Ocular Hypertension Treatment Study
(OHTS II)

Manual of Procedures
Version 4.0
3/10/03

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Please direct any problems to the web master
# 1. Introduction

1.1 Synopsis of the Ocular Hypertension Treatment Study II ..................... 1-2
1.2 Specific Aims of OHTS II ................................................................. 1-3
1.3 Background and Significance ............................................................ 1-4
1.4 Progress Report/Preliminary Studies ................................................. 1-7
   1.4.1 Efficacy of Treatment ................................................................. 1-7
   1.4.2 Preliminary Evidence for a Possible Penalty of Delayed Treatment 1-8
   1.4.3 Evidence of Possible Adverse Effects of Medication ..................... 1-9
   1.4.4 Risk Factors for POAG ............................................................... 1-10
   1.4.5 Evidence of Early Optic Disc and Visual Field Changes Prior to POAG 1-12
   1.4.6 Differential Treatment Protection by Race .................................. 1-13
1.5 Planning Sessions for OHTS II ......................................................... 1-14
1.6 Study Milestones ............................................................................. 1-14
1.7 References ....................................................................................... 1-16

# 2. Study Design

2.1 Synopsis of the OHTS II Study Design ............................................. 2-2
2.1.2 Specific Aims of OHTS II ............................................................. 2-3
2.1.3 Timetable For OHTS I and OHTS II ............................................. 2-4
2.2 Participant Eligibility for OHTS II ................................................... 2-5
   2.2.1 Participant Entry Criteria for OHTS II ........................................ 2-5
   2.2.2 Medical Withdrawal of Participants during Transition to OHTS I ... 2-5
2.3 Rationale for Including all OHTS I Participants in OHTS II ............... 2-6
   2.3.1 Why include participants from OHTS I who have already developed POAG? .......................................................... 2-6
   2.3.2 Why include participants who are not ascertainable for visual field abnormality or optic disc deterioration? ..................... 2-6
   2.3.3 Why include participants in OHTS II who would be ineligible for OHTS I? ................................................................. 2-7
   2.3.4 Why include participants who refuse medication? ...................... 2-7
   2.3.6 Why not limit enrollment in OHTS II to high-risk individuals? .... 2-7
   2.3.7 Is it ethical to initiate medical treatment in all OHTS I participants who enroll in OHTS II? ................................................. 2-7
   2.3.8 Entry Criteria for OHTS I .......................................................... 2-8
2.4 Baseline Characteristics of Participants in OHTS I ............................ 2-8
2.5 Treatment ....................................................................................... 2-9
   2.5.1 Goals of Treatment .................................................................... 2-9
   2.5.2 Medical Regimen ...................................................................... 2-9
   2.5.3 Why not include neuroprotective drugs in OHTS II? ................... 2-10
   2.5.4 Participant Safety and Possible Drug-Related Side Effects ............ 2-10
   2.5.5 Medication Adherence .............................................................. 2-11
2.6 Follow-up Schedule .................................................................2-12
2.6.1 Tests and measures at semi-annual follow-up visits (6, 18 months, etc.) include: .................................................................2-12
2.6.2 Tests and measures at annual follow-up visits (12, 24 months, etc.) include: .................................................................2-12
2.6.3 Tests and measures performed every two years in OHTS II........2-13
2.6.4 One time measurement in OHTS II........................................2-13
2.7 POAG Endpoint Determination .................................................2-14
2.7.1 Optic Disc POAG Endpoint ......................................................2-14
2.7.2 Rationale for Optic Disc Assessment .......................................2-15
2.7.3 Visual Field POAG Endpoint ....................................................2-16
2.7.4 Rationale for Visual Field Assessment .....................................2-17
2.7.5 When a POAG Endpoint is Confirmed ....................................2-18
2.7.6 POAG Treatment Group .........................................................2-18
2.7.7 Protecting Masking at Reading Centers ..................................2-19
2.8 Protection of Participants .........................................................2-20
2.8.1 Safety of Treatment .................................................................2-20
2.8.2 Confidentiality ......................................................................2-20
2.9 Clinical Centers ....................................................................2-21
2.10.1 Participants Available for OHTS II .........................................2-21
2.10.2 Statistical Power for Testing the Hypothesis .........................2-23
2.10.3 Assumptions Used to Estimate Statistical Power..................2-23
2.10.4 Scenarios for Setting the Upper and Lower Boundaries of Statistical Power .................................................................2-24
2.10.5 Analysis of Efficacy ...............................................................2-27
2.10.6 Analysis of Safety .................................................................2-28
2.10.7 Interim Analysis/Safety Monitoring ........................................2-30
2.11 Human Participants .................................................................2-31
2.11.1 Entry Criteria .....................................................................2-31
2.11.2 Exclusion Criteria for OHTS II ..............................................2-32
2.11.3 Confidentiality and Protection of Subjects .............................2-32
2.11.4 Risks ..................................................................................2-33
2.11.5 Benefits .............................................................................2-35
2.12 Literature Cited .....................................................................2-35
Appendix .....................................................................................2-37
OHTS I participants at baseline ....................................................2-38
Procedures for Confirmation of Abnormality ...............................2-41
Participating Clinics, Committees and Resource Centers ..........2-46
3. Eligibility and Exclusion Criteria
   3.1 Introduction .....................................................................................................3-2
   3.2 Eligibility for OHTS II ....................................................................................3-2
   3.3 Exclusion Criteria for OHTS II .......................................................................3-3
   3.4 Eligibility Period for OHTS II.........................................................................3-3

4. Participant Education and Informed Consent
   4.1 Introduction .....................................................................................................4-2
   4.2 Why Informed Consent is Required for OHTS II ...........................................4-2
   4.3 Description of OHTS II Protocol Modifications .............................................4-2
   4.4 Local IRB Approval for OHTS II .....................................................................4-2
   4.5 Issues in Participant Education ......................................................................4-3
   4.6 Signing the Informed Consent Form ................................................................4-4
   4.7 Participants who Decline Medication ............................................................4-5
   4.8 Participants Who Cannot Perform Tests .........................................................4-5
   4.9 Medical Withdrawal .......................................................................................4-6
   4.10 Deferred Consent ..........................................................................................4-6
   4.11 Decline to Participate ...................................................................................4-6
   4.12 Continuing Education ..................................................................................4-6
   Appendix .............................................................................................................4-7
      Human Studies Committee ..............................................................................4-8

5. Schedule of Visits and Form Completion
   5.1 Introduction .....................................................................................................5-2
   5.2 OHTS II Transition .........................................................................................5-2
   5.3 IOP Confirmation Visit ..................................................................................5-2
   5.4 Follow-up Visits .............................................................................................5-3
   5.4.1 Semi-Annual (6-Month) Follow-up Visit .....................................................5-4
   5.4.2 Annual (12-Month) Follow-up Visit ............................................................5-5
   5.5 Visual Field Abnormality Confirmation Visit ................................................5-6
   5.6 Optic Disc Deterioration Confirmation Visit .................................................5-6
   5.7 Unscheduled Visits .......................................................................................5-7
   5.8 Adverse Events (AE) ....................................................................................5-7
   5.9 Participant Retention .....................................................................................5-8
   5.10 Participant Transfer .....................................................................................5-8
   5.11 Participant Death ..........................................................................................5-9
   5.12 Missed Visit ..................................................................................................5-9
   5.13 Inactive Participants ....................................................................................5-9
   5.14 Tests and Measures for Each Visit Type ......................................................5-10
   5.15 Forms Required by Visit Type ......................................................................5-11
   5.16 Forms Required by Event ...........................................................................5-12
   5.17 OHTS II Forms and Current Version Number .............................................5-13
# 6. Clinical Tests and Examinations

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1 Introduction</td>
<td>6-2</td>
</tr>
<tr>
<td>6.2 Refraction</td>
<td>6-2</td>
</tr>
<tr>
<td>6.2.1 Refraction Technique</td>
<td>6-2</td>
</tr>
<tr>
<td>6.3 Visual Acuity</td>
<td>6-5</td>
</tr>
<tr>
<td>6.3.1 Snellen Visual Acuity Technique</td>
<td>6-5</td>
</tr>
<tr>
<td>6.3.2 Snellen Visual Acuity Scoring</td>
<td>6-5</td>
</tr>
<tr>
<td>6.3.3 ETDRS Visual Acuity Technique</td>
<td>6-6</td>
</tr>
<tr>
<td>6.3.4 ETDRS Visual Acuity Scoring</td>
<td>6-7</td>
</tr>
<tr>
<td>6.3.5 ETDRS Visual Acuity Testing Discontinuation</td>
<td>6-7</td>
</tr>
<tr>
<td>6.3.6 ETDRS Visual Acuity Certification</td>
<td>6-7</td>
</tr>
<tr>
<td>6.4 Slit-Lamp Examination</td>
<td>6-7</td>
</tr>
<tr>
<td>6.5 Tonometry</td>
<td>6-8</td>
</tr>
<tr>
<td>6.5.1 Tonometry technique</td>
<td>6-8</td>
</tr>
<tr>
<td>6.6 Gonioscopy</td>
<td>6-10</td>
</tr>
<tr>
<td>6.7 Ophthalmoscopy</td>
<td>6-10</td>
</tr>
<tr>
<td>6.8 Blood Pressure</td>
<td>6-10</td>
</tr>
<tr>
<td>6.9 Pachymetry</td>
<td>6-12</td>
</tr>
<tr>
<td>6.9.1 Overview of Pachymetry Measurements</td>
<td>6-13</td>
</tr>
<tr>
<td>6.9.2 Troubleshooting Pachymeter</td>
<td>6-14</td>
</tr>
<tr>
<td>6.9.3 General Description of DGH-500 Pachymeter</td>
<td>6-15</td>
</tr>
<tr>
<td>6.9.4 Power-up Sequence of Pachymeter</td>
<td>6-16</td>
</tr>
<tr>
<td>6.9.5 Calibration of Pachymeter</td>
<td>6-16</td>
</tr>
<tr>
<td>6.9.6 Pachymetry Measurement Procedure</td>
<td>6-17</td>
</tr>
<tr>
<td>6.10 Visual Fields</td>
<td>6-18</td>
</tr>
<tr>
<td>6.11 Stereoscopic Optic Disc Photography</td>
<td>6-18</td>
</tr>
<tr>
<td>6.12 Additional Measures (AM)</td>
<td>6-19</td>
</tr>
<tr>
<td>6.13 NEI Vision Function Questionnaire (VQ)</td>
<td>6-19</td>
</tr>
<tr>
<td>6.14 Genetics Testing</td>
<td>6-19</td>
</tr>
</tbody>
</table>

# 7. Treatment Regimen

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 Introduction</td>
<td>7-2</td>
</tr>
<tr>
<td>7.2 Goals of Treatment</td>
<td>7-2</td>
</tr>
<tr>
<td>7.3 Medical Regimen</td>
<td>7-2</td>
</tr>
<tr>
<td>7.3.1 Treatment in OHTS II</td>
<td>7-3</td>
</tr>
<tr>
<td>7.4 Compliance</td>
<td>7-4</td>
</tr>
<tr>
<td>7.5 Deviation from Treatment Protocol</td>
<td>7-5</td>
</tr>
<tr>
<td>7.6 Confirmed POAG Group</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7 Drug Supplies</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7.1 Inventory and Distribution</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7.2 Reporting</td>
<td>7-7</td>
</tr>
<tr>
<td>7.8 Adverse Events (AE)</td>
<td>7-8</td>
</tr>
<tr>
<td>Appendix</td>
<td>7-9</td>
</tr>
<tr>
<td>Treatment Regimen</td>
<td>7-10</td>
</tr>
<tr>
<td>Adverse Event Form</td>
<td>7-11</td>
</tr>
</tbody>
</table>
8. Site Visits, Training, Certification, and Performance Monitoring

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 Introduction</td>
<td>8-2</td>
</tr>
<tr>
<td>8.2 Clinic Site Visit</td>
<td>8-2</td>
</tr>
<tr>
<td>8.3 Clinic Investigators</td>
<td>8-2</td>
</tr>
<tr>
<td>8.4 Clinic Coordinators</td>
<td>8-3</td>
</tr>
<tr>
<td>8.5 Photographers</td>
<td>8-3</td>
</tr>
<tr>
<td>8.6 Visual Field Technicians</td>
<td>8-3</td>
</tr>
<tr>
<td>8.7 Clinical Centers</td>
<td>8-4</td>
</tr>
<tr>
<td>8.8 Performance Monitoring</td>
<td>8-4</td>
</tr>
<tr>
<td>8.9 New Personnel</td>
<td>8-5</td>
</tr>
<tr>
<td>8.10 Cross-Training</td>
<td>8-5</td>
</tr>
</tbody>
</table>

9. Study Organization

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Introduction</td>
<td>9-2</td>
</tr>
<tr>
<td>9.1.1 Clinical Centers</td>
<td>9-2</td>
</tr>
<tr>
<td>9.1.2 Coordinating Center</td>
<td>9-2</td>
</tr>
<tr>
<td>9.1.3 Visual Field Reading Center (VFRC)</td>
<td>9-3</td>
</tr>
<tr>
<td>9.1.4 Optic Disc Reading Center (ODRC)</td>
<td>9-3</td>
</tr>
<tr>
<td>9.1.5 Study Chairman’s Office</td>
<td>9-4</td>
</tr>
<tr>
<td>9.1.6 NEI Program Office</td>
<td>9-4</td>
</tr>
<tr>
<td>9.1.7 Confocal Scanning Laser Ophthalmoscopy Reading Center (CSLO)</td>
<td>9-4</td>
</tr>
<tr>
<td>9.1.8 Short Wave-Length Perimetry Reading Center (SWAP)</td>
<td>9-5</td>
</tr>
<tr>
<td>9.1.9 Genetics Center</td>
<td>9-5</td>
</tr>
<tr>
<td>9.2 Committees and Groups</td>
<td>9-5</td>
</tr>
<tr>
<td>9.3 Executive/Steering Committee</td>
<td>9-6</td>
</tr>
<tr>
<td>9.3.1 Executive/Steering Committee Membership</td>
<td>9-6</td>
</tr>
<tr>
<td>9.3.2 Executive/Steering Committee Functions</td>
<td>9-7</td>
</tr>
<tr>
<td>9.3.3 Executive/Steering Committee Meetings</td>
<td>9-7</td>
</tr>
<tr>
<td>9.4 Data and Safety Monitoring Committee (DSMC)</td>
<td>9-7</td>
</tr>
<tr>
<td>9.4.1 DSMC Membership</td>
<td>9-8</td>
</tr>
<tr>
<td>9.4.2 DSMC Functions</td>
<td>9-8</td>
</tr>
<tr>
<td>9.4.3 DSMC Meetings</td>
<td>9-9</td>
</tr>
<tr>
<td>9.5 Full Investigative Group</td>
<td>9-9</td>
</tr>
<tr>
<td>9.5.1 Full Investigative Group Membership</td>
<td>9-9</td>
</tr>
<tr>
<td>9.5.2 Full Investigative Group Functions</td>
<td>9-9</td>
</tr>
<tr>
<td>9.5.3 Full Investigative Group Meetings</td>
<td>9-10</td>
</tr>
<tr>
<td>9.6 Coordinators Group</td>
<td>9-10</td>
</tr>
<tr>
<td>9.6.1 Coordinators Group Functions</td>
<td>9-10</td>
</tr>
<tr>
<td>9.6.2 Coordinators Group Membership</td>
<td>9-10</td>
</tr>
<tr>
<td>9.6.3 Coordinators Group Meetings</td>
<td>9-10</td>
</tr>
<tr>
<td>9.7 Endpoint Committee</td>
<td>9-10</td>
</tr>
<tr>
<td>9.7.1 Endpoint Committee Membership</td>
<td>9-11</td>
</tr>
<tr>
<td>9.7.2 Endpoint Committee Function</td>
<td>9-11</td>
</tr>
<tr>
<td>9.7.3 Endpoint Committee Meetings</td>
<td>9-11</td>
</tr>
<tr>
<td>9.8 Genetics Advisory Committee</td>
<td>9-11</td>
</tr>
<tr>
<td>9.8.1 Genetics Advisory Committee Membership</td>
<td>9-11</td>
</tr>
</tbody>
</table>
10. **Policy Matters**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 IRB Approval</td>
<td>10-2</td>
</tr>
<tr>
<td>10.2 Participant Consent</td>
<td>10-2</td>
</tr>
<tr>
<td>10.3 Publicity</td>
<td>10-2</td>
</tr>
<tr>
<td>10.3.1 Publications and Presentations Policy</td>
<td>10-2</td>
</tr>
<tr>
<td>10.4 Editorial Policy</td>
<td>10-2</td>
</tr>
<tr>
<td>10.4.1 Publication of Trial Design, Methods, and Findings</td>
<td>10-3</td>
</tr>
<tr>
<td>10.4.2 Presentations</td>
<td>10-3</td>
</tr>
<tr>
<td>10.4.3 Publications from Ancillary Studies</td>
<td>10-4</td>
</tr>
<tr>
<td>10.4.4 Publications Concerning Methods</td>
<td>10-4</td>
</tr>
<tr>
<td>10.5 Ancillary Studies</td>
<td>10-5</td>
</tr>
<tr>
<td>10.5.1 Definition of an Ancillary Study</td>
<td>10-5</td>
</tr>
<tr>
<td>10.5.2 Rationale for the Approval Process</td>
<td>10-5</td>
</tr>
<tr>
<td>10.5.3 Preparation of a Request for Approval of an Ancillary Study</td>
<td>10-5</td>
</tr>
<tr>
<td>10.5.4 Procedures for Obtaining Ancillary Study Approval</td>
<td>10-6</td>
</tr>
<tr>
<td>10.5.5 Funding of Ancillary Studies</td>
<td>10-6</td>
</tr>
<tr>
<td>10.5.6 Publication of Ancillary Study Results</td>
<td>10-6</td>
</tr>
<tr>
<td>10.5.7 Progress Reports</td>
<td>10-7</td>
</tr>
<tr>
<td>10.6 Access to Study Information</td>
<td>10-7</td>
</tr>
<tr>
<td>10.6.1 Study Documents</td>
<td>10-7</td>
</tr>
<tr>
<td>10.6.2 Study Data</td>
<td>10-7</td>
</tr>
<tr>
<td>10.7 Participation of Women and Minority Groups</td>
<td>10-7</td>
</tr>
<tr>
<td>10.8 Protection of Human Subjects Certification</td>
<td>10-8</td>
</tr>
<tr>
<td>Appendix</td>
<td>10-9</td>
</tr>
<tr>
<td>Publications and Presentation Policy</td>
<td>10-11</td>
</tr>
<tr>
<td>Manuscript Checklist for Authors</td>
<td>10-12</td>
</tr>
<tr>
<td>Abstract Checklist for Authors</td>
<td>10-13</td>
</tr>
<tr>
<td>Manuscript Review Form</td>
<td>10-14</td>
</tr>
</tbody>
</table>

11. **Clinical Center Procedures**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1 Clinical Center Responsibilities</td>
<td>11-2</td>
</tr>
<tr>
<td>11.2 Clinical Center Personnel</td>
<td>11-3</td>
</tr>
<tr>
<td>11.2.1 Responsibilities of the Principal Investigator</td>
<td>11-3</td>
</tr>
<tr>
<td>11.2.2 Responsibilities of the Clinic Coordinator</td>
<td>11-3</td>
</tr>
<tr>
<td>11.2.3 Responsibilities of the Technician</td>
<td>11-4</td>
</tr>
<tr>
<td>11.2.4 Responsibilities of the Photographer</td>
<td>11-5</td>
</tr>
<tr>
<td>11.3 Study Documents</td>
<td>11-5</td>
</tr>
<tr>
<td>11.4 Scheduling and Coordination of Participant Visits</td>
<td>11-6</td>
</tr>
<tr>
<td>11.4.1 Schedule of Visits</td>
<td>11-6</td>
</tr>
<tr>
<td>11.4.2 Clinic Tracking Report</td>
<td>11-6</td>
</tr>
<tr>
<td>11.5 Checking Completed Examination Forms</td>
<td>11-7</td>
</tr>
<tr>
<td>11.5.1 Completeness</td>
<td>11-7</td>
</tr>
<tr>
<td>11.5.2 Legibility</td>
<td>11-7</td>
</tr>
<tr>
<td>11.5.3 Edits and Corrections</td>
<td>11-7</td>
</tr>
<tr>
<td>11.6 Assuring Completeness of Follow-up</td>
<td>11-8</td>
</tr>
<tr>
<td>11.7 Preparing for Return Visits</td>
<td>11-8</td>
</tr>
<tr>
<td>11.8 Recording Medication Taken by Participant</td>
<td>11-9</td>
</tr>
<tr>
<td>11.8.1 Drug List</td>
<td>11-10</td>
</tr>
<tr>
<td>11.9 Reports and Services on Web</td>
<td>11-21</td>
</tr>
<tr>
<td>Appendix</td>
<td>11-25</td>
</tr>
<tr>
<td>Application for Web Access</td>
<td>11-25</td>
</tr>
</tbody>
</table>
### 12. Chairman's Office

