first disk is prepared, and is increased by 1 for every additional disk side. Note that the number is assigned per disk side. Please note the number that is displayed on the side of the disk which has just been prepared. This is used to locate the images stored on this disk later on.
- (4) Now insert the other side of the disk that has just been prepared into the drive, and repeat Steps (1) to (3).

8.2 BACKUP COPY OF THE DATABASE

All patient-related data, data on the acquisition of the images and information about the type of images that have been acquired and stored, are stored in the database of the Heidelberg Retina Tomograph. In order to prevent possible data loss, it is therefore very important to prepare backup copies of the database at least once a week and preferably after archiving. If you have not created a backup copy for an extended time, you will be asked to do so by the operation software. Proceed as follows:

- (1) In the Main Menu, select the 'Database' menu and the 'Database Backup' menu item.
- (2) You will then be prompted to insert an optical disk into the disk drive. Confirm by selecting 'OK'. A (compressed) backup copy of the database is now written on to this optical disk.

You can create any desired number of backup copies on the same optical disk. You can also use the same disk to archive image files (see Section 8.3).

In a case where you need to have access to this backup copy, please contact the Service Office for your area.

8.3 ARCHIVING IMAGES

The three-dimensional images, aligned images and the topography and mean topography images that are acquired with the Heidelberg Retina Tomograph are initially stored in files on the hard drive of the computer (see Chapter 3.4 of the HRT Operation Manual). Since the hard drive has limited storage capacity, these image files must be archived at regular intervals on to optical or magneto-optical disks. This is accomplished as follows:

- (1) In the Main Menu, select the 'Database' menu and the 'Archive Images' menu item.
- (2) The screen displays a form in which you can indicate the image files that are to be archived. First, in the 'Archive what' field, select the image file types which you would like to archive. You choose the 'Orig.Series' (the originally acquired three-dimensional image series), then select the 'Search' field.

- (3) You will be shown all database entries for which images of the selected type(s) are stored on the hard drive but are not yet archived. Before selecting 'Search', you can impose further restrictions for the images to be archived. In the 'Patient' field, you can indicate the patient ID number (in whole or in part, see also Heidelberg Retina Tomograph Operation Manual Chapter 5.2) and in the 'Search Options' field, you can indicate the first and/or the last acquisition date of examinations whose images you want to archive. The database entries that satisfy your criteria are listed. Now you can either mark individual entries from this list for archiving, by selecting the line in question, or you can mark all displayed entries simultaneously by choosing the 'Select All' field.
- (4) Select the 'Archive' field to start the archiving.
- (5) You are asked to insert an optical disk into the disk drive. Confirm by selecting the 'OK' field. The archiving process will start. During the archiving, you cannot use the computer for any other purpose.

8.4 DELETING ARCHIVED IMAGES FROM THE HARD DRIVE

After archiving images on optical disks they can be deleted from the hard drive in order to increase free disk space for new examinations. Proceed as follows:

- (1) In the Main Menu, select the 'Database' menu and the 'Delete' menu item.
- (2) A selection mask will appear, as described above under 'Archiving. Select the examinations whose images you would like to delete, and select the types of the images to be deleted. In addition to individual images, you can also mark complete database entries for deletion by selecting 'Database Entry' in the 'Delete' field. However, a database entry can only be deleted if no images have been archived for this entry, and if all the images stored on the hard drive under this entry have previously been deleted. Select the 'Delete' field in order to initiate the deletion process.
- (3) If all the images that have been marked for deletion have previously been archived on optical disks, the images are deleted without further interaction. If the images marked for deletion have not been archived, you are informed of this fact and asked for confirmation. Select 'Delete' in order to delete the displayed image. Select the 'All' field in order to

delete the displayed image as well as all other images that are marked for deletion but are not archived. Select the 'Skip' field to keep the displayed image on the hard drive.

8.5 RELOADING ARCHIVED IMAGES ON TO THE HARD DRIVE

Images that have been archived and deleted from the hard drive can no longer be loaded directly for processing or exporting. Instead, they must first be copied back from the optical disk on to the computer's hard drive. This is accomplished as follows:

- (1) In the Main Menu, select the 'Database' menu and the 'Retrieve Images' menu item.
- (2) A selection mask appears, as described above under 'Archiving'. Select the type of the images and the examinations to be retrieved.
- (3) Select the 'Retrieve' field to copy the images on to the hard drive.
- (4) You are asked to insert an optical disk with a specified number into the disk drive. Confirm by selecting the 'OK' field. During the copying process, this request may occur several times if the images to be copied are located on different optical disks.

9.0 TRANSFER OF EXAMINATIONS TO THE CSLORC

OHTS images will be transferred on optical diskettes by Federal Express, along with the corresponding HRT Image Acquisition Logs, to the CSLORC (Confocal Scanning Laser Ophthalmoloscopy Reading Center) upon request by personnel at the CSLORC.

9.1 PRINT LIST FOR CHECKING DATA COMPLETENESS AT THE CSLORC

Before transferring images to the CSLORC, make sure that the patient information entered on the HRT Patient Data Screen is complete and correct. To facilitate this, a specialized menu option Print List, has been provided in the latest HRT software release, version 2.01 or higher, so that each study site can send complete patient data on computer diskette without the image series. In this way, any data entry errors can be corrected before images are sent to the CSLORC. Once the Print List has been reviewed by the CSLORC and all requested corrections have been made, the CSLORC will request series images to be exported. Please do not send images until your Print List has been reviewed and you have received conformation from the CSLORC. Instructions for sending a print list file:

- (1) Put an IBM formatted 3.5" diskette in the "a" drive of your computer.
- (2) In the software Main Menu, select the menu item "Menu Database". Choose "Topic Load" and select "multiple select". Search for relevant images.
- (3) Select all images of eligible patients to send to the CSLORC.

For quick results, type desired date in the Search Options found at the bottom of menu. (e.g. Since: 1/1/97 Before: 4/1/97 then select Search)

- NOTE: If there are extra images or images that do not meet OHTS image quality standards de-select these before hitting "load". Remember, the CSLORC only needs 9 images: 3 OS at 10 degrees, 3 OD at 15 degrees, and 3 OD at 10 degrees.
- (4) Select "load"
- (5) In the software Main Menu, select the menu item "Menu Database". Choose Topic "Print List". To save the file to a floppy diskette select "file".
- (6) Enter Filename as "a:Print" followed by your two digit investigator ID# (e.g. a:PrintS1) (Caution to DOS novices: do not insert a space after the colon.) Select "print". Print list file named "PrintS1" should now be on your 3.5" diskette; to check, quit the HRT software and click the drive A icon on your desktop. For DOS based users type dir a: from the DOS prompt.
- (7) Send Print List on a 3.5" diskette to the CSLORC for approval. Once the Print List is approved by CSLORC, export images on optical drive as described in the next section.

9.2 EXPORTING IMAGES FOR TRANSFER TO THE CSLORC

To transfer OHTS Study patient images to an optical diskette, a separate program, ExportOHTS must be used. This transfers complete examinations (patient information, acquired images, measurement results) between different databases.

- 1. OHTS HRT database, retrieve all the necessary images on hard drive.
- For quick results type desired date in the Search Options found at the bottom of Retrieve Image menu. (e.g. Since: 3/1/97 Before: 5/30/97 then select Search)
- 3. Quit out of OHTS HRT database
- Double click the ExportOHTS icon located on your desktop within the "Export Apps" folder. For DOS base users, at the DOS prompt type: ExportOHTS
- A new Main menu will appear, with the headings, Database, Info, Quit In Database menu select Export Entries
- 6. Then choose the optical drive
- 7. Select Search (The date Search Option can also be used for quicker results)
- 8. Make sure the "Change Name" box is checked (red square) this tells the CSLORC which site the images came from by changing the Patient ID# to the Site ID#.
- 9. Highlight images, then Export.

NOTE: Each export process creates a unique file with the exported data and images on the optical disk. Therefore, the same disk can be used for more than one export processes.

10.0 CERTIFICATION PROCEDURES

Certification of technicians to obtain images of the optic disc using the HRT is supervised by the Coordinator and/or Directors at the CSLORC. Each study site will have at least two imaging technicians certified for OHTS Study HRT imaging. It is the responsibility of the Principal Investigator at each study site to ensure that the appropriate personnel are competent in the OHTS Study HRT protocol. To obtain certification, a technician must demonstrate an understanding of the correct procedures for all aspects of the HRT image acquisition and processing.

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The certification process includes a telephone session with a CSLORC imaging technician. The candidate for certification should study the OHTS Study Heidelberg Retina Tomograph Manual of Procedures and the HRT Operation Manual Version 2.01 or higher.

To make an appointment, the candidate or study site coordinator should contact the CSLORC directly. To initiate the telephone session, the candidate should call the CSLORC. After a satisfactory telephone session, the candidate must submit to the CSLORC, a Print List (once all corrections are made the CSLORC will request images to be sent), and nine images obtained on each of two non-study patients. For each non-study patient, submit three 10-degree images and three 15-degree images of the right eye, and three 10-degree images of the left eye. Certification will be awarded if the images are of satisfactory quality. All certified technicians must maintain their certification by obtaining OHTS Study HRT images on a regular basis.