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1 Introduction</td>
<td>12-2</td>
</tr>
<tr>
<td>12.1.1 Study Chairman</td>
<td>12-2</td>
</tr>
<tr>
<td>12.1.2 Vice-Chairs</td>
<td>12-2</td>
</tr>
<tr>
<td>12.1.3 Project Managers</td>
<td>12-3</td>
</tr>
<tr>
<td>12.1.4 Medical Monitor</td>
<td>12-3</td>
</tr>
</tbody>
</table>

### 13. Coordinating Center

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.1 Introduction</td>
<td>13-2</td>
</tr>
<tr>
<td>13.2 Personnel</td>
<td>13-2</td>
</tr>
<tr>
<td>13.3 Protocol Development and Modifications</td>
<td>13-6</td>
</tr>
<tr>
<td>13.4 Follow-up</td>
<td>13-6</td>
</tr>
<tr>
<td>13.5 Participant and Resource Center Close-out</td>
<td>13-7</td>
</tr>
<tr>
<td>13.6 Study Close-out</td>
<td>13-7</td>
</tr>
<tr>
<td>13.7 Quality Assurance at Clinics</td>
<td>13-7</td>
</tr>
<tr>
<td>13.8 Data Security and Protection of Confidentiality</td>
<td>13-9</td>
</tr>
<tr>
<td>13.9 Records Flow Within the Coordinating Center</td>
<td>13-10</td>
</tr>
<tr>
<td>13.9.1 Reports to Clinical Centers</td>
<td>13-12</td>
</tr>
<tr>
<td>13.10 Form Design</td>
<td>13-13</td>
</tr>
<tr>
<td>13.11 Data Management</td>
<td>13-14</td>
</tr>
<tr>
<td>References</td>
<td>13-15</td>
</tr>
</tbody>
</table>

### 14. Optic Disc Photography

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1 ODRC Objective</td>
<td>14-2</td>
</tr>
<tr>
<td>14.1.1 Personnel</td>
<td>14-2</td>
</tr>
<tr>
<td>14.1.2 Responsibilities of ODRC</td>
<td>14-3</td>
</tr>
<tr>
<td>14.2 Optic Disc Reading Center Procedures</td>
<td>14-3</td>
</tr>
<tr>
<td>14.2.1 Reader Pre-requisite</td>
<td>14-3</td>
</tr>
<tr>
<td>14.2.2 Training and Certification of Optic Disc Readers</td>
<td>14-3</td>
</tr>
<tr>
<td>14.2.3 Logging in Photographs from Clinical Centers</td>
<td>14-4</td>
</tr>
<tr>
<td>14.2.4 Storage of Optic Disc Photographs</td>
<td>14-5</td>
</tr>
<tr>
<td>14.2.5 Evaluation of Stereo and Clarity</td>
<td>14-5</td>
</tr>
<tr>
<td>14.2.6 When Readers Disagree on Technical Quality or Progression Criteria</td>
<td>14-6</td>
</tr>
<tr>
<td>14.2.7 Disc Progression Assessment: Change from Baseline</td>
<td>14-6</td>
</tr>
<tr>
<td>14.2.8 Masked Rereading of Change</td>
<td>14-6</td>
</tr>
<tr>
<td>14.2.9 Confirmatory Change Photographs</td>
<td>14-6</td>
</tr>
<tr>
<td>14.3 Quality Control Procedures</td>
<td>14-7</td>
</tr>
<tr>
<td>14.4 Communications to Clinical Center</td>
<td>14-8</td>
</tr>
<tr>
<td>14.4.1 Communications to the Clinical Coordinators</td>
<td>14-8</td>
</tr>
<tr>
<td>14.4.2 Communications to Clinical Center Principal Investigators</td>
<td>14-9</td>
</tr>
<tr>
<td>14.4.3 Transmission of Data from ODRC to Coordinating Center</td>
<td>14-9</td>
</tr>
<tr>
<td>14.4.4 Data Entry</td>
<td>14-10</td>
</tr>
<tr>
<td>14.4.5 Report Generation</td>
<td>14-10</td>
</tr>
<tr>
<td>14.5 Transmission of Data from Coordinating Center to ODRC</td>
<td>14-11</td>
</tr>
<tr>
<td>14.6 When to take Optic Disc Photographs</td>
<td>14-12</td>
</tr>
<tr>
<td>14.6.1 Who must be certified for Photography</td>
<td>14-12</td>
</tr>
<tr>
<td>14.6.2 Certification for Photography</td>
<td>14-12</td>
</tr>
<tr>
<td>14.6.3 Certification Code</td>
<td>14-13</td>
</tr>
</tbody>
</table>
14.6.4 Continuation of Certification as an OHTS Photographer .................. 14-13
14.6.5 OHTS Cameras & Procedures ............................................................. 14-14
14.7 Optic Disc Photography Protocol ......................................................... 14-14
14.7.1 Determine Eyepiece Setting .............................................................. 14-14
14.7.2 Film ...................................................................................................... 14-14
14.7.3 Dilation .................................................................................................. 14-14
14.7.4 Photography Instruction ....................................................................... 14-14
14.7.5 Developing Film .................................................................................. 14-15
14.7.6 Labeling Slides .................................................................................... 14-15
14.7.7 Mailing Slides to ODRC ................................................................. 14-16
Appendix ........................................................................................................... 14-17
ODRC Disc Hemorrhage Definition .......................................................... 14-18
Figure 1 Placement of Masked Slides for Readers .................................. 14-20
Figure 2 Proper Slide Arrangement for Submission for Photographer
Certification ..................................................................................................... 14-20
Figure 3 Proper Labeling for OHTS Study Slides .................................... 14-21
Figure 4 Correct Placement of OD and OS Slides for Mailing .................... 14-22

15. Visual Field Reading Center Procedures

15.1 Organization .............................................................................................. 15-2
15.1.1 Personnel ............................................................................................... 15-2
15.1.2 Responsibilities of VFRC Personnel .................................................... 15-4
15.2 VFRC Objectives ..................................................................................... 15-6
15.3 VFRC Daily Operations and Procedures ............................................... 15-6
15.3.1 Visual Field Shipments from the Clinical Centers ......................... 15-7
15.3.2 Filing, Back-up, and Review Systems .................................................... 15-8
15.3.3 Management of Humphrey Field Data .............................................. 15-8
15.3.3.1 Humphrey Field Data Files ................................................................. 15-8
15.3.3.2 Conversion of the Humphrey Disk Format ...................................... 15-9
15.3.3.3 Handling of Missing or "Not Tested" Data ........................................ 15-9
15.3.3.4 Conversion of Data into a Format for Analysis .............................. 15-9
15.3.3.5 Visual Field Quality Control Data ..................................................... 15-11
15.3.3.6 Data File Transfers to the Coordinating Center ......................... 15-12
15.3.4 Visual Field POAG Confirmation ....................................................... 15-12
15.3.5 Additional Visual Field Data Considerations ................................... 15-13
15.4 Quality Control Functions ..................................................................... 15-14
15.4.1 Visual Field Quality Control ................................................................. 15-14
15.4.2 Turnaround Time Reporting System ................................................ 15-15
15.4.3 Internal Quality Control System ......................................................... 15-15
15.4.4 Certification of Visual Field Technicians .......................................... 15-15
15.5 Training and Certification of Technicians .............................................. 15-16
15.5.1 Training on the Humphrey Field Analyzer ....................................... 15-16
15.5.2 Certification Procedures ..................................................................... 15-16
15.6 Archival Function of the VFRC .............................................................. 15-17
15.7 Visual Field Abnormality Classification .................................................. 15-18
Perimetry Protocol .......................................................................................... 15-21
Introduction ..................................................................................................... 15-23
Visual Field Testing Procedures ................................................................. 15-23
Transmission of the Visual Field to the VFRC .......................................... 15-29
Technician Certification Procedures ......................................................... 15-30
Visual Field Abnormality Classification ..................................................... 15-34
16. Ancillary Studies

Confocal Scanning Laser Ophthalmoscope (CSLO) ........................................... 16-2
CSLO HRT HEYEX Software Update .......................................................... 16-25
Short Wavelength Automated Perimetry (SWAP) ....................................... 16-51
Genetics Ancillary Testing .......................................................................... 16-59
1. Introduction

1.1 Synopsis of the Ocular Hypertension Treatment Study II .................. 1-2
1.2 Specific Aims of OHTS II ............................................................. 1-3
1.3 Background and Significance ......................................................... 1-4
1.4 Progress Report/Preliminary Studies ............................................ 1-7
1.4.1 Efficacy of Treatment ............................................................... 1-7
1.4.2 Preliminary Evidence for a Possible Penalty of Delayed Treatment ............................................................................. 1-7
1.4.3 Evidence of Possible Adverse Effects of Medication..................... 1-8
1.4.4 Risk Factors for POAG............................................................. 1-9
1.4.5 Evidence of Early Optic Disc and Visual Field Changes
   Prior to POAG................................................................................ 1-10
1.4.6 Differential Treatment Protection by Race ................................ 1-12
1.5 Planning Sessions for OHTS II....................................................... 1-13
1.6 Study Milestones......................................................................... 1-14
1.7 References.................................................................................... 1-14

Appendix.............................................................................................. 1-16

Manuscript “A Randomized Trial Determines that Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open Angle Glaucoma”...................... 1-19
Manuscript “Baseline Factors that Predict the Onset of Primary Open Angle Glaucoma:” ......................................................... 1-20
1.1 Synopsis of the Ocular Hypertension Treatment Study II

Prior to the Ocular Hypertension Treatment Study (OHTS I) there was conflicting evidence as to whether early medical treatment to lower IOP was effective in delaying or preventing the onset of glaucomatous damage in individuals with elevated intraocular pressure (referred to as ocular hypertensive individuals) (Kass, 2002). OHTS I clearly demonstrated that early medical treatment delays or prevents the onset of primary open angle glaucoma (POAG) in ocular hypertensive individuals. In OHTS I, 1,636 participants with intraocular pressures (IOP) of $\geq 24$ mm Hg and $< 32$ mm Hg in one eye and $\geq 21$ mm Hg and $< 32$ mm Hg in the fellow eye were randomized to either treatment with commercially available topical ocular hypotensive medication or to observation. At 60 months, the cumulative frequency of developing POAG was 4.4% in the medication group and 9.5% in the observation group (Kass, 2002).

Now that it has been proven that lowering IOP is effective in delaying or preventing POAG in ocular hypertensive individuals, it is important to determine when treatment should be initiated. Should ocular hypertensive individuals judged to be at moderate or high risk for developing POAG be started on treatment early or should treatment be delayed until early signs of POAG are detected on clinical examination? The answer to this question depends in part on the penalty or disadvantage (if any) of delaying treatment for ocular hypertensive individuals.

OHTS II provides a unique opportunity to determine the penalty of delaying treatment since we have a racially diverse randomized group of ocular hypertensive participants, one half of whom have been treated for 5-7 years (medication group) and one half of whom have been followed without treatment (observation group) for the same period. If we now treat all participants in both groups with ocular hypertensive medication, we should be able to determine if there is a penalty for waiting to institute treatment.

OHTS II, a follow-on study to OHTS I, is designed to compare the cumulative long-term incidence of POAG in the former observation participants of OHTS I who start treatment in OHTS II to the incidence in medication participants who received medication throughout OHTS I and who continue treatment in OHTS II. Participants are 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 deterioration and/or reproducible glaucomatous visual field abnormality in either eye. All visual fields and optic disc photographs are read in masked fashion in Reading Centers. A masked Endpoint Committee makes attribution to POAG. The participants will be followed for a minimum of five years with follow-up continuing until study termination as determined by the Data and Safety Monitoring Committee (DSMC).

The results of OHTS II will guide clinicians about the benefit (and risks) of early medical treatment. OHTS II should also yield important information about which ocular hypertensive participants are at greater risk for developing POAG and thus, may be good
candidates for early treatment. Furthermore, OHTS II will provide information about whether there is a differential response to treatment by race.

As in OHTS I, 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. Clinical Centers are the same as in OHTS I.

1.2 Specific Aims of OHTS II

Primary Aim: to determine if there is a long-term penalty or disadvantage for delaying treatment in ocular hypertensive individuals.

This question will be tested by comparing the long-term cumulative incidence of primary open angle glaucoma in participants who were in the observation group in OHTS I and who start ocular hypotensive treatment in OHTS II to the long-term cumulative incidence in participants who were in the medication group throughout OHTS I and who continue treatment in OHTS II. There may also be downsides to early treatment. One potential downside is drug-related adverse events. This potential downside or disadvantage to early treatment will be assessed by comparing the long-term cumulative incidence of adverse events in participants in these same two randomization groups. Another potential downside is the loss of effectiveness of ocular hypotensive medication with increasing duration of care. This potential downside will be assessed by comparing the percentage of participants in the two original randomization groups who fail to reach IOP goal in OHTS II, or who require multiple medications to reach IOP goal, or who require multiple changes of medication to reach IOP goal.

Secondary Aims:

1. To increase the precision and completeness of the risk model developed in OHTS I to predict which ocular hypertensive participants will develop POAG.

Refinement of the risk model will help to answer two questions, “Who is at risk for developing POAG?” and “Who might benefit from early treatment?” With longer follow-up, we will have a larger number of POAG endpoints which will increase statistical power of the entire model as well as determine if other factors (some of which were borderline in OHTS I) such as gender, heart disease, perfusion pressure, and myopia are risk factors for POAG in this sample.

2. To determine the predictive accuracy of subthreshold visual field and optic disc changes for subsequent development of POAG.

Many participants in OHTS I had changes of the optic disc or visual field that did not meet the OHTS rigorous criteria for POAG endpoints. The longer follow-up in OHTS II will enable us to distinguish reliable early signs of glaucomatous optic...
disc and visual field damage from non-specific changes with little or no prognostic significance.

3. **To determine if there is a racial difference in treatment protection.**

OHTS I data suggested that ocular hypotensive treatment was less protective in African Americans. In OHTS II, all participants (African Americans and “others”) will be on medication and the statistical power to detect differences in the treatment protection by race will increase substantially.

### 1.3 Background and Significance

In all surveys, glaucoma is among the leading causes of blindness in the United States and worldwide (Quigley, 1996; Sommer, 1991; US Dept. of Health, 1973; Quigley, 1997; Hyman, 2001). It is estimated that more than 2.5 million people in the United States have glaucoma and that more than 130,000 persons are legally blind from the disease (Quigley, 1997). Population surveys indicate that fewer than 50% of those with glaucomatous visual field loss have received appropriate diagnosis and treatment (Dielemans, 1994; Leske, 1994; Mitchell, 1996).

Glaucoma is the leading cause of blindness in African Americans (Sommer, 1991; Mason, 1989; Wallace, 1969; Tielsch, 1991; Leske, 2001). In the Baltimore Eye Survey (Sommer, 1991), the age-adjusted prevalence rates of primary open angle glaucoma (POAG) were four to five times higher in African Americans than in whites. The prevalence ranged from 1.2% in African Americans aged 40 through 49 years to 11.3% in those 80 years and older (Tielsch, 1991). These findings were confirmed in the Barbados Eye Study which reported a high prevalence and incidence of POAG among blacks in an Afro-Caribbean population (Leske, 1994; Leske, 2001).

It is estimated that 3 to 6 million people in the United States, including 4% - 7% of the population above age 40, have elevated intraocular pressure (IOP) without detectable glaucomatous damage using standard clinical tests (Leibowitz, 1980). These individuals are at increased risk for developing POAG and are sometimes referred to as ocular hypertensives or glaucoma suspects (Leibowitz, 1980; Armaly, 1980; Quigley, 1994).

Prior to OHTS I, there was no consensus on the safety and efficacy of ocular hypotensive medication in delaying or preventing the onset of POAG. OHTS I clearly demonstrated that early medical treatment delays or prevents the onset of primary open angle glaucoma in ocular hypertensive individuals. In OHTS I, we randomized 1,636 patients with intraocular pressures of \( \geq 24 \text{ mm Hg} \) and \( \leq 32 \text{ mm Hg} \) in one eye and \( \geq 21 \text{ mm Hg} \) and \( \leq 32 \text{ mm Hg} \) in the fellow eye to either treatment with commercially-available, topical ocular hypotensive medication or to observation. At 60 months, the cumulative frequency of developing POAG was 4.4% in the medication group and 9.5% in the observation group (Kass, 2002).
Now that it has been proven that lowering IOP is effective in delaying or preventing the onset of POAG, it is important to determine when treatment should be initiated in ocular hypertensive individuals. One approach to ocular hypertension would be to recommend early treatment for patients at moderate to high risk for developing POAG to prevent later functional visual impairment. Another approach would be to withhold treatment until patients have early signs of POAG. The latter approach could reduce patient burden and cost. However, delayed treatment may allow progressive ganglion cell loss and may start a process of optic nerve deterioration that is less responsive to treatment in the future, i.e., patients who receive delayed treatment may be more likely to develop visual impairment or blindness in their lifetime. Quigley and coworkers reported that a substantial percentage of the optic nerve fibers are lost before glaucomatous visual field defects can be detected by routine perimetry (Kerrigan-Baumrind, 2000).

We are not aware of any published data on whether there is an ongoing penalty for delaying treatment in ocular hypertension. OHTS II will specifically address this issue (primary aim). We may try to draw some inferences about delaying treatment from published studies of POAG. Grant and Burke reported that as damage from glaucoma worsens, patients require progressively lower IOP to prevent blindness (Grant, 1982). Oliver et al. reported that the patients at greatest risk for developing blindness from glaucoma had greater visual field and optic disc damage at the time of diagnosis (Oliver, 2002). Hattenhauer et al. reported that 27% of the patients with glaucomatous visual field or optic disc damage at diagnosis lost central visual acuity in at least one eye and 16% lost central acuity in both eyes despite 20 years of treatment in a leading medical institution (Hattenhauer, 1998). Thus there is evidence that the greater the degree of glaucomatous damage, the worse the prognosis, the less likely that treatment will prevent or slow progressive optic nerve deterioration and the more likely that patients will develop visual impairment.

Evidence from laboratory studies may explain why delaying ocular hypotensive treatment could initiate a process of optic nerve deterioration that is less responsive to treatment in the future. Elevated IOP can produce irreversible structural and cellular changes in the optic nerve head (Quigley, 1994; Neufeld, 1998). Elevated IOP causes changes in the extracellular matrix of the optic nerve head, including the content of elastin, collagen and proteoglycans. (Hernandez, 1997). These changes have been observed in glaucomatous human optic nerves, as well as in tissue from monkeys with glaucoma (Pena, 1998; Hernandez, 2000; Pena, 2001). Elevated IOP also activates astrocytes and microglial cells in the optic nerve head. Normally, astrocytes in the optic nerve head are present only within the cribiform plate. With elevated IOP, these cells become activated and migrate into the nerve bundles. Similarly, microglia are activated and migrate to the peripapillary region. (Neufeld, 1999a). These activated glial cells produce noxious agents, such as nitric oxide and tumor necrosis factor (Neufeld, 1999b; Liu, 2000). Elevated IOP also alters perfusion pressure and may affect blood flow to the optic nerve and other ocular structures. The IOP related structural and cellular changes in the optic nerve head might explain delayed ganglion cell death occurring months to years after elevated intraocular pressure. It is also important to consider the increased susceptibility of optic nerve axons with age (Kawai, 2001). Noxious factors may have a
greater effect on ganglion cells in older people, particularly if the structural and cellular composition of the optic nerve head has been altered by long term elevation of IOP.

In OHTS II, we have an unprecedented opportunity to follow a group of participants, one half of whom were originally randomized to medication for five to seven years and one half of whom were randomized to observation for the same time period. If we now treat all participants in both groups with ocular hypotensive drugs, we should be able to determine if there is a penalty or disadvantage for waiting to institute treatment (primary specific aim).

Let us consider three possible scenarios for the efficacy outcome of OHTS II. In scenario 1 (the divergence scenario), the incidence of POAG in OHTS II continues to be higher in the OHTS I observation group (now on treatment in OHTS II) than in the OHTS I medication group. Thus, the cumulative incidences in the two groups continue to diverge over time. This would indicate a substantial penalty for delaying treatment and would suggest that early treatment would be beneficial for many ocular hypertensive individuals at moderate to high risk for developing POAG. (The three scenarios are discussed further in Chapter 2, Study Design, for estimating statistical power and sample size).

In scenario 2 (the convergence scenario), the incidence of POAG in OHTS II is higher in the original medication group than in the original observation group (now on treatment in OHTS II), perhaps related to loss of effectiveness of medication from long-term use or damage to the trabecular meshwork. Thus, the cumulative incidences in the two groups begin to converge. Thus, there is little evidence of a penalty for delaying treatment. The implication of this scenario is that early medical treatment is not indicated except in the few ocular hypertensive patients at highest risk for developing POAG or in the few patients with IOPs so high that retinal venous occlusion is a concern.

In scenario 3 (stabilization scenario), the incidence of POAG in OHTS II is similar in the two groups after the original observation group has been on treatment for 18 months, i.e., there is a lag phase for medication to exert its protective effect but thereafter the incidence in the two groups is similar. Thus, there is a modest reduction in the cumulative incidence of POAG in the original medication group compared to the original observation group (now on treatment in OHTS II) i.e.; there is only a modest penalty for delaying treatment. In this scenario, early medical treatment would be indicated for some ocular hypertensive people at high risk for developing POAG.

Whichever of these three scenarios actually occurs in OHTS II, the results will have a major impact on the clinical management of ocular hypertensive patients. It is also possible that OHTS II will identify a long-term increase in adverse events associated with medication or a loss of effectiveness of medication with increasing duration of use. Such a finding would have a major effect on the decision to institute early treatment or on the decision of which medication class to choose for early treatment.

It is difficult to imagine that there will ever be another large, racially diverse, randomized sample of ocular hypertensive patients who would lend themselves to a clearer test of
earlier versus later treatment ("treat me now versus treat me later"). This question has important scientific and public health implications. The OHTS sample offers a unique opportunity to address these issues.

The OHTS population also allows us to pursue other important questions on risk factors for POAG, early glaucoma changes and racial differences in the protective effect of treatment. There are several published studies on risk factors that predict which ocular hypertensive individuals will develop POAG. OHTS is well-positioned to improve the predictive model for the development of POAG for the following reasons: large sample size, large African American sample, long-term prospective follow-up, rigorous criteria for POAG endpoints, and a growing number of incident POAG cases. OHTS I confirmed some POAG risk factors previously reported including older age, higher IOP and large cup/disc ratio. OHTS I was the first study to identify corneal thickness as a powerful risk factor. OHTS I also found that the increased risk of POAG in African Americans might be explained by larger baseline cup/disc ratio and thinner central corneal measurement. In OHTS II we will increase the precision and completeness of the risk model to predict which ocular hypertensive individuals will develop POAG (secondary aim 1). This will allow clinicians to make informed recommendations about which ocular hypertensive patients would benefit from early treatment and which could be observed without treatment.

In OHTS II we have long-term prospective follow-up of a large sample of ocular hypertensive individuals. Many of the OHTS II participants have developed subthreshold changes in their optic discs and/or visual fields, which do not meet the rigorous OHTS criteria for POAG endpoint. With longer follow-up we will be able to distinguish reliable early signs of glaucomatous optic disc and visual field damage from nonspecific changes with little or no prognostic significance (secondary aim 2). This may allow us to redefine early glaucomatous damage.

Prior to OHTS I, there were no published data on possible racial differences in the protective effect of medication in ocular hypertensive individuals. In OHTS I there was a trend suggesting that ocular hypotensive medication was less protective in African American participants than in the other participants. In OHTS II all African American and other participants will be on medication and the statistical power to detect differences in treatment protection by race will increase substantially (secondary aim 3). Such data may indicate the need for more rigorous IOP goals in African Americans.

### 1.4 Progress Report/Preliminary Studies

#### 1.4.1 Efficacy of Treatment

The primary specific aim of OHTS I was to determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG in ocular hypertensive individuals judged to be at moderate to high risk of developing primary open angle glaucoma. OHTS I clearly demonstrated that early medical treatment delays
or prevents the onset of POAG in ocular hypertensive individuals. A total of 1,636 participants with no evidence of glaucomatous damage, ages 40-80 years, with IOP ≥ 24 mm Hg and ≤ 32 mm Hg in one eye and ≥ 21 mm Hg and ≤ 32 mm Hg in the fellow eye were randomized in equal proportions to either treatment with commercially available topical ocular hypotensive medication or to observation. The goal in the medication group was to reduce IOP by 20% or more and to reach an IOP ≤ 24 mm Hg. The primary outcome was the development of reproducible visual field abnormality or reproducible optic disc deterioration attributed to POAG. Masked certified readers at the Reading Centers made determination of abnormality; the masked Endpoint Committee made attribution to POAG.

Over the course of the study, the mean reduction in IOP in the medication group was 22.5 ± 9.9%. IOP declined by 4.0 ± 11.6% in the observation group. At 60 months, the cumulative probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group. During the course of the entire study, the cumulative probability of developing POAG was significantly lower in the medication group compared to the observation group (hazard ratio, 0.40; 95% confidence interval, 0.27-0.59, Mantel Haenszel log-rank test; P < 0.001). Additional details on OHTS I are available in the reprint of the primary outcome paper (Kass, 2002) included in the appendix.

1.4.2 Preliminary Evidence for a Possible Penalty of Delayed Treatment

OHTS I provides preliminary data that supports laboratory and clinical findings for a possible penalty of delayed treatment. In OHTS I, 125 participants developed a POAG endpoint, 35 in the medication group and 90 in the observation group. When participants reached an endpoint in one eye, they were treated vigorously in both eyes. Treatment prescribed was at the discretion of the treating clinician and was not dependent upon the original randomization status. We report on the outcome of the fellow eyes of participants who developed unilateral POAG. For this analysis, we excluded "concurrent" cases of POAG, which were defined as those occurring in less than 6 months of the initial POAG endpoint. POAG developed 6 months or more after the initial endpoint in 1 of 35 fellow eyes of participants in the medication group compared to 9 of 81 fellow eyes of participants in the observation group (rate ratio, 0.165; 95% confidence interval of 0.021 to 1.31; Mantel Haenszel log rank P = 0.052).

Fellow eyes that were on treatment all along fared better over the subsequent months than did the fellow eyes from the observation group which were started on treatment only after they reached a POAG endpoint in the opposite eye. With continued follow-up in OHTS II, we will have
additional data on the course of the fellow eyes and whether a penalty of delayed treatment persists. However, these data underestimate the incidence of POAG in fellow eyes because of the limited duration of follow-up after the diagnosis of POAG in the first eye of these participants. The median duration of follow-up after the diagnosis of POAG in the first eye is only 24 months to date. Thus, duration of follow-up is still too short to draw definite conclusions, but this is a thought-provoking finding. Additional follow-up of these participants will answer the question, “Among participants in OHTS I who develop unilateral POAG, is the cumulative proportion of fellow eyes to develop POAG higher in the OHTS I observation group or the OHTS I medication group?”

1.4.3 Evidence of Possible Adverse Effects of Medication

A primary specific aim in OHTS I was to determine the safety of topical ocular hypotensive medication. In OHTS I, the safety of topical medication was systematically monitored at each follow-up visit by participant self-administered surveys (Glaucoma Symptom Survey and Medical Outcomes Short Form SF-36), staff elicited medical histories, and by the measurement of visual acuity (ETDRS). There was no evidence of excess risk in the medication group as determined by participant self-administered surveys throughout the study. Among medication participants prescribed a prostaglandin analogue for six months or longer, changes in iris color, darkening of eyelids and growth of eyelashes was reported in 17% (65 of 380) compared to 7.6% (48 of 631) of the participants in the observation group (P < 0.001). Medical histories indicated no excess risk in the medication group for the overall number of new medical conditions, worsening of pre-existing conditions, hospitalizations or mortality. However, a possible excess of psychiatric and genito-urinary serious adverse events and cataract surgery was noted in the medication group. Clinic staff recorded serious psychiatric adverse events in 1.5% (12 of 800) of the medication participants compared to 0.5% (4 of 802) of the observation participants (P = 0.05). Clinic staff recorded serious genito-urinary adverse events in 5.5% (44 of 800) of the medication participants compared to 3.4% (27 of 802) of the observation participants (P = 0.04). There was a slight excess of cataract surgery and combined filtering/cataract surgery in the medication group, 6.4% (52 of 806) compared to 4.3% (35 of 813) in the observation group (P = 0.055), though the medication group had similar mean visual acuity as the observation group throughout the study.

While these differences between randomization groups were not statistically significant after correcting for multiple comparisons, these findings warrant further study. A specific aim in OHTS II will be to determine the safety of topical ocular hypotensive medications. It is possible that the rate and severity of side effects will increase as OHTS II participants age and as the duration of treatment lengthens. A recent publication from the Barbados Eye Survey reported that individuals on topical ocular hypotensive medication were three times more likely to develop lens opacities compared to ocular hypertensive individuals not receiving topical medication (Leske, 2002). This underscores the importance of a systematic documentation of lens opacity in OHTS II. We will quantitate lens opacity annually in a masked fashion using the LOCS III protocol and evaluate vision specific-quality life every two years with the self-administered NEI-
Visual Function Questionnaire. All other procedures for monitoring safety in OHTS I will remain the same in OHTS II.

With almost all participants in OHTS II receiving medication, we no longer have an untreated control group. However, we do have a long-term treatment group and a short-term treatment group. This will allow us to compare the incidence and severity of adverse events in the two groups and to compare exposure time to different classes of medication. If long-term treatment of ocular hypertension is associated with a substantial increase in adverse events, this would greatly influence any recommendation for early treatment.

### 1.4.4 Risk Factors for POAG

The secondary aim #1 in OHTS I was to identify risk factors that predict which ocular hypertensive individuals were most likely to develop POAG. Baseline demographic and clinical data were collected prior to randomization (except for corneal thickness measurements which were collected during follow-up) for inclusion in a risk factor model of which ocular hypertensive individuals develop POAG. In univariate analyses in OHTS I, baseline factors that predicted the development of POAG included older age, male gender, black race, heart disease, higher IOP, thinner central corneal measurement, larger cup/disc ratio (vertical or horizontal), and higher pattern standard deviation or corrected pattern standard deviation. In multivariate analyses, baseline factors that predicted the development of POAG included age, IOP, corneal thickness, larger cup/disc ratio (vertical or horizontal) and pattern standard deviation. Diabetes was protective of POAG in both univariate and multivariate analyses. A detailed description of the risk factor analysis is presented in a reprint of the risk factor paper (Gordon, 2002) included in the appendix.

An important secondary specific aim in OHTS II is to increase the precision and completeness of the predictive model for POAG. Longer duration of follow-up and a larger number of POAG endpoints will increase the statistical power of the entire model as well as determine if borderline factors from OHTS II such as gender, heart disease, high blood pressure, and myopia for identifying predictors of POAG that had borderline statistical significance in OHTS I (listed in Table 1). The risk factors for POAG in OHTS I were identified using the 125 endpoints.
Table 1. Univariate and Multivariate Hazard Ratios for POAG and 95% CI Intervals

<table>
<thead>
<tr>
<th>Putative Predictive Factor</th>
<th>Hazard Ratios (95% Confidence Interval)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate¹</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>1.87* (1.31 - 2.67)</td>
<td>1.42 (0.98 - 2.05)</td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>2.11* (1.23 - 3.62)</td>
<td>1.71 (0.95 - 3.09)</td>
<td></td>
</tr>
<tr>
<td>Myopia ≥ -1.0 D spherical equivalent</td>
<td>0.91 (0.62 - 1.32)</td>
<td>1.41 (0.94 - 2.11)</td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>1.31 (0.92 - 1.87)</td>
<td>1.33 (0.92 - 1.91)</td>
<td></td>
</tr>
<tr>
<td>Low Blood Pressure</td>
<td>1.49 (0.73 - 3.05)</td>
<td>1.80 (0.87 - 3.72)</td>
<td></td>
</tr>
<tr>
<td>Family history of glaucoma (parent or sibling)</td>
<td>1.10 (0.77 - 1.59)</td>
<td>1.22 (0.84 - 1.77)</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>1.01 (0.58 - 1.76)</td>
<td>1.44 (0.82 - 2.54)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant P < 0.05
1. Multivariate model adjusts for baseline age, IOP, pattern standard deviation, vertical/cup disc ratio and corneal thickness, which was measured after randomization.

In OHTS II, the assessment of high blood pressure and diabetes will be strengthened. High blood pressure in OHTS II will be assessed using an automated blood pressure cuff rather than by medical history as in OHTS I. Diabetes was assessed by a single “Yes”/”No” question in OHTS I. In OHTS II, diabetes will be assessed by a series of questions about treatment as well as distinguish between Type I, Type II and gestational diabetes. A predictive model for POAG with high sensitivity and specificity will allow identification of high risk participants who should be considered for treatment, and equally important, allow identification of low risk participants who could be observed without medication.

OHTS I found that corneal thickness was a powerful predictor of POAG (hazard ratio per 40 microns thinner than the overall mean of 573.0 mm, 1.71, 95% CI, 1.40-2.08). Thirty six percent of the participants in the OHTS I observation group, who were in lowest third of central corneal thickness and the highest third of IOP, developed POAG. Twenty two percent of the participants in the OHTS I observation group, who were in the lowest third of central corneal thickness and the highest third of vertical cup/disc ratio, developed POAG.

In OHTS II, we will re-examine the relationship of corneal thickness to POAG after the initiation of medication treatment in participants originally in the observation group. Central corneal thickness will be measured again once in OHTS II to evaluate the
stability of corneal thickness measurements over time by age, race, gender, and class of medication.

In OHTS I and through OHTS II, blood samples from participants are being banked at the University of Iowa under the supervision of Drs. Wallace L. M. Alward and Edwin M. Stone. The samples will be tested for specific genetic factors as they are described in the future. This should allow us to relate genetic factors to the risk of developing POAG. Genetic information should greatly improve the identification of individuals likely to develop POAG and perhaps those most likely to benefit from treatment.

1.4.5 Evidence of Early Optic Disc and Visual Field Changes Prior to POAG

OHTS I imposed rigorous criteria for the definition of POAG. A POAG endpoint from visual field abnormality required three consecutive abnormal visual fields with the same abnormality in the same location, followed by attribution to POAG by a masked endpoint committee. A POAG endpoint from optic disc deterioration required two consecutive sets of optic disc photographs to be classified as deterioration followed by attribution to POAG by a masked endpoint committee. Many participants had abnormal visual fields or evidence of optic disc deterioration that did not meet these high thresholds for POAG endpoint. Of the 125 POAG endpoints in OHTS I, 55% (69 of 125) were detected by optic disc deterioration in the absence of a visual field abnormality that met the rigorous OHTS criteria. In fact, two-thirds of the participants with POAG endpoints diagnosed by optic disc deterioration had visual field abnormalities that did not reach the OHTS threshold for a POAG visual field abnormality. OHTS II will help determine how many of these eyes with POAG endpoints diagnosed by disc deterioration go on to meet criteria for a POAG visual field endpoint. The following table reports the number of participants in OHTS who did not meet criteria for POAG, but who had abnormal visual fields and/or optic disc photographs judged to show disc deterioration.

Table 2* Number and Percent of Participants who have Abnormal Visual Field Tests or Evidence of Optic Disc Deterioration but have not met OHTS POAG criteria

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Percent of Randomized Participants n=1448</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 abnormal visual field</td>
<td>608</td>
<td>42.0%</td>
</tr>
<tr>
<td>At least 2 abnormal visual fields</td>
<td>248</td>
<td>17.1%</td>
</tr>
<tr>
<td>At least 2 consecutive abnormal visual fields</td>
<td>138</td>
<td>9.5%</td>
</tr>
<tr>
<td>At least 1 set of Disc photographs showing deterioration</td>
<td>79</td>
<td>5.5%</td>
</tr>
<tr>
<td>At least 2 sets of Disc photographs showing deterioration</td>
<td>15</td>
<td>1.0%</td>
</tr>
<tr>
<td>Disc Hemorrhage</td>
<td>87</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

*A participant may be counted twice in this table once for a visual field abnormality and once for an optic disc deterioration.
Secondary specific aim #2 in OHTS II will be to determine the predictive accuracy of early changes in the optic disc and visual field for the development of POAG. The longer follow-up in OHTS II will enable us to distinguish reliable early signs of glaucomatous optic disc and visual field changes from non-specific changes with little or no prognostic significance.

1.4.6 Differential Treatment Protection by Race

In OHTS I, there was a trend for treatment to be less protective among self-identified African American participants (see Table 3).

<table>
<thead>
<tr>
<th>Self-Identified Race</th>
<th>OHTS I Observation Group</th>
<th>OHTS I Medication Group</th>
<th>Hazard Ratio* (95% C I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>12.7% (26 of 205)</td>
<td>6.9% (14 of 203)</td>
<td>0.54 (0.28 to 1.03)</td>
</tr>
<tr>
<td>Others</td>
<td>10.2% (63 of 614)</td>
<td>3.6% (22 of 614)</td>
<td>0.34 (0.21 to 0.56)</td>
</tr>
</tbody>
</table>

*P value for interaction, P= 0.26

Additional follow-up in OHTS II and the larger sample of African American participants on treatment will increase the precision of estimates of the treatment differential by race, if any. The trend for differential treatment benefit by race cannot be explained by differences in baseline IOP or treated IOP because no differences were found in these measures by race.

In OHTS I, African American race was associated with a 59% increase in the risk of developing POAG (hazard ratio, 1.59%; 95% CI 1.09-2.32) compared to “others.” However, African American participants had a larger mean ± SD baseline vertical cup/disc ratio (0.45 ± 0.18) compared with other participants (0.37 ± 0.20) and a thinner mean ± SD central corneal measurement (554.9 ± 38.5) than other participants (578.3 ± 36.5). The inclusion of either baseline vertical cup/disc ratio or corneal thickness caused race to become statistically non-significant in the multivariate model (hazard ratio 0.98; 95% CI 0.65-1.46). OHTS I was never powered to detect differential risk of POAG by race or to detect differential treatment benefit by race.

To our knowledge, the OHTS sample of African American participants with ocular hypertension is the largest sample to date in a randomized treatment study. Secondary specific aim #3 in OHTS II will be to examine potential racial differences in treatment protection. In addition, longer follow-up and a larger number of POAG endpoints in OHTS II will increase the precision of statistical estimates on the inter-relationship between race, POAG, cup/disc ratio and corneal thickness.
1.5 Planning Sessions for OHTS II

October 19, 2001 The DSMC met in St. Louis, Missouri and decided there were sufficient data to answer the primary question of OHTS I. The DSMC approved publication of OHTS I results. The DSMC discussed the transition schedule and the general outline for the OHTS II Protocol.

November 8, 2001 The Executive/Steering Committee met and was informed of the preliminary results of OHTS I. The committee discussed publication and transition plans and the OHTS II protocol in detail.

November 9, 2001 The Full Investigative Group was informed of the preliminary results of OHTS I, and reviewed a draft of the primary outcome papers. The group then discussed publication and transition plans and the OHTS II protocol.