To become certified for OHTS Study HRT imaging, a technician must demonstrate competency in the following:

- formatting an optical disk
- measuring and recording pupil size (during image acquisition)
- measuring corneal curvature (keratometry value)
- calculation of the radius of curvature of the anterior corneal surface (in mm)
- adjusting the comfort features for the patient, such as the chin rest and chair
- refraction adjustment for high myopia and astigmatism using trial lenses
- adjusting the laser target and monitoring fixation during imaging
- selecting the proper imaging parameters (intensity of the laser beam, field of view, etc.)
- entering patient data
- operating the HRT; choosing the appropriate scan depth parameters, adjusting light detector system sensitivity, adjusting fine and coarse focus, and obtaining an image

- adhering to suggestions made by the quality control software
- utilizing the image series (32 images) to adjust focus and depth
- utilizing the movie option to monitor eye movement
- saving the image data, archiving images and making back-ups of the image and database
- transferring patient Print List data (without images) to the CSLORC
- exporting images for transfer to the CSLORC.
- Completing HRT Image Acquisition Log.

Note: The telephone "test" asks the technician to walk through a series of mock images, (i.e. explain each procedure, how to improve image series, and what you would you say to the patient) and how to calculate the k-value.

APPENDIX A: INSPECTION OF IMAGE SERIES FOR QUALITY CONTROL

A.1 INSPECTION OF THE 3D IMAGES FOR BRIGHTNESS

The proper setting of the sensitivity of the light detector system which affects the brightness of the images is important to get reliable measurement results. Both too dark images and too bright images can cause artifacts in the determination of the topography. As a general rule, however, images which appear slightly too bright are more acceptable than those appearing too dark.

- (A.1.1) Observe the three-dimensional image series displayed on the computer monitor. The 32 images are displayed in four rows and eight columns. The top row contains the first eight images of the series, ordered from left to right. The bottom row contains the last eight images; the last image of the series is displayed in the bottom right corner. The last images of the series are those recorded at the deepest locations. The image series must adhere to the following pattern:
 - (1) The first four images of the series should appear dark.
 - (2) The last four images of the series should appear dark.
 - (3) All other images should appear more or less bright.
 - (4) In the middle images, the retina should appear in bright colors.

NOTE: The first and the last images of a series will never appear completely black under normal circumstances. A dark image in the sense of requirements (1) and (2) means that the first/last four images appear obviously darker than the following/preceding images.

(A.1.2) If there are no images with bright colors either the adjustment of the laser scanning camera was not done properly to the center of the pupil, or the sensitivity of the light detector was set too low. The series must be recorded once again; continue with Section 7.2.3, Step 1. (A.1.3) If the series contains images with large solid white fields, the sensitivity of the light detector was set too high. Turn the operation panel control button <Sensitivity> to a lower value and record the series once more; continue with Section 7.2.3, Step 1.

NOTE: During normal operation, sometimes a small region within the image has a much higher reflectivity than other parts of the examined structure; e.g. the bottom of the excavation of an optic nerve head sometimes has a very high reflectivity. In order to avoid underexposure of the majority of the image content, it is acceptable in such cases, that region with high reflectivity is overexposed and appears saturated white.

A.2 INSPECTION OF THE 3D IMAGE FOR AXIAL LOCATION AND SCAN DEPTH

The following steps help to judge the quality of the recorded image series with regard to the proper setting of the position of the focal plane (which determines the axial location of image series) and of the total scan depth. Depending on the appearance of the series, suggestions are made on necessary changes of these scan parameters. If required, use the operation panel control switches <Focus Coarse>, <Focus Fine>, and <Scan Depth> to perform the correction.

(A.2.1) If the image series begins with bright images or with less than four dark images:

The location of the first focal plane of the image series was set too deep; the focal plane has to be set to a more positive value at the operation panel. If the series begins with bright images, change the location of the focal plane by +0.5 diopters, if there are only too few dark images, change by +0.25 diopters.

(A.2.2) If the image series ends with bright images or with less than four dark images: The location of the first focal plane of the image series was set too high; the focal plane has to be set to a more negative value at the operation panel. If the series ends with bright images, change the location of the focal plane by -0.5 diopters, if there are only too few dark images, change by -0.25 diopters. (A.2.3) If the image series begins with too many dark images:

The location of the first focal plane of the image series was set to high; the focal plane has to be set to a more negative value at the operation panel. Depending on the number of dark images, change the location of the focal plane by -0.25 or -0.5 diopters.

(A.2.4) If the image series ends with too many dark images:

The location of the first focal plane of the image series was set to deep; the focal plane has to be set to a more positive value at the operation panel. Depending on the number of dark images, change the location of the focal plane by +0.25 or +0.5 diopters.

- (A.2.5) If the series begins and ends with bright images or with less than four dark images:The total scan depth was too small. Increase the scan depth at the operation panel by 0.5 mm.
- (A.2.6) If the series begins and ends with too many (more than four) dark images:The total scan depth was too high. Decrease the scan depth at the operation panel by 0.5 mm.

If, from the above, any correction of scan parameters is necessary: Record the image series once again; start at Section 7.2.3, Step 1.

The relationship between change in the location of the focal plane or change of the total scan depth and the resulting shift of the images within the series can be estimated by the following rules:

- 0.25 diopters change of the focal plane location shifts the image series by approximately
 2 image planes
- 0.5 mm increase/decrease of the total scan depth compresses/expands the series by approximately 4 image planes on both sides.

The following table summarizes the possible kinds of wrong appearance of the recorded images series and the recommended changes of the focal plane and the scan depth settings.

Series begins with	Series ends with Set focal plane to		Set scan depth to	
= 4 dark images	= 4 dark images			
= 4 dark images	< 4 dark images	more negative	higher value	
= 4 dark images	> 4 dark images		smaller value	
< 4 dark images	= 4 dark images	more positive	higher value	
< 4 dark images	< 4 dark images		higher value	
< 4 dark images	> 4 dark images	more positive		
> 4 dark images	= 4 dark images		smaller value	
> 4 dark images	< 4 dark images	more negative		
> 4 dark images	> 4 dark images		smaller value	

A.3 INSPECTION OF THE 3D IMAGE FOR EYE MOVEMENTS AND BLINKS

Before saving an image, the following steps are required to ensure that artifacts do not blur the content of the acquired image series.

- (A.3.1) Display a movie by selecting topic Movie in the Image Acquisition menu. This displays the 32 images of the series one after the other (press any key of the keyboard to stop the movie).
- (A.3.2) Watch for movements within the image series during movie display. Small movements usually occur and are acceptable; they are corrected automatically by software during subsequent image processing. If strong movements of a quarter of the image size or more occur: The series has to be rejected and recorded once again; continue with Section 7.2.3, Step 1.
- (A.3.3) If a sudden change in the brightness of the images occurs: The patient blinked during the image acquisition period. The series has to be rejected and recorded once again; continue with Section 5.2.3, Step 1.

A.4 INSPECTION OF THE IMAGE SERIES FOR FRAMING

"Framing" appears as black areas around the edges and sides of an image. Framing is the result of misalignment between the HRT laser and the pupil, resulting in uneven distribution of light across the fundus. Often, too large a distance between the HRT lens and the pupil causes framing. **The ideal distance is 15 mm (about a thumb's width).** See the "CSLO

Reading Center HRT Image Quality Control Guidelines" for specific examples. The following are suggestions to help alleviate framing during image acquisition.

- (A.4.1) Framed images should be re-taken after adjustment of the distance and/or alignment of the HRT laser with the patient's eye. To decrease the distance between the HRT camera and pupil in difficult to image (often large) patients, the patient should be seated in the highest chair possible. By having the patient lean over to the chin rest, the patients' eyes can often get closer to the HRT camera than when seated at normal height. If some framing still exists, try to acquire images with no framing in the middle two rows of the 32 frames of the image series.
- (A.4.2) Framing is also a common problem when using corrective lenses (glasses or trial lens). See "Trial Lens Memo I" for specifics on how to minimize this problem.

APPENDIX B: LETTER OF AGREEMENT

The "Quantitative analysis of optic disc/ocular hypertension" ancillary study to the Ocular Hypertension Treatment Study is evaluating a new technology that has no clearly established clinical criteria or efficacy than has been demonstrated to date. As a principal Investigator and treating clinician participating in OHTS, I agree only to acquire topographic data, and not analyze them. In addition, I will not be influenced by any HRT information for patient recruitment or management unless authorized by the Data Safety and Monitoring Committee.