February 18, 2002 The DSMC met via conference call and approved the transition plan to OHTS II and the general features of the OHTS II protocol.

April 12, 2002 The Full Investigative Group met in St. Louis to refine the OHTS II protocol. The Full Investigative Group approved the OHTS II protocol.

June 10, 2002 The DSMC met via conference call and approved the final details of the OHTS II protocol.

1.6 Study Milestones

September 30, 1992 Funding began for OHTS I

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 17, 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 16).

July 1, 1995 Confocal Scanning Laser Ophthalmoscopy Ancillary Study funded, Dr. Robert Weinreb, Principal Investigator, UC-San Diego (Chapter 16).
July 1, 1995  Short Wave-Length Automated Perimetry Ancillary Study funded, Dr. Chris Johnson, Principal Investigator, UC-Davis (Chapter 16).

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.

May, 1999  Manuscript entitled "The Ocular Hypertension Treatment Study: Design and Baseline Description of Participants" is published in *Archives of Ophthalmology*.


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 *Archives of Ophthalmology*.


October, 2001  Manuscript entitled "Central Corneal Thickness in the Ocular Hypertension Treatment Study" is published in *Ophthalmology*.
October, 2001  DSMC determines that sufficient data exist to answer the primary question of OHTS I. Transition plan and OHTS II protocol were discussed.

November, 2001  Executive/Steering Committee and Full Investigative Group are informed of preliminary OHTS I results and discuss transition plan and OHTS II protocol.

January, 2002  Manuscript entitled "The Ocular Hypertension Treatment Study: Reproducibility of Cup/Disk Ratio Measurements Over Time at an Optic Disc Reading Center" is published in the *American Journal of Ophthalmology*.

February, 2002  DSMC approves transition plan and OHTS II protocol

March, 2002  Manuscript entitled "Baseline Visual field Characteristics in the Ocular Hypertension Treatment Study" is published in *Ophthalmology*.

June, 2002  Manuscript entitled The Ocular Hypertension Treatment Study: Topical Ocular Hypotensive Medication Delays or Prevents Onset of Glaucoma is published in the *Archives of Ophthalmology*.

June, 2002  Manuscript entitled Baseline Factors that Predict the Onset of Primary Open Angle Glaucoma is published in the *Archives of Ophthalmology*.

June, 2002  OHTS I Participants begin transition into OHTS II

June 3, 2002  First participant from OHTS I is enrolled in OHTS II

### 1.7 References


Grant WM, Burke JF. Why do some people go blind from glaucoma? Ophthalmology 1982; 89:991-998.


Kerrigan-Baumrind LA, Quigley HA, Pease ME, Kerrigan DF, Mitchell RS. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. Invest Ophthalmol Vis Sci 2000; 41:741-748.


Appendix
To view these articles you will be taken to the website for the Archives of Ophthalmology

www.archophthalmol.com

Manuscript “A Randomized Trial Determines that Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open Angle Glaucoma”

html version | pdf version

Manuscript “Baseline Factors that Predict the Onset of Primary Open Angle Glaucoma”

html version | pdf version
2. Study Design

2.1 Synopsis of the OHTS II Study Design ...............................................................2-2
2.1.2 Specific Aims of OHTS II....................................................................................2-3
2.1.3 Timetable For OHTS I and OHTS II ...................................................................2-4
2.2 Participant Eligibility for OHTS II ......................................................................2-5
2.2.2 Medical Withdrawal of Participants during Transition to OHTS II ...............2-5
2.3 Rationale for Including all OHTS I Participants in OHTS II...............................2-6
2.3.1 Why include participants from OHTS I who have already developed POAG?...2-6
2.3.2 Why include participants who are not ascertainable for visual field
abnormality or optic disc deterioration? ..............................................................2-6
2.3.3 Why include participants in OHTS II who would be ineligible for OHTS I? ....2-7
2.3.4 Why include participants who refuse medication? .............................................2-7
2.3.6 Why not limit enrollment in OHTS II to high-risk individuals? .......................2-7
2.3.7 Is it ethical to initiate medical treatment in all OHTS I participants who enroll
in OHTS II? ...........................................................................................................2-7
2.3.8 Entry Criteria for OHTS I ....................................................................................2-8
2.4 Baseline Characteristics of Participants in OHTS I .............................................2-8
2.5 Treatment .............................................................................................................2-9
2.5.1 Goals of Treatment...............................................................................................2-9
2.5.2 Medical Regimen .................................................................................................2-9
2.5.3 Why not include neuroprotective drugs in OHTS II? ........................................2-10
2.5.4 Participant Safety and Possible Drug-Related Side Effects...............................2-10
2.5.5 Medication Adherence .......................................................................................2-11
2.6 Follow-up Schedule ...........................................................................................2-12
2.6.1 Tests and measures at semi-annual follow-up visits (6, 18 months, etc.)
iclude:...............................................................................................................2-12
2.6.2 Tests and measures at annual follow-up visits (12, 24 months, etc.) include: ...2-12
2.6.3 Tests and measures performed every two years in OHTS II............................2-13
2.6.4 One time measurement in OHTS II....................................................................2-13
2.7 POAG Endpoint Determination ..........................................................................2-14
2.7.1 Optic Disc POAG Endpoint .............................................................................2-14
2.7.2 Rationale for Optic Disc Assessment.................................................................2-15
2.7.3 Visual Field POAG Endpoint..............................................................................2-16
2.7.4 Rationale for Visual Field Assessment ..............................................................2-17
2.7.5 When a POAG Endpoint is Confirmed .............................................................2-18
2.7.6 POAG Treatment Group ....................................................................................2-18
2.7.7 Protecting Masking at Reading Centers.............................................................2-19
2.8 Protection of Participants ...................................................................................2-20
2.8.1 Safety of Treatment.............................................................................................2-20
2.8.2 Confidentiality....................................................................................................2-20
2.9 Clinical Centers ..................................................................................................2-21
2.10.1 Participants Available for OHTS II .................................................................2-21
2.10.2 Statistical Power for Testing the Hypothesis ....................................................2-23
2.10.3 Assumptions Used to Estimate Statistical Power ..............................................2-24
2.10.4 Scenarios for Setting the Upper and Lower Boundaries of Statistical Power ... 2-24
2.10.5 Analysis of Efficacy ...................................................................................... 2-27
2.10.6 Analysis of Safety ....................................................................................... 2-28
2.10.7 Interim Analysis/Safety Monitoring ............................................................... 2-30
2.11 Human Participants ....................................................................................... 2-31
2.11.1 Entry Criteria ............................................................................................. 2-31
2.11.2 Exclusion Criteria for OHTS II .................................................................. 2-32
2.11.3 Confidentiality and Protection of Subjects .................................................. 2-32
2.11.4 Risks ........................................................................................................... 2-33
2.11.5 Benefits ....................................................................................................... 2-35
2.12 Literature Cited ............................................................................................. 2-35

Appendix .................................................................................................................. 2-37
    OHTS I participants at baseline ........................................................................... 2-38
    Procedures for Confirmation of Abnormality ...................................................... 2-41
    Participating Clinics, Committees and Resource Centers .............................. 2-46
2.1 Synopsis of the OHTS II Study Design

Prior to the Ocular Hypertension Treatment Study (OHTS I) there was conflicting evidence as to whether early medical treatment to lower IOP was effective in delaying or preventing the onset of glaucomatous damage in individuals with elevated intraocular pressure (referred to as ocular hypertensive individuals) (Kass, 2002). OHTS I clearly demonstrated that early medical treatment delays or prevents the onset of primary open angle glaucoma (POAG) in ocular hypertensive individuals. In OHTS I, 1,636 patients with intraocular pressures (IOP) of ≥ 24 mm Hg and ≤ 32 mm Hg in one eye and ≥ 21 mm Hg and ≤ 32 mm Hg in the fellow eye were randomized to either treatment with commercially-available, topical ocular hypotensive medication or to observation. At 60 months, the cumulative frequency of developing POAG was 4.4% in the medication group and 9.5% in the observation group (Kass, 2002).

Now that it has been proven that lowering IOP is effective in delaying or preventing POAG in ocular hypertensive individuals, it is important to determine when treatment should be initiated. Should ocular hypertensive individuals judged to be at moderate or high risk for developing POAG be started on treatment early or should treatment be delayed until early signs of POAG are detected on clinical examination? The answer to this question depends in part on the penalty or disadvantage (if any) of delaying treatment for ocular hypertensive individuals.

OHTS II provides a unique opportunity to determine the penalty of delaying treatment since we have a racially diverse randomized group of ocular hypertensive participants, one half of whom have been treated for 5-7 years (medication group) and one half of whom have been followed without treatment (observation group) for the same period. If we now treat all participants in both groups with ocular hypertensive medication, we should be able to determine if there is a penalty for waiting to institute treatment.

Let us consider 3 possible different scenarios for the outcome of OHTS II. In scenario 1 (the divergence scenario), the incidence of POAG in OHTS II continues to be higher in the OHTS I observation group (now on treatment in OHTS II) than in the OHTS I treatment group. This would suggest that early treatment would be beneficial for many ocular hypertensive individuals at moderate to high risk for developing POAG.

In scenario 2 (the convergence scenario), the incidence of POAG in OHTS II is higher in the OHTS I treatment group than in the OHTS I observation group (now on treatment in OHTS II). Thus, the 10-year incidences in the 2 groups begin to converge. The implication of this scenario would be that there is little reason to consider early medical treatment except in the few ocular hypertensive people at highest risk for developing POAG or the few individuals with IOPs so high that retinal venous occlusion is a concern.

In scenario 3 (stabilization scenario), the incidence of POAG in OHTS II is the same in the OHTS I treatment and observation groups after 18 months of treatment for the previous observation group. Thus, after 10 years there is a modest reduction in the incidence of POAG in the OHTS I treatment group. Thus, early medical treatment would be considered only for the ocular hypertensive individuals at highest risk for developing POAG.
The results of OHTS II will guide clinicians about the benefit (and risks) of early medical treatment. OHTS II should also yield important information about which ocular hypertensive participants are at greater risk for developing POAG and thus, may be good candidates for early treatment. Furthermore, OHTS II will provide information about whether there is a differential response to treatment by race.

OHTS II, a follow-on study to OHTS I, is designed to compare the cumulative long-term incidence of POAG in the former observation participants of OHTS I who start treatment in OHTS II to the incidence in medication participants who received medication throughout OHTS I, and who continue treatment in OHTS II. Participants are 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 deterioration and/or reproducible glaucomatous visual field abnormality in either eye. All visual fields and optic disc photographs are read in masked fashion in Reading Centers. A masked Endpoint Committee makes attribution to POAG. The participants will be followed for a minimum of five years with follow-up continuing until study termination as determined by the Data and Safety Monitoring Committee (DSMC).

As in OHTS I, the Study Chairman's Office and the Coordinating Center are at Washington University. The Visual Field Reading Center (VFRC) is located at University of California-Davis and Discoveries in Sight – Legacy Portland Hospitals. The Optic Disc Reading Center (ODRC) is at Bascom Palmer Eye Institute, University of Miami. Clinical Centers are the same as in OHTS I.

### 2.1.2 Specific Aims of OHTS II

**Primary Aim:** to determine if there is a long-term penalty or disadvantage for delaying treatment in ocular hypertensive individuals.

This question will be tested by comparing the long-term cumulative incidence of primary open angle glaucoma in participants who were in the observation group in OHTS I and who start ocular hypotensive treatment in OHTS II to the long-term cumulative incidence in participants who were in the medication group throughout OHTS I and who continue treatment in OHTS II. There may also be downsides to early treatment. One potential downside is drug-related adverse events. This potential downside or disadvantage to early treatment will be assessed by comparing the long-term cumulative incidence of adverse events in participants in these same two randomization groups. Another potential downside is the loss of effectiveness of ocular hypotensive medication with increasing duration of care. This potential downside will be assessed by comparing the percentage of participants in the two original randomization groups who fail to reach IOP goal in OHTS II, or who require multiple medications to reach IOP goal, or who require multiple changes of medication to reach IOP goal.
Secondary Aims:

1. To increase the precision and completeness of the risk model developed in OHTS I to predict which ocular hypertensive participants will develop POAG.

Refinement of the risk model will help to answer two questions, “Who is at risk for developing POAG?” and “Who might benefit from early treatment?” With longer follow-up, we will have a larger number of POAG endpoints which will increase statistical power of the entire model as well as determine if other factors (some of which were borderline in OHTS I) such as gender, heart disease, perfusion pressure, and myopia are risk factors for POAG in this sample.

2. To determine the predictive accuracy of subthreshold visual field and optic disc changes for subsequent development of POAG.

Many participants in OHTS I had changes of the optic disc or visual field that did not meet the OHTS rigorous criteria for POAG endpoints. The longer follow-up in OHTS II will enable us to distinguish reliable early signs of glaucomatous optic disc and visual field damage from non-specific changes with little or no prognostic significance.

3. To determine if there is a racial difference in treatment protection.

OHTS I data suggested that ocular hypotensive treatment was less protective in African Americans. In OHTS II, all participants (African Americans and “others”) will be on medication and the statistical power to detect differences in the treatment protection by race will increase substantially.

2.1.3 Timetable For OHTS I and OHTS II

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb, 1994</td>
<td>Start OHTS I recruitment</td>
</tr>
<tr>
<td>Oct, 1996</td>
<td>End OHTS I recruitment</td>
</tr>
<tr>
<td>Jun, 2002</td>
<td>Publication of Primary Outcome Papers</td>
</tr>
<tr>
<td></td>
<td>Start enrollment of OHTS I participants into OHTS II</td>
</tr>
<tr>
<td>Mar, 2003</td>
<td>Complete scheduled enrollment of OHTS I participants into OHTS II</td>
</tr>
<tr>
<td>Nov, 2003</td>
<td>End of OHTS I funding period for Resource Centers and Participating Clinics</td>
</tr>
<tr>
<td>Apr, 2008</td>
<td>Close follow-up of OHTS II participants</td>
</tr>
<tr>
<td>Nov, 2009</td>
<td>Complete data analyses and publication of primary results</td>
</tr>
</tbody>
</table>
2.2 Participant Eligibility for OHTS II

2.2.1 Participant Entry Criteria for OHTS II

All participants in OHTS I who give written informed consent are eligible for OHTS II. In order to enroll in OHTS II, the participants must be able to cooperate sufficiently and be ascertainable for the onset of visual field abnormality or optic disc deterioration can be determined in at least one eye.

2.2.2 Medical Withdrawal of Participants during Transition to OHTS II

During the transition period to OHTS II, medical withdrawal can be considered for participants unable to cooperate sufficiently or not ascertainable for visual field abnormality or optic disc deterioration in at least one eye. Reasons for a medical withdrawal include medical conditions that preclude travel to the clinic, to cooperate or to be photographed. In a few cases, the medical condition may improve sufficiently to permit resumption of study participation at a later time.

The Clinical Center submits a Medical Withdrawal form (MW) (See Chapter 4) describing the reasons for the medical withdrawal request with the Transition Visit Status form (TV) to the Coordinating Center. Both the Study Chairman and the Medical Monitor review the Medical Withdrawal form (MW). The Clinical Center will be notified of their decision. Participants approved for Medical Withdrawal are not counted in data quality and missed visit reports. These participants can enroll in OHTS II during follow-up at a later time if their medical condition improves sufficiently. Medical withdrawal can occur only during the transition period and does not apply to participants who have enrolled in OHTS II.

To report that a participant is unable to perform a standard protocol test, the Clinic completes a Protocol Exemption form (PE) (see Chapter 4) explaining the reasons why the participant cannot be evaluated. A non-protocol alternative may be possible, e.g., Tonopen IOP as an alternative to Goldmann Applanation Tonometry. The Study Chairman and the Medical Monitor will review the Protocol Exemption form (PE). If the Protocol Exemption is approved, performance reports will allow an “exemption” for that measure for that participant. If the condition/reason for protocol exemption is resolved, the participant may resume the standard protocol test/measure.
2.3 Rationale for Including all OHTS I Participants in OHTS II

2.3.1 Why include participants from OHTS I who have already developed POAG?

Many questions can be answered by additional follow-up of participants who developed POAG in OHTS I.

a. What percentage of participants originally in the observation group who develop unilateral POAG develop POAG in their fellow eye despite initiation of medical treatment to reduce IOP?

b. Do fellow eyes of participants originally in the observation group who develop unilateral POAG in OHTS I have a higher incidence of POAG compared to fellow eyes of medication participants who developed unilateral POAG in OHTS I? Although data currently available in OHTS I suggest that fellow eyes of participants originally in the observation group have a higher incidence of POAG than fellow eyes of participants originally in the medication group, more data are needed to confirm this finding. (These data corroborate the primary specific aim).

c. What percentage of eyes that develop POAG diagnosed by optic disc deterioration, go on to develop POAG diagnosed by visual field abnormality and vice versa (secondary specific aim b)?

2.3.2 Why include participants who are not ascertainable for visual field abnormality or optic disc deterioration?

Why include participants in whom one eye cannot be evaluated for visual field abnormality or optic disc deterioration, e.g., a participant who developed retinal detachment or central retinal vein occlusion in one eye?

Since the two eyes of an individual are highly correlated, the fellow unaffected eye provides important information on visual field abnormality and optic nerve deterioration for all study specific aims. Treating and following the fellow eye in such cases is standard clinical practice.

Why include participants in whom visual field abnormality can be determined but not disc deterioration? And why include participants in whom optic disc deterioration can be determined but not visual field abnormality?

Participants who can do either visual field or optic disc photography should be encouraged to continue in OHTS II because the onset of POAG can be determined by either measure. There is a definite correlation between structural and functional changes due to POAG. Therefore either modality will provide useful information. These participants will provide information for the primary specific aim and most secondary aims. Treating and following such individuals is standard clinical practice.
2.3.3 Why include participants in OHTS II who would be ineligible for OHTS I?

Exclusion of participants from OHTS II who have developed an exclusion criteria for entry into OHTS I could result in bias e.g. a participant who has a disc hemorrhage or a participant who has decreased visual acuity due to cataracts. Treating and following such individuals is standard clinical practice. These participants provide information for all specific aims.

2.3.4 Why include participants who refuse medication?

Exclusion of participants who decline to continue or to initiate medication may introduce bias, particularly if declining is related to randomization assignment in OHTS I. Many of the participants declining medication may be willing to initiate medication at a later time. The analysis of the primary hypothesis in OHTS II is strictly “intention to treat” so that participants are analyzed according to their randomization assignment in OHTS I. It is possible that one of the penalties for delaying treatment is the inability to convince patients of the need for treatment at a later time.

2.3.6 Why not limit enrollment in OHTS II to high-risk individuals?

OHTS I recruited ocular hypertensive individuals judged to be at moderate to high risk of developing POAG based on their IOP being greater or equal to 24 mm Hg in at least one eye. Population surveys confirm that higher IOP is a major risk factor for POAG. Even though we published a risk factor analysis from OHTS I data, the risk model is preliminary and is based on a relatively small number of POAG endpoints. Thus, we do not have sufficient data to designate some OHTS I participants as low risk at this time.

OHTS I may underestimate the “true” incidence of POAG for two reasons. 1) Individuals enrolled in OHTS I were stringently screened, i.e. we excluded individuals with detectable early glaucomatous damage. 2) The occurrence of an abnormal visual field or disc deterioration in OHTS I was not defined as an incident POAG endpoint unless it could be confirmed on separate visits as determined independently by masked readers and then attributed to POAG by a masked Endpoint Committee. The true risk of POAG in OHTS I may be underestimated because the diagnostic criteria for POAG in OHTS I are far more stringent than used in standard clinical practice. Thus, we may find that the incidence of POAG will accelerate with time.

2.3.7 Is it ethical to initiate medical treatment in all OHTS I participants who enroll in OHTS II?

Most participants in OHTS I are at moderate to high risk of developing POAG. In OHTS I, there was little evidence of increased risk of side effects associated with topical hypotensive medication. Clinicians were able to find a safe regimen for most, if not all, participants. Thus, offering medication to all participants in OHTS I is ethical and has an overall favorable risk to benefit ratio.
2.3.8  Entry Criteria for OHTS I

Recruitment for OHTS I started February, 1994 and ended October, 1996. A total of 1,636 eligible patients who provided informed consent were randomized. The eligibility criteria for OHTS I are summarized in Table 1 below.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Inclusion Criteria for OHTS I</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IOP in at least one eye of each participant ≥ 24 mm Hg and ≤ 32 mm Hg</td>
<td></td>
</tr>
<tr>
<td>• IOP in fellow eye of ≥ 21 mm Hg and ≤ 32 mm Hg</td>
<td></td>
</tr>
<tr>
<td>• Age 40 to 80 years, inclusive.</td>
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</tr>
<tr>
<td>• Normal and reliable Humphrey 30-2 visual fields for both eyes as determined by the Visual Field Reading Center.</td>
<td></td>
</tr>
<tr>
<td>• Normal optic discs in both eyes on clinical examination and on stereoscopic photographs as determined by the Optic Disc Reading Center.</td>
<td></td>
</tr>
<tr>
<td>• Informed consent.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria for OHTS I</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Best-corrected visual acuity worse than 20/40 in either eye.</td>
</tr>
<tr>
<td>• Previous intraocular surgery excepting uncomplicated extracapsular cataract extraction with posterior chamber-intraocular lens implant and no escape of vitreous to the anterior chamber, strabismus, cosmetic lid surgery, and radial keratotomy.</td>
</tr>
<tr>
<td>• A life-threatening or debilitating disease.</td>
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<tr>
<td>• Secondary causes of elevated IOP including ocular and systemic corticosteroid use</td>
</tr>
<tr>
<td>• Angle-closure glaucoma or anatomically narrow angles — 75% of the circumference of the angle must be grade II or more by Shaffer criteria.</td>
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<tr>
<td>• Other diseases that cause visual field loss or optic disc abnormalities.</td>
</tr>
<tr>
<td>• Difference in cup/disc ratios (horizontal by contour) of the two eyes &gt; 0.2.</td>
</tr>
<tr>
<td>• Background diabetic retinopathy, defined as at least one microaneurysm seen on direct ophthalmoscopy with a dilated pupil.</td>
</tr>
<tr>
<td>• Inability to visualize or photograph the optic discs.</td>
</tr>
<tr>
<td>• Pregnant or nursing women as determined by participant self-report and testing.</td>
</tr>
</tbody>
</table>

2.4  Baseline Characteristics of Participants in OHTS I

Baseline characteristics of participants in OHTS I are reported in the Appendix.
2.5 Treatment

2.5.1 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 both 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 study. This IOP goal was selected to reflect common medical practice for this group of ocular hypertensive individuals, i.e., if an ocular hypertensive individuals 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).

The method described above for computing the IOP goal in OHTS II is the same as in OHTS I. Since the two randomization groups had the same mean Qualifying and Baseline/Randomization IOPs, the mean IOP goal will also the same. The IOP goal in the medication group that has received treatment from the time of randomization remains the same in OHTS II.

In OHTS I, these treatment goals were effective in reducing the incidence of POAG in the medication group in compared to the observation group. Furthermore, the IOP goal appeared to provide similar protection against POAG over a range of subgroups including older as well as younger participants, participants with higher as well as lower baseline IOP and participants with larger as well as smaller baseline cup/disc ratios. Thus, there was no evidence in OHTS I that suggested that different IOP goals were needed for subgroups at higher risk of developing POAG.

2.5.2 Medical Regimen

Topical ocular hypotensive medication is recommended for all participants in OHTS II. The medical regimen begins in most participants with a topical beta-blocker, a prostaglandin analogue or an alpha 2 agonist. 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. Participants return in 4 ± 2 weeks for an IOP Confirmation Visit to evaluate therapeutic response. If a drug is ineffective or minimally effective (IOP reduction < 10% from the average of the Qualifying IOP and Baseline IOP), it should be stopped and another substituted. If a drug is moderately effective (IOP reduction 10%-20% from the average of the Qualifying IOP and Baseline IOP), the clinician has the choice of substituting another drug or adding a drug. This regimen reflects standard clinical practice in the United States at this time. Participants return for another visit 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. Alcon Laboratories, Allergan Therapeutics, Bausch and Lomb, Ciba Vision Corporation, Merck Research Laboratories, Novartis Pharmaceutical, Otsuka America Pharmaceutical, and Pharmacia & Upjohn have donated the drugs to the study.
As new ocular hypotensive drugs become commercially available, the Executive/Steering Committee will consider expanding the medical regimen. It is important to include new drugs to reflect current practice. OHTS I and OHTS II are not intended to be a test of a specific drug or a specific medical regimen, but rather to evaluate the safety and efficacy of medical reduction of IOP.

### 2.5.3 Why not include neuroprotective drugs in OHTS II?

OHTS has limited drug treatment to commercially available medication. There are no clinically proven or commercially available drugs that provide protection to the optic nerve in ocular hypertension or POAG.

### 2.5.4 Participant Safety and Possible Drug-Related Side Effects

Information on the possible adverse effects of medication will be collected using diverse sources of information as follows:

- **Glaucoma Symptom Scale of 13 ocular and 15 systemic symptoms** is completed by the participants prior to each examination.

- **Medical and ocular history** is taken by clinic personnel at every follow-up visit.

- **Every other year, the NEI-Vision Function Questionnaire** is administered.

- **Hospital discharge summaries** are retrieved for inpatient hospitalizations (> 24 hour stay) if the participant reports an inpatient hospitalization at follow-up visits.

- **ETDRS visual acuity** is completed annually.

- **Lens opacities** will be clinically graded annually by masked readers using LOCS III starting in OHTS II. Recently published studies suggest an increased risk of lens opacification from topical ocular hypotensive medication.

- **An Adverse Event (AE) Form** is completed when:
  - therapy is changed because of side effects
  - when a new health problem is reported
  - an existing medical condition worsens
  - an inpatient hospitalization occurs or surgery has been required.
  - 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 a particular topical ocular medication. An Adverse Event form (AE) must be completed for each ocular or systemic symptom complex.

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).
All participants in OHTS II complete the self-administered vision-specific quality of life assessment every two years using the National Eye Institute Visual Function Questionnaire. Quality of life is assessed once during OHTS II closeout using the self-administered form Medical Outcomes Short Form Quality of Life Assessment (SF-36).

2.5.5 Medication Adherence

The following guidelines represent good clinical practice. 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.

- Free study medication may also increase compliance with the treatment regimen. Medication is distributed by the Study Chairman's Office.
2.6 Follow-up Schedule

The participants are examined every six months from the date of randomization for the duration of the study. 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. All participants should be reminded to take their medication and to bring the bottles of medication to the clinic visit.

2.6.1 Tests and measures at semi-annual follow-up visits (6, 18 months, etc.) include:

- Symptom checklist (SY)
- Update Patient Tracking form (TR) (retained at clinic)
- Review of medications
- Update medical and ocular history
- Blood pressure
- Refraction
- Best corrected visual acuity - Snellen and ETDRS
- Humphrey program 30-2
- External examination
- Slit-lamp examination
- Ophthalmoscopy
- Applanation tonometry
- Gonioscopy (completed every two years at non-photo visits)
- Dispense medication to all participants
- Completion of follow-up visit form (FV)

2.6.2 Tests and measures at annual follow-up visits (12, 24 months, etc.) include:

- Symptom checklist (SY)
- Update Patient Tracking (TR) (retained at clinic)
- Review of medications
- Update medical and ocular history
- Blood pressure
- Snellen visual acuity with current refraction
- Humphrey program 30-2
- External examination
- Slit-lamp examination
- Ophthalmoscopy
- Applanation tonometry
- Dilated ophthalmoscopic exam/indirect ophthalmoscopy
- LOCS III Lens opacity classification
- Stereoscopic optic disc photographs
- Macular photographs and red reflex photographs
- Dispense medication to all participants
- Completion of follow-up visit form (FV)

### 2.6.3 Tests and measures performed every two years in OHTS II

- Gonioscopy (completed every two years at semi annual visits.)

- National Eye Institute Visual Function Questionnaire

### 2.6.4 One time measurement in OHTS II

- One-time pachymetry measurements of central corneal thickness

Pachymetry measurements are performed for all participants at either an annual or semi-annual visit prior to dilation. Pachymetry will be repeated more than once 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).

- One-time Medical Outcomes Short Form Quality of Life Questionnaire (SF-36) at either an annual or semi-annual visit during study closeout.
2.7 POAG Endpoint Determination

2.7.1 Optic Disc POAG Endpoint

Stereoscopic optic disc photographs, 1 X 30° macular photographs and single red reflex photographs are taken once yearly at annual follow-up visits, developed, and mailed to the ODRC. All photographs must be taken by certified study photographers.

An optic disc deterioration is defined (based on a masked comparison of follow-up stereo photographs 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 developed for OHTS I. 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 evidence of optic disc deterioration.

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 ungradeable, the coordinator of the ODRC contacts the Clinical Center to request that a new set of photographs be taken within 4 weeks.

If the ODRC detects optic disc deterioration in the optic disc, the ODRC calls the Clinical Center to request that a repeat set of photos be taken within 4 ± 2 weeks. If the participant has already developed POAG, then the repeat set of photos can be taken at the next regularly scheduled visit. If the deterioration 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 narrative description of the optic disc deterioration 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 the Qualifying Assessment form (QA) medical history page and all follow-up examination forms as well as pertinent Adverse Event (AE), Unscheduled Visit (UN) and IOP Confirmation Visit (CF) forms; 2) all visual fields for both eyes to date; 3) 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 optic disc deterioration is clinically significant and attributable to POAG. If the change is not clinically significant or the change is clinically significant but not attributed to POAG,
the Coordinating Center notifies the Clinical Center to continue regular follow-up visits. If the Endpoint Committee determines that the deterioration is clinically significant and due to POAG, the Coordinating Center notifies the Clinical Center. The clinician has the option of adding medications or considering laser trabeculoplasty or filtering surgery. Participants continue to complete all tests and measures at their regularly scheduled follow-up visits.

If a clinician is concerned about the occurrence of optic disc deterioration 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. If the optic discs are judged unchanged, the participant is followed according to the routine schedule of visits. If optic disc deterioration is detected, the ODRC coordinator calls the clinic coordinator to schedule repeat photographs in 4 + 2 weeks. If the participant has already developed POAG, then the repeat photographs can be taken at the next follow-up visit. If optic disc deterioration is confirmed by the repeat set of photos, the ODRC will call the Coordinating Center to convene the Endpoint Committee.

### 2.7.2 Rationale for Optic Disc Assessment

#### a. The optic disc as an endpoint.

It would have been possible to design OHTS with visual field loss as the only POAG outcome; however, most clinicians believe that progressive cupping precedes a visual field defect in many people with open angle glaucoma. This impression was validated by the results of OHTS I (Kass, 2002).

#### 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 (Nagin, 1985). Only an ODRC (where the readers have been trained, and the techniques and criteria are standardized) can yield reproducible assessments for entry criteria and for optic disc deterioration (Feuer, 2002). The ODRC is responsible for training and certification of the photographers, provides quality control and assures masking of readers as to treatment status.

#### c. Readers.

OHTS employs trained technicians to read photographs rather than ophthalmologists as primary readers at the ODRC. This has proven to be highly reliable and cost effective (Feuer, 2002).

#### d. Repeat photographs.

The OHTS I Planning Committee decided that a repeat set of optic disc photographs was likely to improve specificity of diagnosis. Requesting a repeat set of photographs does not add significantly to the cost of the study, nor does it significantly delay the diagnosis and decision to pursue more vigorous treatment in participants showing deterioration.

#### e. Disc hemorrhages.

The OHTS I 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 (Bengtsson B, 1981; Airaksinen, 1984a; Gordon, 1990). Thus, while a disc hemorrhage is a risk factor, it is not synonymous with glaucomatous damage.

f. **Nerve fiber layer dropout.** The OHTS I Planning Committee decided that nerve fiber layer dropout would not be a POAG endpoint. It is 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 in the diagnosis of POAG is unclear (Airaksinen, 1984b; Klein, 1985).

g. **Optic cup depth.** The OHTS I 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, the plane of focus and stereo separation; thus, it is neither a reliable nor a reproducible sign of optic disc deterioration.

h. **Confocal Scanning Laser Ophthalmoscopy (CSLO).** Heidelberg confocal scanning laser ophthalmoscopy is performed annually in selected clinics as part of an ancillary study. The reading center is located at the University of California-San Diego, San Diego, California. Data from this ancillary study will give us information about the utility of CSLO in clinical trials as well as the early changes in the optic disc and nerve fiber layer.

### 2.7.3 Visual Field POAG Endpoint

Humphrey 30-2 visual fields are performed at six-month follow-up visits 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 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 participant can be retested after a minimum of one hour at the same visit or a maximum of six weeks.

Since 86% of the first reliable, abnormal visual fields that occurred in OHTS I were 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 (Keltner, 2000).

If the VFRC considers the second visual field reliable and abnormal, the VFRC calls the Clinical Center to schedule a repeat (third) visual field in \( 4 \pm 2 \) weeks. If the third visual field is also reliable and abnormal, the VFRC contacts the Coordinating Center to convene the Endpoint Committee. The abnormalities on the three visual fields **must be of the same character and location.** The VFRC sends a narrative description of the defect and copies of visual fields of the affected eye and fellow eye from the Qualifying Assessment to date to the Coordinating Center.
The Coordinating Center sends the following to the Endpoint Committee: 1) masked copies of the Qualifying Assessment (QA) medical history and all follow-up examination forms and pertinent Adverse Event (AE), Confirmation Visit (CF) and Unscheduled Visit (UN) forms, 2) all visual fields, 3) 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 or not the abnormality is attributable to POAG.

If the Endpoint Committee determines that the abnormality is not attributable to POAG, the Coordinating Center notifies the Clinical Center of this decision. The participant continues routine follow-up. If the Endpoint Committee determines that the abnormality is due to POAG, the Coordinating Center notifies the Clinical Center of this decision. The clinician has the option of adding medications or considering laser trabeculoplasty or filtering surgery. Participants continue to complete all tests and measures at their regularly scheduled follow-up visits.

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 Assessment

A Visual Field Reading Center. One important issue was whether a VFRC is necessary. The OHTS I 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 clinicians or technicians in the Clinical Center and, in effect, these people become a reading center, but one without standardization, masking, expertise or backup. The VFRC is responsible for the initial training and certification of technicians, quality control, and masking of readers as to treatment.

Readers. The VFRC uses trained, certified, highly skilled and experienced readers.

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 after the participant has a one-hour break. The retest must be completed within 8 weeks. Careful training of technicians together with strong quality assurance procedures have enabled OHTS I to achieve a high rate of reliable visual fields (96% of all study visual field tests were reliable in OHTS I).

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 a long track record and the newer techniques have not been evaluated in large-scale clinical trials. The advantages of STATPAC II analysis include norms based on large population studies, and known sensitivity and specificity characteristics. 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.
The OHTS I 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 study. The OHTS I 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.

Other psychophysical tests. The Planning Committee decided not to use a variety of other potential endpoints such as color vision loss, pattern or multi-focal 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 many 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.

Short wave length perimetry (SWAP) was performed in selected clinics in OHTS I. The reading center is located at Discoveries in Sight, Devers Eye Institute, Portland, Oregon. Discontinuation of additional SWAP testing in OHTS II was approved in the Spring 2002 by the Data and Safety Monitoring Committee, the Executive/Steering Committee and the Full Investigative Group. This decision was based on the availability of adequate data to answer the specific aims of the SWAP ancillary study and the need to protect retention of study participants in OHTS II.

### 2.7.5 When a POAG Endpoint is Confirmed

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

For participants 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 POAG Treatment Group

Participants are moved to the POAG treatment group if either of the following occur:

- **When the Endpoint Committee attributes confirmed optic disc deterioration to POAG.** The Coordinating Center notifies the Clinical Center of the Endpoint Committee decision. The clinician has the option of adding medications or
considering laser trabeculoplasty or filtering surgery. Participants continue to complete all tests and measures at their regularly scheduled follow-up visits.

- **When the Endpoint Committee attributes confirmed visual field abnormality to POAG.** The Coordinating Center notifies the clinician of the Endpoint Committee decision. The clinician has the option of adding medications or considering laser trabeculoplasty or filtering surgery. Participants continue to complete all tests and measures at their regularly scheduled follow-up visits.

Participants moved to the POAG treatment group continue their regularly scheduled follow-up visits and continue to complete all routine tests including visual fields and stereo optic disc photography until study completion. All study data continue to be collected.

### 2.7.7 Protecting Masking at Reading Centers

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 original randomization assignment or clinical status including treatment, medical history, ocular co-morbidity, etc.

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

Visual Field Reading Center staff and Optic Disc Reading Center staff must be vigilant and deter inadvertent disclosure by Clinical Centers 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 Protection of Participants

2.8.1 Safety of Treatment

Protection of participants is achieved at several different levels starting with the Clinical Center where the participant receives care, at the level of resource centers which monitor for potential glaucoma damage using standardized criteria, and at the national level where oversight is the responsibility of the Executive/Steering Committee, Full Investigative Group, the NEI Project Officer, and the Data and Safety Monitoring Committee (DSMC), which reviews accumulating study outcome data at 6 month intervals. Changes to the study protocol require approval by the Executive/Steering Committee, the DSMC, the Full Investigative Group and the local IRB.

At each participating OHTS Clinical Center, the principal investigator and coordinator must complete certification for human studies protection that is approved by their local IRB. The local IRB approves renewal of the OHTS protocol annually and approves protocol modifications as needed. No protocol changes can be implemented prior to approval by the local IRB. OHTS participants return for examinations every six months and are closely monitored by glaucoma specialists using a standard protocol. In addition to the clinician at the Clinical Center, trained and certified experts at reading centers monitor clinical tests using a standardized protocol. Early evidence of POAG must be reproduced in subsequent tests to prevent a change in medical management from variability in testing.

The DSMC monitors the ethical conduct of the study and the accumulating data for evidence of adverse and beneficial treatment effects. Annually, the DSMC prepares a report to the local IRB of participating Clinical Centers on the overall safety experience of the study. This Committee decides when results from OHTS II may be released to study investigators, study participants, the medical community and the public. The DSMC reports to Paul Sieving, M.D., Director of the National Eye Institute. See Chapter 9, Study Organization, for a detailed description of the membership and responsibilities of the DSMC.

Information on the safety of treatment is collected every six months by surveys completed by participants as well as by medical and ocular history as elicited by medical personnel. Medication is selected or altered to reduce or avoid side effects. When appropriate, additional information on adverse events is collected to describe severity of symptoms, organ system affected and possible relatedness of symptoms to ocular medication. These data are analyzed and reported by the Coordinating Center to the DSMC every six months. The DSMC provides a summary report of the safety experience in the study to the local IRB annually.

2.8.2 Confidentiality

Research data consist of written records, optic disc photographs, visual fields and electronic files. All study information on hard copy is kept in locked file cabinets and is available only to the physicians and coordinators at the various Clinical Centers. Some information about the participant's previous medical history is utilized in the study. No material will be published or released with a participant's name, social security number, or other identifier.
To protect the confidentiality of participants, all study information is coded by identification numbers at Clinical Centers and at Resource Centers.

OHTS is committed to being in compliance with Health Insurance Portability and Accountability Act guidelines and requirements.

### 2.9 Clinical Centers

The Clinical Centers in OHTS I were selected by an RFA mechanism developed jointly by the Study Chairman, the Coordinating Center, and the NEI staff. Each Clinical Center demonstrated it is qualified to participate in OHTS II by virtue of its performance in OHTS I. This was judged by recruitment, data quality and retention of study participants.

OHTS II has 22 participating clinical centers. Clinical Center personnel consist of a principal investigator, clinic coordinator, technician, and photographer (See Appendix for listing of Clinical Centers). 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 (see Chapter 12, Clinical Center, for more information).

### 2.10 Statistical Considerations

In OHTS II, the goals of data analysis include monitoring the long-term cumulative safety and efficacy of medication (primary hypothesis) as well as testing secondary hypotheses. Comparisons between randomization groups for the primary hypothesis will be made on an intention-to-treat basis and will include all randomized participants, all POAG endpoints, and all safety data from the time of randomization in OHTS I to the end of OHTS II.