Signature

Date

Name

APPENDIX C: IMAGE ACQUISITION LOG

OHTS HRT IMAGE ACQUIS	ITION For Rea	ding Center Entered by	· Purposes	Only
OHTS Site ID'	Operator Initia	als		
OHTS Patient ID:	Da	ite:		
Visit Code:	Consent Da	te:		
Patient Information	OD			OS
1 Pupil Size	mm			mm
2 Corrective Lenses Used	U None			ne
				ntacts
	Trial Lens		🔲 Tria	al Lens
3 Clear Media (Lens and Cornea)	YES NO		YE	S NO
4 Patient Able to Fixate	YES NO		YE	S NO
		·		
Quality Control	OD 15º	OD 1	00 0	S 10º
 Optic Nerve Centered (<1/4 of disc outside of target circle) 	YES NO 1 2 3 1 2 3	YES N 1231	2 3 1 2	:S NO : 3 1 2 3
2 All images obtained at identical and	YES NO	YES N	NO YE	S NO
appropriate scan depth	123123	1231	2 3 1 2	3123
3 Movie has minimal movement	YES NO	YES N 1231	10 YE	S NO
4 No floaters over optic disk	YES NO	YES N 1 2 3 1	NO YE	S NO
5 Image sharp and clear (appearance of blood vessels, ontic disc, and retina)	YES NO	YES N	VO YE	S NO
	125125			
6 Appropriate dark/light/dark pattern of the 32 optical sections	YES NO 1 2 3 1 2 3	YES N 1231	VO YE 23 12	:S NO :3 1 2 3
7 Quality control software says "OK"	YES NO	YES N	NO YE	S NO
•If not, specify all depths and focuses	123123	1231	23 12	3123
attempted for each eye and angleDepths A	ttempted:	┨ ┣────	_ _	
Focuses A	ttempted:	┨┠───		
8 Other Comments:				

•1 2 3 refer to the images at that eye and angle - 1 is the first image, 2 the second, 3 is the third

MANUAL OF PROCEDURES

For

SHORT WAVELENGTH AUTOMATED PERIMETRY (SWAP)

Ocular Hypertension Treatment Study (OHTS) Ancillary Study

Appendix to OHTS Visual Field Manual of Procedures

Participating Centers: Bascom Palmer Eye Institute (Miami) Devers Eye Institute (Portland) Henry Ford Hospital (Detroit) University of California, Davis University of California, San Diego

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I. Introduction

Short Wavelength Automated Perimetry (SWAP) is a new visual field test procedure that utilizes a bright yellow background (100 cd / m^2 ; 315 asb) and a large (size V) blue test object to isolate and measure the sensitivity of short-wavelengthsensitive pathways throughout the central visual field. Prospective longitudinal studies performed at two independent laboratories (University of California, San Diego and University of California, Davis) have reported that SWAP deficits are predictive of the onset and progression of visual field loss for conventional automated perimetry, and are typically larger in extent than standard visual field deficits. These results, in conjunction with cross-sectional studies performed in other laboratories, strongly suggest that SWAP is able to detect early losses of visual function in glaucoma patients and glaucoma suspects.

Because of its potential as a visual field test procedure capable of detecting glaucomatous damage at an earlier stage than conventional automated perimetry, an ancillary study of SWAP testing in OHTS patients was approved for evaluation at five OHTS clinical centers (Bascom Palmer Eye Institute, Devers Eye Institute, Henry Ford Hospital, University of California, Davis and University of California, San Diego). The main objectives of this ancillary study are: (1) to determine whether treatment reverses the early deficits observed with SWAP, (2) to determine whether treatment reduces the rate of progression and the incidence of SWAP deficits, (3) to confirm previous study results that have reported SWAP to be predictive of the onset and progression of glaucomatous visual field loss for conventional automated perimetry, and (4) to determine whether the prevalence and incidence of SWAP deficits is greater among African American patients with ocular hypertension.

II. Impact of SWAP on the OHTS Trial

Since the SWAP investigation is an ancillary study, it is important that it does not adversely impact the main OHTS trial by affecting recruitment or retention of patients, influencing the clinical judgment or clinical management impressions of the Principal Investigators, or any other factors that may impair the ability to obtain a clear outcome for the main OHTS trial. Several safeguards are included in the design of the ancillary SWAP study to ensure that no adverse impact occurs.

All the patients enrolled in the OHTS trial at the clinical centers participating in the ancillary SWAP trial are potential candidates. When OHTS patients are presented with the opportunity to participate in the SWAP ancillary study, they will be fully informed of its purpose, the amount of additional time and testing that the study entails. Patients will be clearly informed that their decision as to whether to participate in the ancillary SWAP study is entirely independent of their decision to participate in OHTS. Other aspects of informed consent are included in the next section. To avoid confusion, informed consent for the SWAP ancillary study will be obtained at the time of their randomization visit or at another suitable time that is separate from the time that they provided informed consent to participate in OHTS.

At the randomization visit (or at the first visit that SWAP testing can be obtained), both eyes will be evaluated with SWAP. This testing will occur after all standard OHTS visual fields have been performed. Following the first SWAP baseline visual fields, only one eye will be tested at each six month followup visit to minimize the amount of additional testing the patient will undergo. The eye with the highest IOP (or if both eyes have the same IOP, the right eye) will be tested on the first followup visit, with the fellow eye on the next followup visit, continuing in an alternating order throughout the remainder of the study.

Clinic coordinators are to save the SWAP results on floppy disks. The floppy disks should be different from the ones used for storing standard automated perimetry results. The clinic should keep one copy and a backup copy, with a third floppy disk to be sent to the Visual Field Reading Center. <u>Printed copies of SWAP results should not be made</u>. Principal Investigators are not allowed to see the SWAP results. The SWAP disks will be stored separately from the standard OHTS visual field materials. Principal Investigators will sign a letter of agreement that they will not look at SWAP visual field results or use the information for patient management decisions. A copy of the letter of agreement is included in Appendix A. No feedback will be provided to the clinical centers concerning SWAP results, other than those that are directly related to quality control issues.

III. Informed Consent

At the present time, all centers participating in the SWAP ancillary study have obtained IRB approval for SWAP testing. A copy of a representative Informed Consent form (from UC Davis) is included in Appendix B. It will be clearly indicated to all candidates for the ancillary SWAP study that their participation is entirely voluntary, and that their decision whether or not to participate in the ancillary study is independent of their decision to participate in OHTS. It will be clearly indicated to each ancillary study candidate that their decisions concerning the ancillary study will not affect their treatment or quality of care, their participation in OHTS or any related factors. They will also be informed that they can withdraw from the ancillary study at any time and still continue their participation in OHTS without any risk to their quality of care, treatment or other related factors.

To minimize confusion and assure that the decision to participate in the ancillary study is independent of the decision to participate in OHTS, informed consent will be obtained at a visit that is separate from the time that they provide their initial consent to participate in OHTS. For newly recruited OHTS patients, informed consent for the ancillary SWAP study will typically be obtained at the randomization visit. Since some patients entered OHTS prior to beginning the ancillary SWAP study, informed consent for the ancillary study should be obtained at the 6, 12, or 18 month visit.

IV. Patient Visit Timetable

OHTS patients participating in the ancillary SWAP study will be given a SWAP test in both eyes at baseline. To minimize the amount of extra time and effort associated with SWAP testing, only one eye will be given a SWAP test at each 6 month visit. The eye with the highest initial IOP will be tested at the 6 month visit and at yearly intervals thereafter (18 months, 30 months, etc.). The fellow eye will be tested at the 12 month visit and at yearly intervals thereafter (24 months, 36 months, etc.). If the initial IOP is the same in both eyes, then the right eye should be tested first at the 6 month visit. Because the ancillary study began after recruitment for OHTS was underway, some patients were not given the opportunity to participate in the ancillary SWAP study at baseline. In these cases, patients should be presented with the opportunity to participate at their regularly scheduled 6, 12, or 18 month visit.

V. Testing Protocol

In general, the same procedures that are used for standard automated perimetry are to be employed for SWAP testing. Refer to the "Perimetry Protocol for the Ocular Hypertension Treatment Study" manual produced by the Visual Field Reading Center for specific protocol and test procedure details. <u>Patient data entry, including ID code, should be done in the same manner as for standard automated perimetry testing</u>. Select the FULL THRESHOLD strategy and the 30-2 target presentation pattern. At this point there are a few differences in the standard OHTS automated perimetry test procedure that must be performed for SWAP testing. Prior to testing, select CHANGE PARAMETERS from the display screen options. In the lower right corner is an option labeled BLUE-YELLOW. Make sure this is set to ON. If it is OFF, touch the light pen to the adjacent lighted box to turn it ON. Also, set the Blind Spot Check Size to III, but leave stimulus size at V.

When you are done, check to see that the following parameters are set:

•	Threshold Strategy	Full threshold
•	Fixation target	Central
•	Blind Spot Check Size	III
•	Stimulus Size	V
•	Stimulus color	Blue
•	Test Speed	Normal
•	Foveal Threshold	ON
•	Fluctuation	ON
•	FASTPAC	OFF
•	Blue-Yellow	ON

Other aspects of testing are the same as for standard OHTS automated perimetry. Data is to be saved on an original disk and two backup disks. The original and one backup are to be kept at the clinical center, and one backup copy is to be sent to the Visual Field Reading Center. <u>The disks for the SWAP ancillary study must be kept</u> <u>separately from the rest of the patient's OHTS information and clinical records</u>. <u>Do not</u> <u>make a hard copy printout of the SWAP results</u>. <u>The Principle Investigator is not allowed</u> <u>to view SWAP results at any time, and should not be allowed access to the disks and</u> <u>storage area containing SWAP results</u>. <u>Patients are not to be informed of their test results</u> <u>for SWAP, and copies of their test results should not be given to them</u>. No retesting will be performed for SWAP, even if the test results are unreliable, in order to minimize the likelihood that the ancillary SWAP study will present in a significant burden for patients and thereby affect retention.