#### 2.10.1 Participants Available for OHTS II

Because OHTS II is a follow-on study to OHTS I, the number and composition of participants available to enroll in OHTS II could introduce bias. We examined if differential loss to follow-up of participants in OHTS I could result in a biased sample of participants available to enroll in OHTS II. Current to 6/1/2002, the date for initiating transition to OHTS II, 64 deaths, approximately equally distributed in the 2 randomization groups, had occurred among the 1,636 participants randomized in OHTS I (1,636-64=1,572). As of 6/1/2002, 88% (1,385 of the 1,572) of the surviving participants were defined as “active,” and 12% (187 of the 1,572) were defined as inactive, i.e., missed two or more of their last scheduled visits. We compared active and inactive participants to determine if loss to follow-up had introduced bias. There was little or no evidence of differences between “active” and “inactive” participants for any of the putative risk factors identified in OHTS I or for randomization assignment. We concluded that the participants who are available for OHTS II closely resemble the original sample randomized in OHTS I.
Table 2. Comparison of Active and Inactive Participants in OHTS I at the time of transition to OHTS II starting 6/1/2002

“Inactive”=Participants missing 2 or more of their last scheduled visits

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% Active</th>
<th>% Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,572</td>
<td>n=1,385</td>
<td>n=187</td>
</tr>
<tr>
<td>Randomization Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>787</td>
<td>87.8%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Observation</td>
<td>785</td>
<td>88.4%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>394</td>
<td>86.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Other</td>
<td>1178</td>
<td>88.7%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>668</td>
<td>88.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Female</td>
<td>904</td>
<td>88.1%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>536</td>
<td>83.4%</td>
<td>16.6%</td>
</tr>
<tr>
<td>&gt; 50 through 61</td>
<td>522</td>
<td>90.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>&gt; 61</td>
<td>514</td>
<td>91.1%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Baseline IOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 23.75</td>
<td>550</td>
<td>89.3%</td>
<td>10.7%</td>
</tr>
<tr>
<td>&gt; 23.75 through 25.75</td>
<td>523</td>
<td>84.5%</td>
<td>15.5%</td>
</tr>
<tr>
<td>&gt; 25.75</td>
<td>499</td>
<td>90.6%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Vertical Cup Disc Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.30</td>
<td>524</td>
<td>89.3%</td>
<td>10.7%</td>
</tr>
<tr>
<td>0.3 through 0.5</td>
<td>592</td>
<td>86.8%</td>
<td>13.2%</td>
</tr>
<tr>
<td>&gt; 0.5</td>
<td>456</td>
<td>88.4%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Central Corneal Thickness (CCT)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 555</td>
<td>462</td>
<td>95.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>&gt;555 through 588</td>
<td>463</td>
<td>97.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>&gt; 588</td>
<td>477</td>
<td>96.4%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>
*Corneal thickness measurements were initiated in 1998, 2 years after the close of randomization; therefore, the percentage of inactive participants with CCT measurements is lower compared to the other measurements which were performed at baseline.

In other analyses, we examined if there was a differential loss to follow-up of participants with various putative risk factors between the randomization groups. No differences were found between the two randomization groups in the loss to follow-up of participants with various risk factors i.e. participants with various risk factors dropped out at the same rate from the medication and observation groups in OHTS I. These data suggest that at the time of transition to OHTS II, the original observation group and original medication group, which were equivalent at study inception, have remained similar with regard to various putative risk factors.

### 2.10.2 Statistical Power for Testing the Hypothesis

The primary hypothesis of OHTS II will be tested by comparing the long-term cumulative proportion of participants originally randomized to observation who develop POAG compared to the long-term cumulative proportion of participants originally randomized to medication who develop POAG. The sample for the primary analysis includes POAG endpoints from the time of randomization in OHTS I through the end of OHTS II. The same rationale applies to safety outcomes.

**Why are POAG Endpoints in OHTS I Counted?**

The primary efficacy question of OHTS II is whether there is a penalty for delaying treatment in ocular hypertension. In order to address this question, we must consider the incidence of POAG from the time of the original decision to begin or to withhold treatment. Therefore, all POAG endpoints must be counted from the time of randomization in OHTS I.

Another way to analyze the data is to compare the relative rate of developing POAG in OHTS II to the rate in OHTS I. We intend to do this analysis but do not believe it is the appropriate analysis for the primary hypothesis. We realize that the comparison of POAG incidence in OHTS II to that in OHTS I may be limited by a lower rate of POAG endpoints in the original observation group which receives treatment in OHTS II as well as the smaller sample size due to death, loss to follow-up and conversion to POAG.

**Estimating Long-Term Cumulative Incidence of POAG in the Original Randomization Groups**

To estimate the long-term POAG rate in the original observation group and the original medication group, we constructed 3 possible scenarios (divergence, convergence and stabilization). The 3 scenarios, which illustrate different relative risks for the development of POAG, serve to define the upper and lower boundaries of the statistical power of the study. The relative risk is the ratio of the POAG rates per person-year between the original medication group and the original observation group. The Planning Committee for OHTS I had decided that prophylactic treatment should produce at least a 40% reduction in the incidence of POAG in the medication group to justify chronic treatment in ocular hypertensive individuals at moderate to high risk of developing POAG. Since
2.10.3 Assumptions Used to Estimate Statistical Power

The statistical power reported in Tables 3 and 4 below to detect projected differences in the cumulative incidence of POAG between the original observation group and the original medication group for the various scenarios was computed under the following assumptions.

- The null hypothesis, that the two randomization groups have the same POAG rates, is tested using a chi-square test with 1 degree of freedom as described by Breslow and Day (1987). Events are assumed to occur instantaneously at the time of randomization. Time to failure is ignored for the purpose of estimating statistical power. Analytic methods that take time to failure into consideration as described in the analysis section are likely to have greater power than reported in Tables 6 and 7.
- Two-sided nominal alpha = 0.05
- Sample size: Estimates of statistical power are calculated assuming that 20% or 277 of the 1,385 of the active participants in OHTS I as of 5/31/02 are lost to follow-up in OHTS II or are not adherent to the protocol. Statistical power reported in Tables 3 and 4 is based on 1,100 participants (1,385–277=1,108). The estimate of statistical power which is calculated using 1,100 participants is conservative because the effective sample in the primary analysis includes data from 1,618 randomized participants with at least one follow-up visit.

2.10.4 Scenarios for Setting the Upper and Lower Boundaries of Statistical Power

To calculate the long-term cumulative incidence of POAG through the end of OHTS II for the different scenarios, we used the 5-year incidence rates in OHTS I, i.e., 4.4% in the medication group and 9.5% in the observation group. Since the cohort is now 5-7 years older than at randomization, the projected 5-year incidence of POAG in OHTS II is increased by 1.5% in both randomization groups. Since both randomization groups will be on medication, we estimated the effect of age on the incidence of POAG by extrapolating from POAG rates observed in the medication group in OHTS I. In OHTS I, the percentage of participants in the medication group who developed POAG by age decades (40 - 50, 50 - 60, > 60) was 1.5%, 4.0%, 8.1% respectively. The 5-year age adjustment was half of the observed increase by decade of 2.5% to 4% in the incidence of POAG. The projected long-term cumulative incidence of POAG from the beginning of OHTS I to the end of OHTS II for each randomization group is the sum of the observed 5-year incidence in OHTS I and the estimated 5-year incidence in OHTS II under the different scenarios as described below plus the age adjustment of 1.5%.
Scenario 1: Divergence Scenario

In the divergence scenario, the incidence of POAG in OHTS II continues to be higher in the original observation group (now on treatment in OHTS II) than in the original medication group. Thus, the cumulative incidences in the two groups continue to diverge over the course of OHTS II. The incidence of POAG in OHTS II in the original observation group is projected to be 7%, which is lower than in OHTS I (9.5%) but higher than the incidence in the original medication group in OHTS I (4.4%). The long-term cumulative incidence of POAG in the divergence scenario is projected to be 18% in the original observation group and 10.3% in the original medication group (relative risk is 0.53). Statistical power to detect this projected difference is 0.99 assuming a conservative estimate of sample size of 1108 (see Table 3). Because different cumulative incidences of POAG for each group can be projected, the statistical power for other projections is provided in Table 4.

Scenario 2: Convergence Scenario

In the convergence scenario, the incidence of POAG in OHTS II in the original observation group is projected at 4.4% reflecting immediate protective benefit of medication. The incidence of POAG in the original medication group is projected to increase to 7% reflecting an escape from the protective benefit of medication. Thus the cumulative incidences of POAG in the two groups begin to converge. The long-term cumulative incidence of POAG in the convergence scenario is projected to be 15.4% in the original observation group and 12.9% in the original medication group (relative risk=0.77 is below criteria for clinical significance). Statistical power to detect this projected difference is 0.42 (See Tables 3 and 4). We believe this is the least likely of the 3 scenarios.

Scenario 3: Stabilization Scenario

In the stabilization scenario, the incidence of POAG in OHTS II becomes similar in the two groups after the original observation group has been on treatment for 18 months. Thus, we project a reduction in the cumulative incidence of POAG in the original observation group from 9.5% in OHTS I to 5.0% in OHTS II. The incidence of POAG in the original medication group is projected to be 4.4%, the same as in OHTS I. The long-term cumulative incidence of POAG in the stabilization scenario is projected to be 16.0% in the original observation group and 10.3% in the original medication group (relative risk is 0.62). Statistical power to detect this projected difference is 0.89 assuming a conservative estimate of sample size of 1108 (See Tables 3 and 4).
Table 3. Long-Term, Cumulative Incidence of POAG in the Original Observation Group and the Original Medication Group for 3 Possible Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Original Observation Group</th>
<th>Original Medication Group</th>
<th>Relative Risk (95% Confidence Interval) &amp; Statistical Power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Divergence Scenario</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHTS I 5-year incidence</td>
<td>9.5%</td>
<td>4.4%</td>
<td>RR=0.53 (0.39,0.71)</td>
</tr>
<tr>
<td>Age Adjustment</td>
<td>1.5%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>OHTS II 5-year incidence</td>
<td>7.0%</td>
<td>10.3%</td>
<td></td>
</tr>
<tr>
<td>10 year incidence total for OHTS I &amp; OHTS II</td>
<td>18.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Convergence Scenario</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHTS I 5-year incidence</td>
<td>9.5%</td>
<td>4.4%</td>
<td>RR=0.77 (0.57,1.03)</td>
</tr>
<tr>
<td>Age Adjustment</td>
<td>1.5%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>OHTS II 5-year incidence</td>
<td>4.4%</td>
<td>7.0%</td>
<td></td>
</tr>
<tr>
<td>10 year incidence total for OHTS I &amp; OHTS II</td>
<td>15.4%</td>
<td>12.9%</td>
<td>Power=0.42</td>
</tr>
<tr>
<td><strong>Stabilization Scenario</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHTS I 5-year incidence</td>
<td>9.5%</td>
<td>4.4%</td>
<td>RR=0.62 (0.45,0.83)</td>
</tr>
<tr>
<td>Age Adjustment</td>
<td>1.5%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>OHTS II 5-year incidence</td>
<td>5.0%</td>
<td>10.3%</td>
<td></td>
</tr>
<tr>
<td>10 year incidence total for OHTS I &amp; OHTS II</td>
<td>16.0%</td>
<td></td>
<td>Power=0.89</td>
</tr>
</tbody>
</table>

These scenarios use incidence rates for the purpose of illustration; however because of the different number of person years in OHTS I and OHTS II, all power calculations are based on the test for comparing POAG rate per person-year between the two groups using a chi-square test with 1 degree of freedom as described by Breslow and Day (1987).
Table 4. Power to detect differences in the Cumulative Proportions of Participants Developing POAG in the original randomization groups

<table>
<thead>
<tr>
<th>Cumulative Proportion developing POAG in the Original Observation Group</th>
<th>Each cell reports Relative Risk (RR) and Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>0.07</td>
<td>RR=0.49</td>
</tr>
<tr>
<td></td>
<td>Power=0.99</td>
</tr>
<tr>
<td>0.08</td>
<td>RR=0.55</td>
</tr>
<tr>
<td></td>
<td>Power=0.95</td>
</tr>
<tr>
<td>0.09</td>
<td>RR=0.61</td>
</tr>
<tr>
<td></td>
<td>Power=0.87</td>
</tr>
<tr>
<td>0.10</td>
<td>RR=0.67</td>
</tr>
<tr>
<td></td>
<td>Power=0.72</td>
</tr>
<tr>
<td>0.13</td>
<td>RR=0.85</td>
</tr>
<tr>
<td></td>
<td>Power=0.20</td>
</tr>
</tbody>
</table>

The sample provides statistical power of 0.80 or greater to detect projected differences in the long-term cumulative incidence of POAG under the divergence and stabilization scenarios, but not the convergence scenario. The projected difference in the convergence scenario is lower than the level considered by the Executive/Steering Committee to be clinically useful. Thus, the sample of 1,100 (see Table 4) participants provides statistical power of 0.80 or greater for all differences in cumulative proportions that have clinical significance defined as a relative risk of 0.60 or less.

2.10.5 Analysis of Efficacy

In the primary analysis, the null hypothesis is that there is no difference in the long-term cumulative POAG rates between the original observation group and the original medication group. The alternative hypothesis for which the study is powered at 80% is that the incidence of POAG in the original medication group is reduced by 40% or more compared to the incidence in the original observation group. As in OHTS I, the first eye to develop POAG by either visual field POAG endpoint or optic disc POAG endpoint defines the participant as developing POAG. Thus, analysis of the primary hypothesis is based on the individual and not on separate eyes. It is important to note...
that the primary hypothesis in OHTS II tests for differences between the two original randomization groups in the long term cumulative POAG rates, not differences in the time to the onset of POAG between the two original randomization groups. This distinction is important since OHTS I has already demonstrated that POAG occurs more frequently and earlier in the observation group.

The primary hypothesis will be tested using an asymptotic χ²-test with one degree of freedom to test for a difference in the cumulative POAG rates in the original observation group and participants in the original medication group. This test was described by Breslow and Day (1987). The test statistic is computed as:

$$\chi^2 = \left( \frac{O_2 - N_2O / N \cdot 0.5}{ON_1N_2 / N^2} \right),$$

where \(O_2\) is the number of POAGs for the original medication group, \(O\) is the total number of POAGs from both the original medication and observation group, \(N_2\) and \(N_1\) are the number of person-years for the original medication and observation group, respectively, and \(N=N_1+N_2\).

The asymptotic χ²-test is an appropriate test for the primary hypothesis because the key comparison is the cumulative rate of participants developing POAG in each randomization group. A large sample 95% confidence interval estimate about the difference in the cumulative POAG rates between the two original randomization groups will be calculated. The estimate of the long term POAG incidence (and 95% confidence interval) in the original medication and original observation groups will be an important finding.

Additional analysis will compare the survival time from the beginning of the OHTS II to the development of POAG between the two original randomization groups. The comparison will be conducted on the subgroup of participants in the original observation group and original medication group who did not develop POAG in OHTS I. The comparison of the survival functions in the two original randomization groups will be done by the log rank test (Lawless, 1982).

### 2.10.6 Analysis of Safety

Safety of topical treatment will be assessed from several sources of information including participant self-report (Glaucoma Symptom Checklist of ocular and systemic, NEI-Visual Function Questionnaire, and SF-36), medical and ocular history as elicited by clinical staff (new medical conditions, worsening medical conditions, hospitalizations, surgery), and clinical measures (ETDRS visual acuity and LOCS III). The effect of longer duration of medication in the original medication group on safety events can be compared to shorter duration of medication in the original observation group by comparing the cumulative proportions of these safety events or the event rates per person-year from the time of randomization using asymptotic χ²-test with one degree of freedom. The survival curve from the time of randomization to the first occurrence of safety events will be compared between the two randomization groups using the log rank test. The potential effect of covariates will be assessed using the Cox proportional hazards models (Lawless, 1982).
We will examine possible indicators of diminishing effectiveness of medication by comparing the randomization groups as to the percentage of participants who reach IOP goal, the number of medications needed to reach IOP goal and the frequency of changes in medications required to reach IOP goal. The number of different medications and number of medication changes by randomization group will be compared using an asymptotic standard normal z-test. The same z-test will also be used to compare randomization groups in the percent of participants meeting IOP goal in both eyes.

Differences between the original randomization groups in LOCS III gradings will be analyzed both cross-sectionally and longitudinally. The first LOCS III measurement will occur in OHTS II when the differences in exposure to treatment are greatest. When the first LOCS III gradings are available, we will compare the two original randomization groups on the distributions on LOCS III gradings using either a Student’s t-test or a nonparametric Wilcoxon rank sum test. Table 8 presents the mean difference between the two groups that can be detected with at least 80% power on four LOCS III gradings with the projected sample sizes for OHTS II. These power analyses are based on a Student’s t-test at 5% significance level and estimated standard deviations of LOCS III gradings as reported by Srinivasan (1997). The OHTS II sample provides power to detect differences between groups in LOCS III lens opacification gradings cross-sectionally or longitudinally well below the level of 0.5 LOCS III unit difference that would be considered clinically significant.

Table 5. Mean difference in LOCS III Grade to be detected with at least 80% power

<table>
<thead>
<tr>
<th>Types of Lens Opacity</th>
<th>Difference in the mean to be detected</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>0.065</td>
<td>0.360</td>
</tr>
<tr>
<td>Nuclear Opalescence</td>
<td>0.065</td>
<td>0.360</td>
</tr>
<tr>
<td>Posterior Subcapsular</td>
<td>0.045</td>
<td>0.248</td>
</tr>
<tr>
<td>Nuclear Colour</td>
<td>0.080</td>
<td>0.468</td>
</tr>
</tbody>
</table>

When longitudinal measurements of LOCS III gradings are compared, the assessment of change over time will be based on general linear mixed models such as the random coefficient models as described by Laird and Ware (1982). These general linear mixed models will also allow the assessment of the effect of important covariates such as age, sex, race, time on medication, beta blockers or all aqueous suppressants, and corticosteroid use.

Another approach would be to examine the incidence of changes that meet or exceed a certain threshold (e.g. presence of cataract as defined by a 2.0 grade; Leske, 1997). For analyses of threshold events, the survival curves from baseline to the time of the threshold change between the two original randomization groups will be estimated by Kaplan-Meier product-limit method and tested by log-rank test (Lawless, 1982). The effects of covariates such as age, sex, race, time on medication (e.g. beta-blockers or all aqueous humor suppressants), and corticosteroid use will be assessed in a Cox proportional hazards model.

The statistical analysis strategy for NEI-Visual Function Questionnaire and its subscales is similar to that of LOCS III gradings. Both cross-sectional and longitudinal analysis will be used to assess the difference on NEI-Visual Function Questionnaire scores or its subscales between the two original
randomization groups. The available sample sizes in OHTS II will allow detection of a difference of as small as 1.5 in the mean overall NEI-Visual Function Questionnaire score (i.e. 0.17 of a standard deviation unit of 8.88) between the two groups with an 80% statistical power. The study will have adequate power to detect differences far below the 10 units, which some investigators have defined as the minimum clinically significant difference. This power analysis is based on a Student’s t-test at 5% significance level and an estimated standard deviation of 8.88 using data from the first administration of the NEI-Visual Function Questionnaire in OHTS I.

The rate of mortality will be compared between randomization groups and to the national expectations based on appropriate age, gender, and race classifications.

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

### 2.10.7 Interim Analysis/Safety Monitoring

Interim analyses provide input about the possibility that OHTS II should be terminated early or the study protocol should be modified. There are several possibilities in which the interim analysis for monitoring safety and efficacy will be important: (1) when early data indicate that the available sample size is insufficient to reach the projected statistical power due to various reasons; (2) when the initiation of medication in the observation group has such protective effect that it erases the difference in the incidences of POAG between the two original randomization groups indicating that it is unnecessary to continue the study; (3) when the introduction of medication in the observation group is so ineffective that it does not significantly change the incidences of POAG in the two randomization groups, indicating that the penalty of delaying treatment will last and may even increase. Because of the significant difference in the POAG incidence rates between the two randomization groups at the end of OHTS I, interim analyses may be more informative later the course of OHTS II; (4) when evidence of excess risk of adverse experiences occurs in the medication group suggesting a need to modify the protocol or terminate the study early due to a lack of a favorable risk/benefit ratio.