VI. Data Shipment

Data is to be shipped on a <u>monthly</u> basis to the Visual Field Reading Center. Shipments of SWAP data should be done in the same manner as for standard OHTS visual fields, except that the printout of test results should not be included. However, the shipment should include a directory listing of the contents of the disk, with check marks to indicate that the disk contents have been verified. On the shipping label, please indicate "attn: Chris Johnson" and "SWAP DATA" so that it will not be confused with standard OHTS visual fields.

VII. Quality Control Assessment Procedures

All SWAP visual fields will undergo the same quality control assessment procedures as standard OHTS visual fields. Beginning in January 1996, quality control assessment reports for each individual SWAP test will be sent back to participating centers on a monthly basis.

SWAP data will be stored on a computer system and Humphrey SWAP disks will be stored in the Optics and Visual Assessment lab (OVAL) to assure that the data will be separate from the standard OHTS perimetry data kept by the Visual Field Reading Center. OVAL will make a backup copy of each Humphrey floppy disk, and will have at least two daily backup copies and one weekly backup copy of the processed database of SWAP results. Backup copies will be stored in a separate location from the originals. Quarterly reports pertaining to patient recruitment, retention, data quality and test reliability for SWAP ancillary study participants will be sent to the Coordinating Center and the Data Safety and Monitoring Committee.

VIII. Certification

Since SWAP testing has minimal differences from standard OHTS automated perimetry, a separate certification procedure will not be necessary for technicians participating in the SWAP study, as long as they have been certified for visual field testing for the main OHTS trial. A telephone question/answer session will be conducted for all personal conducting SWAP testing to insure that procedures are being conducted properly.

IX. Appendix

Letter of Agreement

The Short Wavelength Automated Perimetry (SWAP) ancillary study is being conducted in conjunction with the Ocular Hypertension treatment Study (OHTS). SWAP is a new perimetric test procedure whose clinical efficacy in defining early glaucomatous damage is not clearly established. Part of the purpose of this ancillary study is to further elucidate the value of SWAP for detection and management of glaucoma.

As a Principal Investigator and treatment clinician for the OHTS trial, I agree to the following conditions as part of my participation in the SWAP ancillary study:

- 1. I will make sure that the Clinic Coordinator stores the SWAP test results in a location separate from OHTS data and from patient clinic charts.
- 2. I will not examine any SWAP test results and I will remain masked to them.
- 3. I will make sure that the Clinic Coordinator does not Make printed copies of SWAP test results.
- neither I nor my staff will provide printed copies of SWAP results or any information pertaining to SWAP Testing to the patient, unless instructed to do so by the Data Safety and Monitoring Committee.
- 5. I will not be influenced by SWAP testing or SWAP Results in any manner for patient recruitment, treatment or management, or any other clinical decisions.

Signature

Date

Printed Name

17-34 OHTS Procedure Manual

Pachymetry Measurements in the Ocular Hypertension Treatment Study

Literature Review, Summary of Protocol and Manual of Procedures

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Introduction

The Ocular Hypertension Treatment Study (OHTS) is a multi-center clinical trial designed to evaluate the safety and efficacy of topical ocular hypotensive medications in preventing or delaying the onset of visual field loss and/or optic nerve damage in ocular hypertensive individuals at moderate risk of developing primary open angle glaucoma. In the OHTS, intraocular pressure (IOP) is determined by Goldmann applanation tonometry.

When he first described his tonometer, Goldmann¹ discussed the effect of central corneal thickness (CCT) on IOP as measured by this device, but he believed that variations in corneal thickness in the absence of corneal disease occurred only rarely. He assumed a corneal thickness of 500μ M and emphasized that at least theoretically; the corneal thickness might influence the applanation reading.

As optical pachometers and later ultrasonic pachymeters[†] came into widespread use, it became clear that corneal thickness does indeed have a positive correlation with IOP as measured by Goldmann applanation tonometry^{2,3}, and in some cases the difference may be clinically significant.⁴ It is also apparent that CCT is more variable among clinically normal individuals than Goldmann recognized.

This ancillary study to the OHTS is based on the increasing recognition that among patients currently classified as having 'Ocular Hypertension'; some may suffer from no more than anatomically thickened, clinically normal corneas. These asymptomatic, thickened corneas in turn cause Goldmann applanation measurements to be erroneously elevated. This has important implications for the OHTS and for the clinical practice of glaucoma diagnosis and treatment.

Significance and Rationale

In recent years there has been increasing interest in whether or not CCT may be increased in some patients in whom the diagnosis of ocular hypertension has been made. Argus⁵ examined 36 patients with ocular hypertension and compared their CCT with that measured in 29 control subjects and 31 patients with glaucoma. He found that corneal thickness was increased in the patients with ocular hypertension compared to both the control and glaucoma patients. In a more recent study, Herndon et al.⁶ examined 184 eyes of 109 patients in whom 48 patients (74 eyes) had glaucoma, 28 patients (51 eyes) had ocular hypertension and 33 patients (59 eyes) were normal. These investigators found that the CCT (mean \pm SD) of eyes of patients with ocular hypertension was significantly greater (606 ± 41 μ M) than that of eyes of patients with glaucoma (554 ± 22 μ M) (P < .001) or of eyes of normal controls (561 \pm 26 μ M) (P < .001). They found no significant difference in CCT between normal and glaucomatous eyes (P = .40).

Morad et al.7 recently reported that CCT is decreased in patients with the diagnosis of 'low tension glaucoma', suggesting that in at least some of these individuals, IOP is being underestimated because of thin corneas. Ehlers and Hansen⁸ had previously reported similar findings in seven individuals in 1974.

The terms pachometry and pachymetry are often used interchangably; although the term pachometry is the correct one, pachymetry has largely supplanted it. For the purposes of this discussion, pachometry refers to optical methods, pachymetry refers to ultrasound techniques. Version 1.0 1/13/99

The studies by Argus, Herndon and others would suggest that in at least some of the patients we currently classify as having "ocular hypertension", this classification is erroneous and is an artifact of these patients' increased central corneal thickness. If this is true in a significant number of patients, this finding would have important implications both for the OHTS and general clinical practice:

- Patients with increased CCT may have 'corrected' IOPs that fall within a statistically 'normal' range and place these patients at much lower risk of glaucoma than previously recognized. If this group of patients represents a large proportion of OHTS subjects, the OHTS may not have enrolled enough patients with 'true' IOP-related glaucoma risk to answer the principal question of the study.
- A large body of evidence suggests that there is a dose-response relationship between IOP and glaucoma risk; if CCT is a significant variable in the determination of IOP in these patients, it may be found that 'corrected' IOP will have a much closer risk relationship to glaucoma than 'uncorrected' IOP. The CCT-corrected IOP could be used for Specific Aim 2 of the OHTS to identify risk factors for the development of primary open-angle glaucoma.

There is a growing interest in the glaucoma community regarding these issues. It seems likely that if the OHTS does not make an attempt to measure CCT as part of the study and determine whether CCT substantially alters IOP assessment, the OHTS will be criticized for this omission. Indeed, because the topical agents used in the OHTS may have effects on CCT, the OHTS will undoubtedly be criticized in retrospect for not having measured the CCT at the onset of the study before the medications were introduced.

Although not directly related to the OHTS, the demonstration of a significant impact that corneal thickness may have in determining glaucoma risk may turn out to be of increasing importance as laser surgery for myopia becomes ever more common. These procedures thin the central cornea, and a number of investigators have demonstrated that this thinning can be related to a lowered IOP measurement.^{9,10} Many in the glaucoma community believe that we are about to witness an epidemic of iatrogenic 'low tension glaucoma', in which glaucoma risk (on the basis of tonometry) will be under-estimated or missed in patients with laser-thinned corneas.

Corneal Thickness Measurements – Background

During the 18^{th} and 19^{th} centuries, the thickness of the cornea was of only passing interest to ocular anatomists. Contemporary textbooks give estimates of corneal thickness that vary from 400 μ M to 1,200 μ M. Two of the leading ocular anatomists of the late 19^{th} century gave estimates of 800 μ M (Salzmann) to 950 μ M (Jaeger). Given these values, we can assume that the measurements were performed on dead eyes. The first measurements in the living eye were reported in 1881 by Blix¹¹ using an ophthalmometer of his own design; he measured 10 eyes and found a range of 482 to 576 μ M, remarkably close to the range we now recognize as present in clinically normal eyes.

Von Bahr¹² described the first practical optical pachometer in 1948. His device employed two identical microscopes set horizontally at an angle of 40° to each other. By the 1950s, a variety of devices employing image-doubling optics appeared; the Haag-Streit pachometer as modified by Mishima and Hedbys¹³ was introduced in 1968 and gained widespread acceptance. The device was

easy to operate and provided results sufficiently accurate for the clinical needs of the time; contemporary studies showed them to have good intra- and inter-observer variability ^{14,15}.

The accuracy of the optical pachometers (and the ease and speed of measurement in daily use) was not, however, sufficient for the needs of modern keratorefractive surgery, and in 1985 Kremer¹⁶ introduced ultrasonic pachymetry. At present, ultrasonic pachymetry has largely supplanted optical pachometers in clinical practice. The current generation of ultrasonic pachymeters are relatively inexpensive and can be easily operated by ancillary personnel. All have internal software-based safeguards to assure proper alignment (usually $\leq 3^{\circ}$ from perpendicular) and accurate measurements; they can be calibrated against known machined standards. Some investigators^{15,17} have compared optical and ultrasound devices and reported that the two devices are, for clinical purposes, comparable. However, Salz and co-workers¹⁸ compared optical and ultrasonic devices and found that the optical instruments had 2 to 3 times as much intra-session variation as the ultrasound device, significant inter-observer variation (p = 0.015) and significant differences between right and left eyes (p ≤ 0.005).

Corneal thickness measurements performed using the ultrasound devices are highly reproducible. In a study of 19 eyes measured repeatedly over a two week period, Higgens and co-workers¹⁹ reported a mean central corneal thickness of $506 \pm 21 \,\mu\text{m}$, with a 95% confidence interval of 41 μm . Wheeler *et al.*²⁰ compared two commercially-available ultrasound pachymeters and found reliability coefficients of 93.7% (DGH 1000) and 94.5% (Bio-Rad PachPenTM). Gordon and colleagues²¹ reported interobserver and intersession variabilities of 11 μm and 14 μm , respectively.

Some investigators have found a measurable diurnal variation in corneal thickness. Investigators using optical pachometers have noted that corneas are relatively thick in early morning^{22,23}; this is followed by a gradual thinning in daytime until late afternoon, with a subsequent thickening during the night. Using ultrasound pachymetry other investigators have not reproduced this diurnal variation^{18,19} and have suggested this difference is related to diurnal changes in tear film thickness and composition, something that is unlikely to impact applanation measurements.

Essentially nothing is known about the long-term stability of corneal thickness measurements in individuals followed over time. Studies of the inter-session variability of the measurements have generally been short term (<2 weeks) with investigators making the assumption that corneal thickness was stable over such a short period. In subjects of the PERK study, Villaseñor and co-workers²⁴ compared corneal thickness measurements obtained at a pre-operative visit at a variable time before radial keratotomy to the measurements obtained intraoperatively; they found no statistical difference between the two.

A variety of cross-sectional studies give some clues as to the long-term changes in corneal thickness. Ehlers and colleagues²⁵ found newborn corneas to be moderately thickened compared to adults; the corneas thinned to adult levels by 3 or 4 years of age. Using ultrasound, Autzen and Bjørnstrøm²⁶ confirmed that central corneal thickness was increased at 584 \pm 42 μ m in full-term newborns.

In the largest cross-sectional study performed to date, Alsbirk²⁷ performed an oculometric survey of 839 clinically normal Greenland Eskimos, aged 7 to 89 years of age and compared them to a sample of 98 Danes living in Greenland. Using a Haag-Streit optical pachometer, he found a

significant corneal thinning with age, predominantly in males. He estimated the rate of thinning to be 0.7 μ m/year, and noted that this thinning in males resulted in a sex difference > 19 μ m above the age of 40. In a later paper related to his oculometric study, Alsbirk reported a strong genetic influence on central corneal thickness²⁸, with a heritability estimate of 0.6 to 0.7.

Other potential factors that may impact corneal thickness include hormonal status and topical drugs. Weinreb and co-workers²⁹ reported corneal thickness to be increased 16 μ m in pregnant women compared to non-gravid and post-partum women. Kiely³⁰ reported that corneal thickness varies with the menstrual cycle and suggested that the measurement was most influenced by estrogen levels; however this conclusion was based on only three patients followed through one complete menstrual cycle.

Topical medications used to treat glaucoma may influence corneal thickness. Some investigators have reported that dorzolamide increases corneal thickness^{6,31} while others have found the corneal thickening to be not statistically significant and occurs only on the first day of treatment³². Pilocarpine and β-blockers do not appear to affect corneal thickness³³. There are no published reports evaluating the effect of the newest topical glaucoma drugs, brinzolamide (AzoptTM), latanoprost (XalatanTM), apraclonidine (IopidineTM) or brimonidine (AlphaganTM) on corneal thickness, but it is likely that the manufacturers of these compounds have such proprietary data available.

Ancillary Study of Pachymetry in OHTS

Based on the increasing recognition of corneal thickness as a confounding variable in the determination of IOP, this ancillary study to the OHTS has been developed with the following specific aims:

Specific Aim 1: To describe the distribution of corneal thickness in all patients enrolled in the OHTS

Specific Aim 2: To determine if corneal thickness is related to race, use of estrogen hormone replacement therapy or topical medication utilization

Some data regarding corneal thickness measurements in the OHTS cohort has already been acquired by William Bourne at the Mayo Clinic site as part of the ancillary study examining endothelial cell function in those patients. At least some of these patients have thickened corneas (Bourne – personal communication), suggesting that similar findings may hold for the entire OHTS cohort. The Mayo subset is small and racially homogeneous, however, which raises an important point. A careful review of the literature on corneal thickness reveals that **no corneal thickness data exist for African American patients.** The most-quoted corneal thickness studies were performed in Scandinavia and Greenland; the largest US study³⁴ was performed in Iowa City on a relatively homogeneous Caucasian population (Rapuano – personal communication).

The OHTS went to great efforts to recruit sufficient numbers of African American patients so that the principal question of the study is answered for this high risk population. If, as is proposed here, corneal thickness plays an important role in evaluating IOP-related glaucoma risk, it would be important to determine the role corneal thickness plays in the African American OHTS cohort. Imagine if this ancillary study found that African-Americans have *thinner* corneas than their agematched Caucasian counterparts. Such a finding would indicate that the *true* IOP in these patients

was even higher than measured by Goldmann applanation, and an even stronger dose-response relationship between IOP and glaucoma risk would follow from this finding. Because no data exist, the preceding is pure speculation, but illustrates the importance of performing this measurement on the entire cohort of OHTS patients in order to capture the entire African-American cohort.

Specific Aim 3: To recalculate IOP for both eyes of patients enrolled in OHTS based on a cross-sectional measurement of corneal thickness

Because corneal thickness is a confounding variable in the determination of IOP, it will be possible to re-calculate the Goldmann applanation measurements to better reflect 'true' IOP. It may turn out that the corrected 'true' IOP is a better predictor of glaucoma conversion risk. If so, the ultimate analysis of the OHTS data may be strengthened by using a corrected IOP. For this reason, it is imperative that *all* OHTS patients have their corneal thickness measured at least once. Because corneal thickness can be altered following trauma (surgical or otherwise) or intentionally (following photorefractive surgery), the 'correction factor' derived from the initial corneal thickness measurement may become incorrect following such an event. For this reason, it is recommended that corneal thickness measurements be repeated in any OHTS patient who sustains [significant] ocular trauma or undergoes intraocular or photorefractive surgery so that a new 'correction factor' can be determined.

The question of the best manner in which to 'correct' IOP based on corneal thickness remains unanswered. Ehlers *et al.* ² created a correction table (reproduced below) for CCT measurements greater or less than the mean CCT in their study. They estimated that applanation tonometry over- or under-estimated IOP by approximately 5 mmHg for every 70 μ M in CCT.

Corneal	A	pplanation	Reading (Goldmann)
Thickness (µM)	10	15	20	25	30
450	4.2	4.7	5.2	5.7	6.2
460	3.5	4.0	4.4	4.8	5.3
470	2.9	3.3	3.7	4.1	4.5
480	2.2	2.6	2.9	3.3	3.6
490	1.5	1.8	2.2	2.5	2.8
500	0.9	1.2	1.4	1.7	1.9
510	0.3	0.5	0.7	0.9	1.1
520	-0.4	-0.2	0.0	0.1	0.3
530	-1.0	-0.8	-0.7	-0.6	-0.5
540	-1.6	-1.5	-1.4	-1.3	-1.2
550	-2.2	-2.1	-2.1	-2.0	-2.0
560	-2.8	-2.8	-2.8	-2.8	-2.7
570	-3.4	-3.4	-3.4	-3.4	-3.4
580	-3.9	-4.0	-4.1	-4.1	-4.2
590	-4.5	-4.6	-4.7	-4.8	-4.9

Although the above table could be easily employed in the OHTS to create a 'corrected' IOP, Ehlers' table was based on a limited number of cannulated human eyes, and does not extend into the low 600 μ m range where recent publications suggest some ocular hypertensive patients lie. Ongoing research in several laboratories may provide us with more specific guidelines as to a 'correction factor' for IOP by the time this analysis is to be performed.

Additional Issues

Location of corneal thickness measurements

The question of whether or not the central corneal thickness is representative of the entire cornea, and more importantly whether simply measuring at a single (central) site is sufficient to assess the contribution of corneal thickness to IOP measurement, remains unanswered. Rapuano and co-workers³⁴ obtained central, paracentral and peripheral corneal thickness measurements in 303 normal corneas; they found that central corneal thickness measurements were not correlated with age, but paracentral and peripheral thickness measurements were not correlated with age, but paracentral and peripheral thickness measurements tended to become thinner with age. Currently, technologies that can create a 2-dimensional map of corneal thickness are investigational^{35,36} and are impractical for use in the OHTS. Furthermore, such technologies are unlikely to ever be used in widespread clinical practice, whereas most ophthalmologists have access to ultrasonic pachymeters. Thus measurement of central corneal thickness, while admittedly an incomplete collection of data, probably represents a workable compromise that reflects clinical practice and will not impact patient retention by extending visits more than a couple of minutes.