To monitor for the possibility that the initiation of medication in OHTS II in the observation group is so ineffective that the original observation group continues to exhibit a higher rate of POAG incidence compared to the original medication group (divergence scenario), the O’Brien-Fleming group sequential testing method will be used (O’Brien, Fleming, 1979). The survival curves of the two randomization groups from the beginning of OHTS II to the development of POAG will be compared by conditioning on the subgroup of participants in the original observation group and original medication group who did not develop POAG in OHTS I. This group sequential testing procedure will test for the equality of two survival curves against the one-sided alternative that the survival curve for the original observation group is below that for the original medication group. The O’Brien-Fleming method is chosen because it not only achieves the 5% overall nominal significance level over repeated hypothesis tests of the survival data but also allows the choice of low significance levels during the early tests. The latter is important because we believe on that early termination
should be more difficult at the beginning of OHTS II since OHTS I has demonstrated a significant difference on the POAG incidence rates between the two randomization groups. Monitoring of safety and efficacy outcomes will be conducted at 6 month intervals and as requested by the DSMC. Specific details of the interim monitoring plan will be developed in collaboration with the DSMC.

2.11 Human Participants

2.11.1 Entry Criteria

With rare exceptions specified below, all participants randomized in OHTS I are eligible for OHTS II.

Participants who are eligible for OHTS II includes those who…

a. have been inactive in OHTS I.
   Participants who have been inactive in OHTS I should be encouraged to enroll at any time during OHTS II, even after the transition period. Enroll and obtain consent for inactive participants even if they have not been seen for study visits in years. Their participation will reduce potential bias and be valuable to OHTS.

b. have developed POAG in one or both eyes.
   It is particularly important to enroll participants in OHTS II who developed POAG during OHTS I because they will provide important information about early visual field and optic disc change in POAG, the rate of progression of glaucomatous damage, the rate of conversion to POAG in fellow eyes and the effect of treatment on fellow eyes.

c. have developed a medical condition in OHTS I that would have excluded them from OHTS I. Some participants have developed a medical condition that would have excluded them from enrolling in OHTS I. These participants are eligible for OHTS II so long as they were randomized in OHTS I.

d. are unable to perform reliable visual fields in one or both eyes.
   These participants should be enrolled in OHTS II so long as one eye can be ascertained for the onset of POAG due to visual field abnormality or optic disc deterioration.

e. are unable to provide readable optic disc photographs in one or both eyes.
   These participants should be enrolled in OHTS II so long as one eye can be assessed either for visual field abnormality.

f. have lost vision in one eye from non-glaucomatous causes.
   These participants should be enrolled in OHTS II so long as one eye can be ascertained for POAG due to visual field abnormality or optic disc deterioration.
g. refuse medication.

These participants, whether they were originally randomized to the observation group or to the medication group in OHTS I, can be followed off medication in OHTS II. Over the course of follow-up, they may reconsider taking topical ocular hypotensive medication as per protocol.

2.11.2 Exclusion Criteria for OHTS II

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

a. If both eyes of a participant cannot be assessed for visual field and optic disc endpoint, and the condition is likely to be permanent, then a medical withdrawal may be necessary. (See section 4.9, for completion of the Medical Withdrawal form). If a condition is temporary or treatable (e.g. cataracts that can be removed) reassess the participant after intervention and try to enroll the participant if he or she is now eligible.

2.11.3 Confidentiality and Protection of Subjects

All reasonable measures are taken to protect the confidentiality of study records and participant identity. The protocol requires that study information on hard copy is kept in locked file cabinets and is available only to the OHTS clinicians and coordinators at the various Clinical Centers. At clinic site visits, central coordinators confirm that study data are stored in locked cabinets and that the cabinets are in a room that can be secured. Study information is coded by ID number only with no personal identifiers or locator information. Random ID’s are used to protect masking at ancillary study reading centers and resource centers. The confidentiality of all study related records will be maintained in accordance with State and Federal laws. OHTS is committed to being in compliance with Health Insurance Portability and Accountability Act guidelines and requirements.

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

OHTS II provides protection of participants at several different levels starting with the clinic where the participant receives care, at the level of resource centers which monitor for potential glaucoma damage using standardized criteria, and at the national level where oversight is provided by the Executive/Steering Committee, Full Investigative Group, NEI project officer, and the DSMC. The DSMC reviews accumulating study outcome data at six-month intervals or more frequently as needed.

At each participating OHTS Clinical Center, the principal investigator and coordinator must complete certification for human studies research that is approved by their local IRB. The local IRB approves renewal of the OHTS protocol annually and approves protocol modifications as needed. No protocol changes can be implemented prior to approval by the local IRB. Participants return for examinations every six-months and are closely monitored by glaucoma specialists at the OHTS Clinical Center using a standard protocol. In addition to the clinician at the Clinical Center, trained and certified
experts at reading centers monitor clinical tests using a standardized protocol. The study endpoints are reproducible optic nerve deterioration and/or reproducible visual field abnormalities attributable to POAG. All visual fields and optic disc photographs are read in standardized, masked fashion in reading centers to minimize bias and variability. Attribution to POAG is made by a masked Endpoint Committee.

Information on the safety of treatment is collected every six months by surveys completed by participants as well as by medical and ocular history as elicited by medical personnel. The Clinical Center is responsible for compliance with reporting requirements of adverse events to their local IRB. The clinician tailors medical treatment for each participant to reduce or avoid side effects.

The DSMC is responsible for monitoring the ethical conduct of the study and the accumulating data for evidence of adverse and beneficial treatment effects. This committee consists of seven voting members some with overlapping expertise as follows; four ophthalmologists, one epidemiologist, two biostatisticians and one ethicist. Efficacy and safety information are analyzed and reported by the Coordinating Center to the DSMC every six months or more frequently as needed. A summary report from the DSMC on the study-wide safety experience is distributed to local IRB’s following each meeting and more frequently as needed. This committee decides when results from OHTS may be released to study investigators, study participants, the medical community and the public. The DSMC reports to Paul Sieving, M.D., Director of the National Eye Institute. Chapter 9 “Study Organization” provides a detailed description of the membership and responsibilities of the DSMC.

2.11.4 Risks

The primary risk of participation in OHTS II is the development of a side effect to one of the prescribed medications. All medications used in OHTS are approved by the Food and Drug Administration (FDA) and are commercially available. As the FDA approves new medications, the Executive/Steering Committee will consider their addition to the study central pharmacy. Local IRB’s are informed of the side effects of medications that are added to the study. The consent form for OHTS II currently lists the following risks associated with topical ocular hypotensive medication. As new medications are added, the consent form is revised to include their side effects. OHTS utilizes highly skilled glaucoma specialists who are trained and certified in the study protocol. They will choose medication to minimize side effects. New medications are added or substituted in one-eyed trials. Thus, the frequency and severity of drug-related side effects is likely to be lower in OHTS II than standard clinical practice.

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, 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, macular edema.

Topical alpha-2 agonists (brimonidine or apraclonidine): Burning and stinging, 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.

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.

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

Combination Therapy (timolol and dorzolamide): 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.

There is some recent evidence that topical hypotensive medication may increase the incidence of lens opacification (Leske, 2002; Heijl, 2002). It is not clear whether the increased risk is related to a specific medication, a specific class of medication, or all medications. OHTS II will carefully monitor lens opacification using LOCS III and masked observers. See Section 6.15 for more information regarding determination of lens opacity classification.

Other risks to participants include developing conditions that could occur with at least equal frequency whether the participant is in OHTS II or not. These include developing POAG, a corneal abrasion or subconjunctival hemorrhage related to examination. Participants in OHTS II have elevated IOP and are at risk for developing POAG whether they participate in the study or not. All participants in OHTS II will be offered topical ocular hypotensive medication, which will decrease their risk of developing POAG. In addition, the participants in OHTS II receive their care from highly skilled glaucoma specialists at follow-up visits scheduled at 6-month intervals or less. Visual fields and optic disc photographs are reviewed in standardized fashion by trained, certified technicians and ophthalmologists. Thus, the standard of care in OHS II exceeds the standard of care in the community.

Participants in OHTS II could develop a corneal abrasion or a subconjunctival hemorrhage from clinical examination. OHTS II includes routine clinical tests performed by highly skilled certified clinicians. Thus, the rate of these events should be lower than in the community.
2.11.5 Benefits

Participants in this study will receive eye care that meets or exceeds the standard quality of care. Participants will also receive eye drop medications free of charge. The benefits of this study to society are great. Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. Given the large number of individuals with glaucoma and the serious consequences of this disease, information about the benefits and risks of early treatment and who should receive treatment have great public health importance.

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

2.12 Literature Cited


Appendix
## OHTS I participants at baseline

### Table 6  Distribution of Race in OHTS I, 1994

<table>
<thead>
<tr>
<th>Race</th>
<th>Number of Subjects</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>African American</td>
<td>409</td>
<td>25.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>59</td>
<td>3.6</td>
</tr>
<tr>
<td>White</td>
<td>1137</td>
<td>69.5</td>
</tr>
<tr>
<td>Other or Unknown</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1636</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 7  Baseline Demographic Characteristics reported for African American Participants and Other Participants Enrolled in OHTS I

<table>
<thead>
<tr>
<th></th>
<th>African American</th>
<th>Other</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140</td>
<td>34</td>
<td>565</td>
</tr>
<tr>
<td>Female</td>
<td>269</td>
<td>66</td>
<td>663</td>
</tr>
<tr>
<td>Mean Age ± S.D. (years)</td>
<td>54.5 ± 9.0</td>
<td>55.7 ± 9.7</td>
<td>55.4 ± 9.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 &lt;= age &lt;50</td>
<td>137</td>
<td>34</td>
<td>385</td>
</tr>
<tr>
<td>50 &lt;= age &lt;60</td>
<td>143</td>
<td>35</td>
<td>400</td>
</tr>
<tr>
<td>60 &lt;= age &lt;70</td>
<td>107</td>
<td>26</td>
<td>318</td>
</tr>
<tr>
<td>70 &lt;= age &lt;80</td>
<td>22</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>65</td>
<td>16</td>
<td>146</td>
</tr>
<tr>
<td>Married</td>
<td>198</td>
<td>48</td>
<td>857</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>102</td>
<td>25</td>
<td>158</td>
</tr>
<tr>
<td>Widowed</td>
<td>44</td>
<td>11</td>
<td>67</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 6th grade</td>
<td>4</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Grade 7-11</td>
<td>53</td>
<td>13</td>
<td>44</td>
</tr>
<tr>
<td>Grade 12/GED</td>
<td>141</td>
<td>35</td>
<td>287</td>
</tr>
<tr>
<td>1+ years of college</td>
<td>171</td>
<td>42</td>
<td>584</td>
</tr>
<tr>
<td>1+ years of graduate school</td>
<td>40</td>
<td>10</td>
<td>300</td>
</tr>
</tbody>
</table>
Table 8 Baseline Clinical Characteristics of African American Participants and Other Participants Enrolled in OHTS I.

<table>
<thead>
<tr>
<th></th>
<th>African American</th>
<th>Other</th>
<th>Overall&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
<td>OD</td>
</tr>
<tr>
<td><strong>Intraocular Pressure</strong>&lt;sup&gt;1&lt;/sup&gt; Mean ± S.D. (mm Hg)</td>
<td>25.2 ± 3.0</td>
<td>25.0 ± 3.1</td>
<td>25.0 ± 3.0</td>
</tr>
<tr>
<td><strong>Refractive Error</strong>&lt;sup&gt;1&lt;/sup&gt; Spherical Equivalent (D) ± S.D.</td>
<td>-0.35 ±2.01</td>
<td>-0.32 ±1.99</td>
<td>-0.72 ±2.46</td>
</tr>
<tr>
<td><strong>C/D Ratio (Mean ± S.D.)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.42 ± 0.18</td>
<td>0.42 ± 0.17</td>
<td>0.34 ± 0.19</td>
</tr>
<tr>
<td><strong>Visual Field Mean Deviation (dB)</strong>&lt;sup&gt;1&lt;/sup&gt; ± S.D.</td>
<td>0.06 ± 1.11</td>
<td>0.06 ± 1.14</td>
<td>0.29 ± 1.07</td>
</tr>
<tr>
<td><strong>Visual Field Pattern Standard Deviation (dB)</strong>&lt;sup&gt;1&lt;/sup&gt; ± S.D.</td>
<td>1.93 ± 0.25</td>
<td>1.91 ±0.24</td>
<td>1.92 ±0.24</td>
</tr>
<tr>
<td><strong>Visual Field Corrected Pattern Standard Deviation (dB)</strong>&lt;sup&gt;1&lt;/sup&gt; ± S.D.</td>
<td>1.06 ± 0.46</td>
<td>1.10 ± 0.45</td>
<td>1.14 ± 0.45</td>
</tr>
<tr>
<td><strong>Previous Topical Ocular Hypotensive Medication</strong></td>
<td>38%</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Family History of Glaucoma</strong></td>
<td>43%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>High Blood Pressure</strong></td>
<td>56%</td>
<td>32%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Heart Disease</strong></td>
<td>9%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>19%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

<sup>1</sup> For eye specific variables the overall represents the average of the mean for the right and left eye.
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; and whether the optic disc deterioration is clinically significant. 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.

1. POAG

<table>
<thead>
<tr>
<th>Recommendation for Future Testing</th>
<th>Clinic Action</th>
<th>Reading Center Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Not Applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Continue follow-up and</td>
<td>- Schedule unscheduled visit.</td>
<td>Expect routine follow-up tests in the future for this eye/modality.</td>
</tr>
<tr>
<td>discontinue confirmation</td>
<td>- Perform routine follow-up tests at future follow-up visits for this eye/modality.</td>
<td></td>
</tr>
<tr>
<td>testing for this eye.</td>
<td>- Do not perform confirmation testing for this eye/modality.</td>
<td></td>
</tr>
<tr>
<td>c) Discontinue routine follow-up</td>
<td>- Schedule unscheduled visit.</td>
<td>Do not expect any further tests for this eye/modality.</td>
</tr>
<tr>
<td>testing and discontinue</td>
<td>- Do not perform any further tests for this eye/modality.</td>
<td></td>
</tr>
<tr>
<td>confirmation testing for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>this eye.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. NOT POAG (ocular, artifact, systemic, unknown, other)

<table>
<thead>
<tr>
<th>Recommendation for Future Testing</th>
<th>Clinic Action</th>
<th>Reading Center Action</th>
</tr>
</thead>
</table>
| 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)

<table>
<thead>
<tr>
<th>Recommendation for Future Testing</th>
<th>Clinic Action</th>
<th>Reading Center Action</th>
</tr>
</thead>
</table>
| 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. |
Confirmation of Abnormal Visual Fields

Confirmation of visual field abnormality is defined as three abnormal visual fields in a row with the same abnormality in the same location.
Ocular Hypertension Treatment Study (OHTS)

Confirmation of Optic Disc Progression

Confirmed disc progression is defined as two consecutive optic disc photos showing progression.

Patient Follow-Up Visit

Optic Disc Progression?

- No → See patient at next follow-up visit
- Yes → Has patient previously reached POAG Endpoint?

- No → Confirm photos in 4 weeks
- Yes → Confirm photos at next follow-up visit

- No → Confirmed optic disc progression?
  - No → See patient at next follow-up visit (Start count over)
  - Yes → ODRC notifies Coordinating Center

ODRC notifies Coordinating Center

Coordinating Center convenes Endpoint Committee

Version 4.0 3/10/03
Ocular Hypertension Treatment Study (OHTS)

Attribution of Cause of Abnormality by Endpoint Committee

1. Coordinating Center convenes Endpoint Committee

2. Endpoint Committee notifies Coordinating Center of Decision (POAG, Not POAG, No Change)

3. Coordinating Center notifies VFRC, ODRC, Clinic with decision

4. Questions, concerns from VFRC, ODRC, Clinics regarding endpoint routed through Coordinating Center

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.
Participating Clinics, Committees and Resource Centers in the Ocular Hypertension Treatment Study

Study Centers and Groups

Clinical Centers

Bascom Palmer Eye Institute, University of Miami, Miami, Florida

Eye Consultants of Atlanta
Formerly M. Angela Vela, MD, PC
Atlanta, Georgia

Cullen Eye Institute, Baylor College of Medicine, Houston, Texas

Devers Eye Institute,
Portland, Oregon

Emory University Eye Center,
Atlanta, Georgia

Henry Ford Medical Center,
Troy Michigan

Johns Hopkins University School of Medicine, Baltimore, Maryland

Charles R. Drew University, Jules Stein Eye Institute, UCLA,
Los Angeles, California

W.K. Kellogg Eye Center,
Ann Arbor, Michigan

Kresge Eye Institute, Wayne State University,
Detroit, Michigan

Great Lakes Eye Institute Saginaw, Michigan

University of Louisville,
Louisville, Kentucky

Mayo Clinic/Foundation,
Rochester, Minnesota

New York Eye & Ear Infirmary,
New York, New York

Ohio State University,
Columbus, Ohio

Pennsylvania College of Optometry/MCP Hahnemann University School of Medicine, Philadelphia,
Pennsylvania

Scheie Eye Institute, University of Pennsylvania,
Philadelphia, Pennsylvania

University of California-Davis, Sacramento, California

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Nauman R. Imami, MD

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Donald J. Zack, MD, PhD

*Donald A. Abrams, MD

*Eve J. Higginbotham, MD

*Irvne P. Pollack, MD

*Alan L. Robin, MD

Anne L. Coleman, MD, PhD

*Richard S. Baker, MD

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Bret A. Hughes, MD

John M. O’Grady, MD

Joern B. Soltau, MD

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Michael V. Drake, MD

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Mae E. Gordon, PhD
Dale K. Heuer, MD
Eve J. Higginbotham, MD
Chris A. Johnson, Ph.D.
Michael A. Kass, MD (Chair)
John L. Keltner, MD
Richard K. Parrish II, MD
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John Connett, PhD
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Mark Sherwood, MD
Gregory L. Skuta, MD

Endpoint Committee
Dale K. Heuer, MD
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Richard K. Parrish II, MD
Mae O. Gordon, PhD
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Washington University School of Medicine,  
St. Louis, Missouri  
Mae O. Gordon, PhD

Chairman’s Office -  
Washington University School of Medicine,  
St. Louis, Missouri  
Michael A. Kass, MD

Project Office,  
National Eye Institute, Rockville, Maryland  
Donald F. Everett, MA

Optic Disc Reading Center, Bascom Palmer Eye Institute,  
University of Miami,  
Miami, Florida  
Richard K. Parrish II, MD

Visual Field Reading Center,  
University of California, Davis, Sacramento, California  
1Discoveries in Sight, Devers Eye Institute, Portland, Oregon  
John L. Keltner, MD

Ancillary Study Reading Centers

Confocal Scanning Laser Ophthalmoscopy Reading Center,  
University of California - San Diego,  
La Jolla, California  
Robert N. Weinreb, MD

Short Wave Length Automated Perimetry Reading Center,  
Devers Eye Institute, Legacy Portland Hospitals,  
Portland, Oregon  
Chris A. Johnson, PhD

Corneal Endothelial Cell Density Reading Center,  
Mayo Clinic/Foundation,  
Rochester, Minnesota  
William M. Bourne, MD

* Satellite Principal Investigator
3. **Eligibility and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>3-2</td>
</tr>
<tr>
<td>3.2</td>
<td>Eligibility for OHTS II</td>
<td>3-2</td>
</tr>
<tr>
<td>3.3</td>
<td>Exclusion Criteria for OHTS II</td>
<td>3-3</td>
</tr>
<tr>
<td>3.4</td>
<td>Eligibility Period for OHTS II</td>
<td>3-3</td>
</tr>
</tbody>
</table>
3.1 Introduction

With rare exceptions specified below, all participants randomized in OHTS I are eligible for OHTS II.

3.2 Eligibility for OHTS II

Participants who are eligible for OHTS II includes those who...

a. …have been inactive in OHTS I.