Safety & Risks

Ultrasonic pachymetry is a non-invasive, painless measurement that involves the placement of a plastic, ultrasonic probe on the central cornea for the few seconds necessary to make the measurement. It is performed under topical anesthetic and can be done immediately after Goldmann applanation tonometry. The risks of the procedure are similar to that of tonometry, namely that of mild corneal abrasion and of infectious transmission. These risks are extremely remote in the hands of well-trained individuals. Ultrasonic pachymetry is a routine procedure in ophthalmic practice.

Impact on OHTS patient retention

Ultrasonic pachymetry takes only a few seconds per eye; the data is acquired by the device, stored and printed at the end of the measurement session. It is believed that such an additional test will not adversely impact patient retention, particularly if the patients are educated about the rationale for the measurement (both in person and in the OHTS patient newsletter prior to the initiation of the proposed protocol).

Pachymetry measurements will be performed only once in most patients. The measurements will be repeated only in those patients who sustain trauma or who undergo intraocular or refractive surgery after which corneal thickness is likely to be altered.

Informed Consent and IRB Issues

Ultrasonic pachymetry is a minimal risk, routine ophthalmic procedure. The OHTS Data & Safety Monitoring Committee recommended that the addition of this measurement to the battery of tests the OHTS subjects undergo does not alter the risk to the patients and it was felt that the pachymetry measurements be considered a 'protocol modification' that does not require patients to sign a separate consent form for pachymetry measurements. As occurred previously for the protocol modification involving the number and timing of confirmatory visual fields, the Coordinating Center will provide Clinical Centers with a memo outlining the protocol change and the minimal risk nature of the change; the Clinical Centers will then notify their institutional review boards of the protocol modification.

Instrument(s) to be used

Potential Publications

It is anticipated that once the first year CCT data was collected, a paper presenting the baseline measurements in the OHTS cohort would be of significant interest to the ophthalmic community. In the final outcome analysis of the OHTS, it is possible that the data will demonstrate a stronger glaucoma risk relationship with 'corrected' IOP than with 'uncorrected' IOP, and this would be of widespread clinical significance. As noted above, no data exist for CCT in African-American patients. If a racial difference in CCT is discovered, this finding would be of profound interest.

Funding

No additional funding will be requested from the NEI for either the clinical centers or for the OHTS Coordinating Center for this study. The instruments will be donated by the manufacturer.

Timetable

1998	4 th Quarter	Protocol finalized
1999	1 st Quarter	Protocol finalized
		IRB Amendment process initiated by clinics
		Training/certification initiated
		DGH Pachymeters delivered to clinical sites
		Pachymetry measurements begin
	4 th Quarter	Expanded effort to obtain missing measurements
2000	2 nd Quarter	Data analysis
	3 rd Quarter	Baseline paper submitted

Overview of Pachymetry Measurements in OHTS

- All examinations must be performed by OHTS certified personnel.
- Certification of personnel will be carried out by telephone by Dr. James Brandt and/or his designees; field personnel trained by DGH Technologies may be able to visit clinical centers to provide an in-service for such personnel.
- The measurements of the entire OHTS cohort should be completed within 12 months of the start of this protocol.
- Measurements will occur at the time of *either* the annual dilated exam visit, after visual fields and tonometry, prior to dilation, or at the mid-year exam visit, after visual fields and tonometry.
- Five measurements will be made of central corneal thickness in each eye, right eye first.
- The pachymeter will be tested with the calibration box provided by the instrument manufacturer on a monthly basis; calibration errors will be reported to the Coordinating Center so that a repair or replacement instrument can be arranged for.
- The pachymeter has an internal testing routine which determines the quality of the probe at power-up. This "probe quality factor" (PQF) will be recorded on the data collection form. The pachymeter will not allow measurements if the PQF drops below 85% of the level recorded when it left the factory. The Coordinating Center will record the PQF in order to monitor whether the ultrasound probe at any one center is deteriorating, so that a replacement probe can be ordered.
- Data collection forms will be transmitted to the Coordinating Center along with the rest of the data forms generated by the patient visit.
- The Coordinating Center will monitor data collection and provide clinic coordinators on a monthly basis with a printout of those OHTS patients for whom pachymetry data has not yet been collected. In this manner, the coordinators will be able to 'flag' upcoming visits to obtain the data.
- Along with the quarterly clinic 'report cards', the Coordinating Center will provide the investigators group with an update on the proportion of the OHTS cohort who have had their corneal thickness measurements made.

Troubleshooting

Problems with the use of the pachymeter (e.g., frequent "POOR APPL" messages on the display, failure to calibrate, PQF numbers deteriorating towards 85%, broken or defective probes) should be addressed to the Ancillary Study PI and Clinical Coordinator as follows:

James D. Brandt, M.D. (916) 734-6969 office/voice mail (916) 762-6826 pager jdbrandt@ucdavis.edu Vickie Jaicheun (916) 734-6316 office/voice mail (916) 762-4185 pager vjaicheun@ucdavis.edu

Operation of DGH-500 Pachymeter (Pachette™)

General Description



Figure 1: The DGH-500 Pachymeter (Pachette[™])

- **PROBE INTERFACE** BNC connector located on front panel which mates to BNC connector on Probe cable.
- **FOOT PEDAL INTERFACE** Phone jack located on rear panel, which accepts phone plug connection on end of foot pedal cable.
- **DISPLAYS** Two (2) 4-character LED displays and one(1) 2-character LED display used to present information to the operator.
- **POWER SWITCH** Located on right hand side of front panel. Pressing "1" side of switch turns PachetteTM on. Pressing "0" side of switch turns PachetteTM off.
- **PQT SWITCH** Used to perform probe quality test when pressed and released. Used to initiate the main configuration mode when pressed and held.
- CLEAR SWITCH used to clear all measurements from memory and re-initiate measurements at position 1 when pressed and released. Used to initiate the velocity configuration mode or to initiate the printer – neither of these features will be used in the OHTS ancillary study
- " "OR " "ROCKER SWITCH Used to program options and numerical values presented on displays

Power-up Sequence

1) Plug AC cord into three prong outlet.

- 2) Verify Probe is connected to front panel.
- 3) Turn on unit.
- 4) The PachetteTM will perform an internal self-test function and then test the displays as indicated by all dots on the displays being lit for approximately three seconds.
- 5) The Pachette[™] will automatically perform the Probe Quality Test and display the appropriate message indicating the quality of the probe. A probe of satisfactory quality will yield a Probe Quality Factor of 85% to 100% as indicated on the display as "PQF XXX%" for approximately two seconds, where XXX is a number between 85 and 100. Any other message indicates the probe quality is not satisfactory and pachymetry measurements will be inhibited. Refer to Section VII of the full operators manual for a detailed description of the Probe Quality Test Command.

NOTE: The most common cause of a low PQF is water or dirt on the tip of the probe, which disperses the ultrasound energy. If you get a low (<85%) PQF, clean the probe and re-start the machine. If you still get a low PQF, do not take pachymetry measurements. Contact the Pachymetry Study Coordinator who will help you troubleshoot the problem and/or arrange for a replacement probe.

- 6) Record the PQF on the OHTS Pachymetry Data Form
- 7) The initialization sequence is now complete and the display will indicate "Position 1" with "0" readings in both the actual and biased displays. The Pachette[™] is now ready to take pachymetry measurements.

Calibration Procedure

The Pachette[™] should be calibrated once a month using the calibration box that is supplied with the machine. A calibration log will be provided that will be affixed to the machine on which the date of calibration and the person performing the calibration will be recorded.

The box is attached to the PachetteTM console where the probe normally goes, and sends the internal computer a timed impulse that the machine should interpret as representing a corneal thickness of $800\pm5 \,\mu\text{M}$. The instructions for the calibration procedure are printed on the calibration box.

If your machine fails to calibrate within the acceptable range, contact the Pachymetry Study Coordinator immediately for help in troubleshooting the problem before proceeding with any further measurements.

Pachymetry Measurement Procedure

- 1) Perform the Power-Up Sequence as described above, noting the PQF reading that appears while the machine self-calibrates.
- 2) Record the "PQF" reading on the Data Collection Form
- 3) Position Pachette[™] for easy visibility during patient examination.
- 4) Clean/sterilize the probe tip with an alcohol swab containing 70% isopropyl alcohol. Allow the tip to air dry.



Figure 2: Proper positioning of the pachymetry probe for central corneal thickness measurement.

- 5) With patient in supine position and visualizing a fixation spot on the ceiling, position the probe tip on the cornea on the visual axis (*i.e.*, centered on the pupil; Figure 2). A measurement is taken and stored simply by properly applanating the probe. A short "beep" indicates that the measurement is complete. If a measurement is not obtained within three seconds, the display will show "POOR APPL" to indicate poor applanation and a longer "beep" occurs. The audible feedback is provided so that the operator can concentrate on probe tip alignment and positioning.
- 6) When an acceptable measurement has been made, the top display indicates the actual corneal thickness in microns. The corneal thickness is based on a velocity of sound in the cornea of 1,640 m/second. Although the Pachette[™] can be customized to calculate corneal thickness using any velocity of sound, we will use this generally accepted, factory-set value.
- 7) After an acceptable first measurement has been obtained and the probe removed from the cornea, the Pachette will automatically store the current measurement in memory at Position "1" and advance to the next measurement position. A short double "beep" is sounded to

inform the operator that the advancement has occurred. The Pachette can store up to 33 measurements in its memory. In this study, 5 measurements will be taken from the central cornea in each eye, for a total of 10. We will likely configure the instruments for this study to store only 10 measurements at any given time to avoid any confusion. Thus in sequence, five measurements will be taken from the right eye, then five from the left eye. This measurements/storage sequence should be continued until all positions have been measured and recorded into memory.

- 8) All measurements can be reviewed by either using the front panel rocker switch marked "" or "" or by pressing the left side of the foot pedal. A new measurement may be taken at any position by causing the appropriate position number to appear on the display by using the foot pedal or """ or """ switch taking a new measurement, and storing that new measurement in memory.
- 9) Once the 10 measurements have been obtained, the operator will transcribe the data onto the data collection form. Thus the data in positions 1 5 will correspond to the right eye measurements, and the data in positions 6 10 will correspond to the left eye measurements.
- 10) All measurements will remain in memory until the "CLEAR" switch is pressed, which will clear all measurements from memory and reinitialize the Pachette[™] for a measurement at Position 1. *Do not press the "CLEAR" switch until the data has been transcribed, or the data will be lost.*
- 11) If a measurement is not obtained and a message of "POOR APPL" appears on the display, check to ensure the probe tip actually touches the cornea and is perpendicular to the corneal surface. If a measurement is still not obtained, perform the Probe Quality Test by pressing the "PQT" switch. The Probe Quality Test can be performed at any point in the measurement sequence.

Suggested text for memo to IRB regarding protocol modification

We wish to request a modification to protocol XX, the Ocular Hypertension Treatment Study (OHTS). Specifically, we wish to add a one-time measurement of the corneal thickness of all OHTS participants using a non-invasive ultrasound device already in widespread clinical use. We believe that the modification is a minor one that does not alter the risk to participants in the study, and feel that the consent documents do not need to be altered to incorporate this protocol change. We hope you will agree.

The rationale for this protocol modification is as follows:

The OHTS is a multi-center clinical trial designed to evaluate the safety and efficacy of topical ocular hypotensive medications in preventing or delaying the onset of visual field loss and/or optic nerve damage in ocular hypertensive individuals at moderate risk of developing primary open angle glaucoma. In the OHTS, intraocular pressure (IOP) is determined by Goldmann applanation tonometry.

When he first described his tonometer, Goldmann discussed the effect of central corneal thickness (CCT) on IOP as measured by this device, but he believed that variations in corneal thickness in the absence of corneal disease occurred only rarely. He assumed a corneal thickness of 500 μ M and emphasized that at least theoretically, the corneal thickness might influence the applanation reading.

As devices to measure CCT accurately have come into widespread use, it became clear that corneal thickness does indeed have a positive correlation with IOP as measured by Goldmann applanation tonometry, and in some cases the difference may be clinically significant. It is also apparent that CCT is more variable among clinically normal individuals than Goldmann recognized.

This ancillary study to the OHTS is based on the increasing recognition that among patients currently classified as having 'Ocular Hypertension', some may suffer from no more than anatomically thickened, clinically normal corneas. These asymptomatic, thickened corneas in turn cause Goldmann applanation measurements to be erroneously elevated. This has important implications for the OHTS and for the clinical practice of glaucoma diagnosis and treatment.

It is our intention to make a one-time measurement of the CCT in each of the more than 1,600 patients enrolled in the OHTS nationwide. The purpose of obtaining this measurement will be to 1) describe the distribution of CCT in all patients enrolled in the OHTS; 2) determine whether CCT is related to race; and 3) re-calculate IOPs based on this CCT measurement.

The corneal thickness measurements are made with an ultrasound device that contacts the eye for a second or two, using the same topical (eyedrop) anesthetic that is instilled to make the pressure measurements. The tip of the device is sterilized between uses and there is no additional risk to the patient(s) by adding this measurement to the OHTS. The National Eye Institute and the OHTS independent Data & Safety Monitoring Committee recommended the addition of these measurements to the protocol and felt that this should be considered a 'protocol modification' that does not require patients to sign a separate consent form for the corneal thickness measurements.

We hope that you will agree that this protocol modification represents a minor change that can be handled administratively without requiring a full IRB review. I will be happy to discuss this with you or your staff if you have further questions.

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OCULAR HYPERTENSION TREATMENT STUDY (OHTS):

ANCILLARY GENETIC TESTING STUDY

Principal Investigator: Michael A. Kass, M.D. Department of Ophthalmology & Visual Sciences Washington University School of Medicine

ABSTRACT

The Ocular Hypertension Treatment Study (OHTS) is designed to determine whether medical reduction of intraocular pressure prevents or delays the onset of glaucomatous visual field loss and optic nerve damage in ocular hypertensive patients judged to be at moderate risk for developing openangle glaucoma. The OHTS has enrolled 1,636 participants at 22 clinical centers nationwide. The participants are examined twice yearly for a minimum of five years. An ancillary study to the OHTS is proposed to determine whether there is a genetic risk for ocular hypertension and glaucoma. We wish to draw blood from all participants in OHTS and then test the blood for genes linked to glaucoma and ocular hypertension. Following consent, blood samples will be drawn at the participant's OHTS Clinical Center or a nearby laboratory and shipped to the University of Iowa for preparation and storage. Scientists from around the world will submit requests to use the blood to the OHTS Executive and Data and Safety Monitoring Committees for review. The Committees will select those proposals that have high scientific merit.

<u>Hypothesis</u>. Specific genes greatly increase the risk that ocular hypertensive patients will develop open-angle glaucoma. We wish to determine which genes related to ocular hypertension and open-angle glaucoma are found in high prevalence in this group of ocular hypertensive patients and which genes are associated with a high rate of conversion to glaucoma. Genetic information will be incorporated into statistical models of risk. We will also determine the influence of specific genes on the response to medical treatment, i.e., response of intraocular pressure to topical beta blockers or latanoprost.

RESEARCH PLAN

We propose to collect and bank blood from the 1,636 patients currently participating in the Ocular Hypertension Treatment Study (OHTS). This proposal will be reviewed by the Washington University Institutional Review Board (IRB), and we will obtain IRB approval from the 22 participating clinical sites nationwide in the next few months.

Each patient will be informed about the OHTS genetic study and asked to volunteer for a venipuncture to obtain approximately 10cc of blood. The blood will be shipped to Edwin M. Stone, M.D., Ph.D., at the University of Iowa School of Medicine. Doctor Stone's laboratory will prepare the samples in the manner described below and then bank the blood for future investigations. We anticipate that scientists at many different institutions worldwide will want to utilize the blood drawn from the OHTS

population. They will be required to submit a two- or three-page proposal to the OHTS Executive and the Data and Safety Monitoring Committees. These committees will select the scientific proposals of highest merit. Blood will be supplied to these investigators for their testing, and the blood will be coded so the investigators have no indication of the patient's name or any other identifier. The only key to the code will be in the OHTS Coordinating Center at Washington University.

Ultimately, we will be able to correlate the presence of specific genes with the risk of developing glaucoma in this ocular hypertensive population. We will incorporate the genetic information into multivariate models of risk that will include a variety of factors, such as level of intraocular pressure, age, sex, race, family history of glaucoma, baseline cup/disc ratio, presence of diabetes mellitus, presence of hypertension and other vascular diseases, refractive error, smoking, corneal thickness, and treatment for elevated intraocular pressure. OHTS should yield the best estimates of risk for individual patients to develop open-angle glaucoma. The fact that OHTS has enrolled more than 400 African-American participants should allow us to perform separate analyses of genetic influence in this population at high risk for developing glaucoma.

Approximately 50% of the patients in OHTS are receiving topical medications to lower intraocular pressure. All medications are added in one-eyed therapeutic trials. The measurement of intraocular pressure in OHTS is made according to a detailed protocol. Thus, we should be able to correlate genetic information with intraocular pressure response to various medications, including beta blockers or latanoprost.

It is likely that genes related to ocular hypertension in glaucoma will be detected and sequenced over the next 10-20 years. Thus, it is possible that some of the requests for OHTS blood samples may arrive after OHTS is no longer functional. In that situation, we anticipate that a committee from the National Eye Institute will supervise the review and management of requests for blood obtained in the OHTS trial. Ocular Hypertension Treatment Study Genetics Ancillary Study Description

Attached is a copy of the consent for the Genetics Ancillary Study approved by the Washington University Institutional Review Board. Please modify this consent to fit the needs of your own institutional review board. A videotaped sample informed consent session with a participant to obtain a blood sample will be sent. You may wish to forward a copy of the tape to your IRB.

Following approval by your IRB, please notify your Central Coordinator. Supplies for drawing the bloods will be forwarded to you. If you will be contracting out for blood draws, please see below.

In House Phlebotomy

The following materials are supplied:

Purple top vacutainer Vacutainer needle Vacutainer Luer adapter Biohazard box (if requested) Participant ID labels (1 OHTS ID, 2 random D) Box for shipping samples Shipping form

If Participant Declines to Participate

If the participant does not wish to donate a sample, a Decline to Participate in Genetics (DG) form should be completed and mailed to the Coordinating Center.

If Participant Consents to Participate

- Step 1: Participant signs consent to participate.
 Clinic completes Genetics Consent (GC) form for each participant by affixing one Random ID label and one OHTS ID label.
 Clinic sends Genetics Consent (GC) form to Coordinating Center.
- Step 2: Clinic personnel draws blood using one purple-topped tube for each participant -Record date of blood draw on random ID label provided -Affix 1 random ID label to tube
- Step 3: Clinic mails sample and packing slip via regular mail to: Edwin Stone, MD, PhD University of Iowa Department of Ophthalmology 200 Hawkins Drive Iowa City, IA 52242
- *Note: Costs of mailing samples will be borne by the clinic.*

Contracted Phlebotomy

To set up service with an outside lab, please contact Ellen Long after lab has been identified at 314-747-1340 or via email at ellen@vrcc.wustl.edu. Ms. Long will set up a purchase order for lab fees to be automatically paid following receipt of invoice. Ms. Long will need the following information: Lab name, address, phone number and estimated number of participants who will use the lab. Outside lab costs should not exceed \$10.00. All lab supplies should be included in price. No spinning or processing of bloods is necessary.

The following materials are supplied by OHTS: Participant ID labels (2 randomly assigned, 1 OHTS ID) Instructions for lab

If Participant Declines to Participate

If the participant does not wish to donate a sample, a Decline to Participate in Genetics (DG) form should be completed and mailed to the Coordinating Center.

If Participant Consents to Participate

- Step 1: Participant signs consent to participate.
 Clinic completes Genetics Consent (GC) form for each participant by affixing one Random ID label and one OHTS ID label.
 Clinic sends Genetics Consent (GC) to Coordinating Center.
- Step 2: Clinic gives the following to the participant:
 -Directions to lab
 -Instructions for lab
 (Includes billing address and purchase order, random ID label with space to write in date blood is drawn)
 -Random ID label for vacutainer
 -Completed packing slip

Instructions for Outside Lab

The participant carries the following to the outside lab:

Packing Slip (completed by coordinator) Random ID label

Please complete the following information:

-Record date of blood draw on vacutainer -Record date of blood draw on packing slip -Mail sample to: Edwin Stone MD, PhD University of Iowa Department of Ophthalmology 200 Hawkins Drive Iowa City, IA 52242

For Billing:

Please send bill to: Ellen Long Washington University School of Medicine Box 8203, 660 South Euclid St. Louis, MO 63110-1093

Ocular Hypertension Treatment Study Genetics Ancillary Study

Packing Slip to Accompany Blood Sample To University of Iowa

Date shipped:_____

Clinic Name:_____

Contact Person:_____

Fax #:_____

	Genetics Random ID #	Date of Blood Draw	Patient's Gender
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			

Sample should be mailed to University of Iowa the same day it is obtained.

Dr. Edwin Stone University of Iowa Department of Ophthalmology 200 Hawkins Drive Iowa City, IA 52242



Form #2a 2/6/01 Human Studies Committee

INFORMED CONSENT FOR PARTICIPATION IN GENETIC RESEARCH INVOLVING CODED TISSUE AND/OR DATA

Participant		HSC Approval Number	
Principal Investigator	Michael A. Kass, M.D.	PI's Phone Number	362-3724
Title of Project:	Ocular Hypertension Treatment Study (O	HTS): Ancillary Genetic	Testing Study

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

Before making a decision about participating in a genetic research study, please read this consent form carefully and discuss any questions you might have with the researcher. You may also want to discuss your participation with family members or a friend before making a decision to participate in genetic research.

An invitation to participate in genetic research does not necessarily imply that you or other family members suffer from a particular disorder or are genetically at risk for that disorder.

1. You are already participating in the Ocular Hypertension Treatment Study (OHTS). The purpose of the OHTS is to determine whether lowering eye pressure (intraocular pressure) with eye drop medicines prevents or delays the onset of glaucoma in individuals with increased eye pressure.

You are being asked to participate in an ancillary research study conducted by Dr. Kass and colleagues. The overall purpose of this component of the OHTS study is to determine if there is a genetic cause of elevated eye pressure and glaucoma. To study this question, Researchers will collect a blood sample from OHTS participants to look for differences in the genes (DNA) that can cause increased eye pressure or glaucoma. Only genes that have been shown to play a role in ocular hypertension or glaucoma will be screened. We will not screen for any other conditions or diseases.

Ultimately, the goal of this research is to save vision.

2. Your participation will involve:

You will be asked to donate a blood sample (approximately 3 tablespoons) one time only. A physician or another trained person will draw blood at the OHTS Clinical Center or an approved outpatient laboratory.

In addition to your blood, this research requires information from your OHTS record. Donation of blood plus health information should help researchers to discover relationships between genes and ocular hypertension.

3. There are certain risks and discomforts that may be associated with this research. They include:

You may experience discomfort, bruising, and/or bleeding at the site of blood drawing. Occasionally some people experience dizziness or feel faint.

Certain genetic research may reveal that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers. We will test only for genes related to increased eye pressure and glaucoma.

If your participation in a genetic study becomes known outside of the research (for example, if your participation were to be noted in your medical record) you (and family members) may be unable to obtain health, life, or disability insurance. You might also be refused employment or be terminated from your current employment. This could happen if you choose to discuss your participation with your doctor without requesting that the information be kept out of your medical record. Inclusion of genetic (or any other) information in your medical record may allow insurance providers to access such information.

In order to prevent these problems, your genetic test results will not become part of your hospital or clinical record. Information from genetic test results used for scientific publications will not include names or any other identifier. You will not be identified in any reports on this study. Blood samples will be stored in a locked freezer at the University of Iowa and will not be labeled with names or OHTS ID numbers. Your blood and data will be assigned a specific code number. A master list linking the code number and your identity will be kept separate from the research data. The master list will be kept in a locked file at Washington University in St. Louis, Missouri and only designated members of the research team will have access to the master list. Every effort will be made to protect your research data and your confidentiality; there is, however, always the possibility of a breach of confidentiality.

4. The possible benefits to you and society from this research are:

This study is for research purposes only. You will not receive any medical or financial benefit from participating in this research, nor can you claim ownership rights to any medical or scientific product that results from research with your blood. By agreeing to participate, you make a free and generous

gift of your blood to research that may benefit others. The study of your blood may one day result in new tests or treatments, or may help to prevent or cure glaucoma. Scientific knowledge often advances slowly, but it may greatly benefit future generations. Researchers at Washington University consider you an important partner in the battle against disease and are grateful to those who choose to participate.

Research results will not be available to you or your physician. Genetic results will be published and you can choose to be tested in an approved clinical laboratory at a later time.

- 5. Your participation is voluntary and you may choose not to participate in this research study or withdraw your consent at any time. If you choose to participate in a study that uses code numbers to link participants to blood and later change your mind, the tissue can be destroyed upon request. To withdraw your consent, call Dr. Kass at (314) 362-3724. Any research results already obtained cannot be destroyed or recalled.
- 6. All reasonable measures to protect the confidentiality of your records and your identity will be taken. Your identity will not be revealed in any publication that may result from this study. The confidentiality of all study related records will be maintained in accordance with State and Federal laws. There is a possibility that your medical research record, including identifying information, may be inspected and photocopied by officials of Federal or State government agencies and the University Human Studies Committee.
- If you have any questions or concerns regarding this study, or if any problems arise, you may call the Principal Investigator at 314-362-3724. You may also ask questions or state concerns regarding your rights as a research participant to Dr. Philip Ludbrook, Chairman of the Human Studies Committee, at (314) 362-3244 or (800) 438-0445.
- 8. Washington University investigators and their colleagues who provide services at Washington University Medical Center hospitals and facilities recognize the importance of your contribution to research studies that are trying to improve medical care. Washington University investigators and their staffs will make every effort to minimize, control, and treat any complications that may arise as a result of this research. If you believe that you are injured as the result of the research question being asked in the study, please contact the Principal Investigator and/or the Chairman of the Human Studies Committee as stated in item 7. Washington University reserves the right to make decisions concerning payment for medical treatment for injuries solely and directly relating to your participation in biomedical or behavioral research.
- 9. You will be informed of any significant new findings developed during the course of participation in this research that may have a bearing on your willingness to continue in the study. The investigator may withdraw you from this research if circumstances arise (such as non-compliance with the protocol and non-tolerance of a study medication) which warrant doing so.

10. This research is not intended for the purpose of diagnosing or treating any medical problems not specifically stated in the purpose of the research. Participation in a research study does not take the place of routine physical examinations or visits to your personal physician.

I have read this consent form and have been given the opportunity to ask questions. I will also be given a signed copy of this consent form for my records. I hereby consent to my participation in the research described above, titled: Ocular Hypertension Treatment Study (OHTS): Ancillary Genetic Testing Study.

Parent or legal guardian's signature on
Date
participants' behalf if participant is less than 13
years of age or not legally competent. (Blood
drawing only: Less than 17 years of age.)

Participant's Signature Date

Relationship to Child Date

Informed Consent provided by:

Signature of Principal or Collaborating Investigator when informed consent responsibility is entrusted to a designee. (See HSC Guidelines on *Who May Obtain Consent to Participate in Research Activities.*) Signature of Principal Investigator or Designee Date

This form is valid only if the Human Studies Committee's current stamp of approval is shown below.

Patient Initials	
Date	
Version #	

17-66 OHTS Manual of Procedures