Participants who have been inactive in OHTS I should be encouraged to enroll at any time during OHTS II, even after the transition period. Enroll and obtain consent for inactive participants even if they have not been seen for study visits in years. Their participation will reduce potential bias and be valuable to OHTS II.

b. …have developed POAG in one or both eyes.

It is particularly important to enroll participants in OHTS II who developed POAG during OHTS I because they will provide important information about early visual field and optic disc change in POAG, the rate of progression of glaucomatous damage, the rate of conversion to POAG in fellow eyes and the effect of treatment on fellow eyes.

c. …have developed a medical condition in OHTS I that would have excluded them from OHTS I. Some participants have developed a medical condition that would have excluded them from enrolling in OHTS I. These participants are eligible for OHTS II so long as they were randomized in OHTS I.

d. …are unable to perform reliable visual fields in one or both eyes.

These participants should be enrolled in OHTS II so long as one eye can be assessed either for visual field or optic disc endpoints.

e. …are unable to provide readable optic disc photographs in one or both eyes.

These participants should be enrolled in OHTS II so long as one eye can be assessed either for visual field or optic disc endpoints.

f. …have lost vision in one eye from non-glaucomatous causes.

These participants should be enrolled in OHTS II so long as one eye can be assessed either for visual field or optic disc endpoints.

g. …refuse medication.

These participants, whether they were originally randomized to the observation group or to the medication group in OHTS I, can be followed off medication in OHTS II. Over the course of follow-up, they should be encouraged to reconsider taking topical ocular hypotensive medication as per protocol.
**3.3 Exclusion Criteria for OHTS II**

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

a. If both eyes of a participant cannot be assessed for visual field and optic disc endpoint, and the condition is likely to be permanent, then a medical withdrawal may be necessary. (See section 4.9, for completion of the Medical Withdrawal form (MW)). If a condition is temporary or treatable (e.g. cataracts that can be removed) reassess the participant after intervention and try to enroll the participant if he or she is now eligible.

**3.4 Eligibility Period for OHTS II**

There are no restrictions on the time OHTS I participants can enroll in OHTS II. Participants randomized in OHTS I can enroll anytime while OHTS II is ongoing. Enrollment in OHTS II requires the clinic staff to provide information to participants about OHTS II and the participant to provide informed consent. However, we wish to recruit as many OHTS I participants as possible to OHTS II by March 31, 2003. It is critical that at least 80% of the active OHTS I participants enroll in OHTS II in order for OHTS II to be valid.
4. Participant Education and Informed Consent

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>4-2</td>
</tr>
<tr>
<td>4.2</td>
<td>Why Informed Consent is Required for OHTS II</td>
<td>4-2</td>
</tr>
<tr>
<td>4.3</td>
<td>Description of OHTS II Protocol Modifications</td>
<td>4-2</td>
</tr>
<tr>
<td>4.4</td>
<td>Local IRB Approval for OHTS II</td>
<td>4-2</td>
</tr>
<tr>
<td>4.5</td>
<td>Issues in Participant Education</td>
<td>4-3</td>
</tr>
<tr>
<td>4.6</td>
<td>Signing the Informed Consent Form</td>
<td>4-4</td>
</tr>
<tr>
<td>4.7</td>
<td>Participants who Decline Medication</td>
<td>4-5</td>
</tr>
<tr>
<td>4.8</td>
<td>Participants Who Cannot Perform Tests</td>
<td>4-5</td>
</tr>
<tr>
<td>4.9</td>
<td>Medical Withdrawal</td>
<td>4-6</td>
</tr>
<tr>
<td>4.10</td>
<td>Deferred Consent</td>
<td>4-6</td>
</tr>
<tr>
<td>4.11</td>
<td>Decline to Participate</td>
<td>4-6</td>
</tr>
<tr>
<td>4.12</td>
<td>Continuing Education</td>
<td>4-6</td>
</tr>
</tbody>
</table>

Appendix .......................................................................................................................... 4-7

Human Studies Committee ............................................................................................... 4-8
4.1 Introduction

In an effort to enroll all individuals from OHTS I into OHTS II, considerable attention is given to education of the participant as well as family members or friends so they have a good understanding of ocular hypertension, glaucoma, the treatment options available, the results of OHTS I and the importance of OHTS II. 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, possible treatment side effects and the rationale for the study makes it more likely that participants will return for follow-up, will tolerate inconvenience associated with study participation and adhere to medication schedules. This should reduce participant dropout.

4.2 Why Informed Consent is Required for OHTS II

Informed consent is required for participation in OHTS II because the primary research questions have changed and the protocol has been modified. OHTS I answered questions about the safety and efficacy of topical hypotensive medication in the prevention of POAG. OHTS II will answer questions about the possible long-term difference in the risk of developing POAG between those who received treatment early (participants originally in the medication group) and those who received treatment later (participants originally in the observation group). Since OHTS I demonstrated that topical hypotensive medication was effective in delaying or preventing POAG, it is now important to answer the question of when treatment should be initiated. If treatment can be delayed with little or no increase in POAG, then delay in treatment would be the preferable public health policy for most ocular hypertensive individuals.

4.3 Description of OHTS II Protocol Modifications

In OHTS II, all participants will be offered topical ocular hypotensive medication. The study includes all topical ocular hypotensive medications commercially available in the United States. Participants in the OHTS I observation group who begin treatment in OHTS II will use the same medications, therapeutic regimen and IOP goals as the participants in the OHTS I medication group. During the transition period, no other protocol changes will be implemented. Tests, measures and examinations in OHTS I will remain the same in OHTS II to keep the transition as simple as possible.

This protocol modification has been approved by the OHTS Executive/Steering Committee, the Data and Safety Monitoring Committee, the Full Investigative Group and the National Eye Institute.

4.4 Local IRB Approval for OHTS II

OHTS I participating clinics must have local IRB approval for OHTS II before transitioning participants to OHTS II. All participants in OHTS I are eligible as participants in OHTS II even though the participant may have developed medical or ocular conditions that would have excluded them from OHTS I originally (see Chapter 3, Eligibility and Exclusion Criteria).
4.5 Issues in Participant Education

The principal investigator and the clinic coordinator must explain OHTS I results and their implication to eye care. 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 but not be limited to the following:

1. Glaucoma is one of the leading causes of blindness in the United States. Glaucoma is the leading cause of blindness in African Americans. In most cases, glaucoma damage is linked to pressure in the eye.

2. Everyone in OHTS I started the OHTS with high eye pressure but no glaucoma damage. Previously, it was not clear whether treating individuals with eye drops to lower eye pressure would prevent the development of glaucoma. There have been many small studies on this question but there was no consensus up to this point to guide doctors or patients in this matter.

3. OHTS I showed clearly that participants taking eye drop medicine had a much lower rate of developing glaucoma than did the participants not taking eye drops; the rate for developing glaucoma was 60% lower among participants receiving eye drop medication. This is an important scientific finding that helps develop health policy. Since glaucoma runs in families, this information may be important to the children and grandchildren and other family members of OHTS participants.

4. Based on the Study results, we want to offer eye drop medication to everyone in OHTS II. We can learn whether eye drops to lower eye pressure are just as effective when started later compared to earlier treatment. The medicines used in OHTS II are commercially available in the United States and are provided free of charge to participants. Each OHTS II clinic investigator will discuss potential side effects of the eye drops and recommend an eye drop that is likely to be safe for each participant.

5. Examinations in OHTS II will continue every six months. There are no co-payments or charges for visits or for eye drops. The participant’s insurance is billed for standard care; the Study pays for any additional tests or visits. As an active participant in the Study, participants may save hundreds of dollars per year for co-payments and medicines.

6. Because we have changed OHTS to recommend eye drop treatment for all participants, every participant will need to sign a new consent form.

7. All of the participant’s questions or concerns about OHTS II.

8. Individuals may watch a video summarizing OHTS I results and describing OHTS II before signing the consent.

9. This study was successful because of the continued effort and assistance of the participants and we appreciate all that they have done to make the OHTS successful.
Points for Participants in the Observation Group

1. Up to now, we did not know whether treating people with high eye pressure and no glaucomatous damage would prevent them from developing glaucoma.

2. OHTS I has shown that eye drops to lower eye pressure protect individuals from developing glaucoma.

3. We recommend starting eye drops to lower eye pressure to reduce the chances of developing glaucoma. There are many different eye drops to choose from. The clinician will try to choose one that is convenient to use and safe for the participant. The participant will try this eye drop for a few weeks and then be examined to be sure it is effective and safe. All eye drop medications are provided free of charge and are commercially available in the United States. No experimental drugs are used in OHTS II.

4. In OHTS II, we can learn whether eye drops to lower eye pressure are just as effective when started later compared to earlier treatment. We will also learn how long it takes for eye drops to reach their full protective effect against developing glaucoma.

If an observation participant is reluctant to receive eye drop medication, emphasize the safety and efficacy of medication and the person’s potential risk for developing glaucoma. An observation patient can continue in the Study without medication, although we prefer to treat as many participants as possible. The participant should be encouraged to begin medication on subsequent visits.

Points for Participants in the Medication Group

1. OHTS I has shown clearly that eye drops that lower eye pressure reduce the chances of developing glaucoma.

2. We want the medication participants to continue medications as before. The medication should continue to protect the participants from developing glaucoma.

3. The schedule of visits and tests in OHTS II will be similar to those in OHTS I.

4. By continuing in OHTS II, we hope to learn more about the long-term protective effect of eye drop treatment.

If a medication participant wants to stop medication, emphasize the protective effect of topical treatment and its safety. Also consider the participant’s risk of developing glaucoma. The participant can stay in the Study without taking medication, although we prefer to treat as many participants as possible. The participant should be encouraged to begin medication on subsequent visits.

4.6 Signing the Informed Consent Form

After the educational discussions outlined in section 4.5, the principal investigator asks the participant to sign the informed consent form to participate in OHTS II. Individuals are informed that they can withdraw from OHTS II 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.

An informed consent for OHTS II (Appendix) must be signed at the transition visit or at the next scheduled follow-up visit. Failure to obtain written informed consent, for any reason, makes the individual ineligible for OHTS II until written informed consent is obtained.

One copy of the signed informed consent is supplied to the participant and one is filed with the study records at the Clinical Center. To protect confidentiality, copies of the signed informed consent form are not sent to the Coordinating Center. Signed informed consent forms for OHTS II are audited at clinic site visits to confirm that they have been signed and are in proper order. The original OHTS I consent and reconsent, and OHTS II consent must be available for verification at all times. Original consents are kept on file at the clinic for as long as required by the local IRB at the Clinical Center after study close.

### 4.7 Participants Who Decline Medication

Not all participants, whether originally randomized to medication or to observation in OHTS I, will choose to receive medications in OHTS II despite efforts to persuade the participant. These participants should be enthusiastically encouraged to continue in OHTS II. They need to sign an informed consent form to be in OHTS II even though they decline to use topical ocular hypotensive medication.

All participants, whether on medication or not, complete regular follow-up OHTS II examinations and tests according to the OHTS II protocol. Participants who initially decline medication can start topical ocular hypotensive medication anytime during follow-up without needing to sign an additional informed consent form. Because medication status of participants is recorded at each follow-up visit, this information is kept current and does not require special reporting.

### 4.8 Participants Who Cannot Perform Tests

Acquisition of useable visual fields, optic disc photographs or IOP measurements may no longer be possible in some participants due to ocular and systemic conditions, e.g. stroke, Alzheimer’s disease and so forth. Participants who can do either visual fields or optic disc photographs in at least one eye should be encouraged to continue in OHTS II because the onset of POAG can be determined by either measure.

To report that a participant is unable to perform a standard protocol test, the Clinical Center completes a Protocol Exemption form (PE) explaining the reasons why the participant cannot be evaluated. A non-protocol alternative may be possible, e.g., Tonopen IOP as an alternative to Goldmann Applanation Tonometry. The Protocol Exemption form (PE) will be reviewed by the Study Chairman and the Medical Monitor. If the Protocol Exemption is approved, performance reports will allow an “exemption” for that measure for that participant.

If the condition/reason for protocol exemption is resolved, the participant may resume the standard protocol test/measure.

Participants who cannot do visual fields and optic disc photographs in at least one eye due to medical causes should be considered for medical withdrawal from the study (see section 4.9 for more information regarding Medical Withdrawal).
4.9 Medical Withdrawal

Only during the transition period, participants whose health prevents their participation in OHTS II or participants with an untreatable condition that precludes determination of the onset of POAG by visual field testing and optic disc photography in both eyes can be withdrawn from the study. A medical withdrawal can be considered for participants with less than one year of life expectation. If the participant can provide a year of data, the participant should be encouraged to enroll in OHTS II.

The Clinical Center submits a Medical Withdrawal form (MW) describing the reasons for the medical withdrawal request along with the Transition Visit Status form (TV) to the Coordinating Center. The request is reviewed by both the Study Chairman and the Medical Monitor. The Clinical Center will be notified of their decision by the Coordinating Center. Participants approved for Medical Withdrawal are not counted in data quality and missed visit reports.

If the medical condition is resolved and the participant wishes to resume study participation, the participant should be encouraged to do so. The Clinical Center will notify the Coordinating Center. If the participant had already signed an informed consent form for participation in OHTS II, an additional informed consent form does not need to be signed. If the participant has not signed an informed consent form for OHTS II, then an informed consent form for participation in OHTS II would need to be signed and an OHTS II Transition Visit Status form (TV) should be completed and sent to the Coordinating Center with the visit form.

4.10 Deferred Consent

Participants who decline to participate in OHTS II during the transition period may enroll in OHTS II at a later date by signing an informed consent form anytime during OHTS II follow-up. This provision allows the Clinical Centers to enroll participants who initially declined to participate in OHTS II, who did not complete a follow-up visit during the transition period, or who were not able to be contacted.

4.11 Decline to Participate

Participants who decline participation in OHTS II should complete a Decline to Participate form (DC). The individual can choose to receive care where he/she wishes. The date of the Decline to Participate form (DC) should be recorded on the Transition Status Visit form (TV) and sent with the last Follow-up Visit form (FV) to the Coordinating Center. Participants who decline to participate can enroll in OHTS II anytime during follow-up by signing an informed consent form for participation in OHTS II.

4.12 Continuing Education

During each visit the clinician and clinic coordinator review the medical regimen, including the method and time of medication administration, and answer 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, general health and the progress of the study. Other educational materials to encourage participant involvement and continued study participation will be developed throughout the duration of the study.
Appendix
INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participant: ____________________________  HSC Approval Number: _____________

Principal Investigator: _____________________  PI’s Phone Number: _____________

Title of Project: Ocular Hypertension Treatment Study (OHTS)

You are invited to participate in a research study conducted by Dr. Gordon and/or colleagues.

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.

1. PURPOSE:

You have been participating in a research project (Ocular Hypertension Treatment Study – OHTS) conducted by Dr. Gordon and/or colleagues. The overall purpose of this research is to determine whether lowering high eye pressure (intraocular pressure) with eye drop medication prevents or delays glaucoma in individuals with increased eye pressure. We now have information from OHTS that eye drops help to prevent glaucoma damage. These results have been reviewed by an independent committee of experts appointed by the U.S. Government (National Eye Institute, National Institutes of Health, Bethesda, Maryland).

All participants are being invited to continue in a new phase of the study. Based on the results of OHTS, we are recommending offering to all participants in OHTS receive eye drop medication to lower eye pressure. Your continued participation will enable the study to answer the question of whether eye drops to lower eye pressure are as effective when started later compared to earlier treatment. We will also learn how long it takes for eyedrops to have their full protective effect against the development of glaucoma.

2. PARTICIPATION:

Your examination schedule stays the same (every six months) until the close of the study. 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. This study has guaranteed funding through November 2003. The OHTS Executive/Steering Committee is currently developing a plan to extend the study to 2008.

All participants are encouraged to be offered eye drop medications, which will be prescribed free of charge. All participants will continue to fill out a questionnaire at each visit.

Version 4.0 3/10/03
Your visual fields and optic disc photographs will continue to be reviewed by a team of nationally recognized glaucoma experts.

You may be invited to view a videotape, which will demonstrate what your continued participation will entail as well as the results gathered thus far in OHTS.

3. **COSTS TO PARTICIPANTS:**

There are no costs to you as a participant of the Ocular Hypertension Treatment Study. As a participant in this federally funded study, you will receive eye care that meets or exceeds the standard quality of care. You will be offered eye drop medications at no cost to you. There will be no direct payments to you for participating in this study.

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

The primary risk of the study is that you could develop a side effect to one of the prescribed medications. All medications used in OHTS are approved by the Food and Drug Administration (FDA) and are commercially available. As the FDA approves new medications they will be added to the study. 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, 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, 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.

**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.

**Topical prostaglandin analogue (latanaprost, unoprostone, travaprost, bimatoprost):** 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 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.

Participation in this study may cause all or some of the side effects listed above. In addition, there is always the risk of developing previously unknown side effects.

The investigator is willing to discuss any questions you might have about these risks and discomforts.

5. **BENEFITS:**

As a participant in this federally funded study, you will receive eye care that meets or exceeds the standard quality of care. You will also receive eye drop medications free of charge. The benefits of this study to society are great. Glaucoma is one of the leading causes of blindness in the United States and other industrialized countries. Given the large number of individuals with glaucoma and the serious consequences of this disease, information about the best time to begin treatment is very important.

6. **ALTERNATIVES:** Other than non-participation in the research, available alternatives include:

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 doctor 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: receiving eye care from other ophthalmologists and optometrists.

7. **PROTECTED HEALTH INFORMATION (PHI):** is any health information through which you can be identified. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). A decision to participate in this research means that you agree to let the research team use and share your PHI for the study explained above. The OHTS will utilize your physician/clinic records for eye-related visits, exams and surgeries, lab reports relating to your eye care, and your date of birth. Your PHI will not be shared with anyone outside the OHTS Coordinating Center. The OHTS will utilize your physician/clinic records for eye-related visits, exams and surgeries, lab reports relating to your eye care, and your date of birth. Your name and names of your relatives and your social security number will be kept at the Clinical Center where you are seen as well as at the Coordinating Center at Washington University. A master list linking your OHTS ID number to your name and social security number will be kept in a password-protected electronic database. Hard copy form with this information, which was completed when you began OHTS, will be kept in a locked cabinet located within a locked suite at Coordinating Center at Washington University. Only designated members of the Coordinating Center will have access to the electronic and hard copy versions of the master list. Your PHI will not be shared with anyone outside the OHTS Coordinating Center.
WUMC will protect your information according to State and Federal laws. There is always the possibility that your information could be shared in a way that it would no longer be protected by law. Your identity will not be revealed in any publication that may result from this study.

Officials of Federal or State government agencies or the University may look at, use, or copy information in your research file to complete Federal, State or University responsibilities. A representative of the Sponsor, (insert Sponsor’s name or delete this sentence) the National Eye Institute, may also have access to your file.

The research team will use and share your information until the completion of data collection. At that point, the investigator will remove the identifiers from your information, making it impossible to link you to the study.

Your participation is voluntary and you may choose not to participate in this research study or withdraw at any time. Your choice will not 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. If you decide to end your participation in the study, please complete the withdrawal letter, found at http://medicine.wustl.edu/~hsc/hipaa/, or you may request that the Investigator send you a copy of the letter.

Do you already have contact restrictions in place with WUMC?    []Yes   []No

(Example – no calls at home, no messages left for you, etc.)

Please specify any contact restrictions you want to request for this study only.

8. **CONTACTS:** If you have any questions or concerns about this study, or if any problems arise, you may call the Investigator ______________. You may also ask questions or state concerns about your rights as a research subject, or express any feelings of pressure to participate to Dr. Philip Ludbrook, Chairman of the University's Human Studies Committee, at (314) 633-7400 or (800) 438-0445. If you have questions or concerns about your privacy and the use of your PHI, please contact Joan Podleski, the University’s Privacy Officer, at 866-747-4975.

9. Washington University investigators and their staffs will try to reduce, control, and treat any complications from this research. If you feel that you are injured because of the study, please contact the Investigator and/or the Human Studies Committee Chairman from Item 8. Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University and the Sponsor, (insert Sponsor’s name or delete this portion the National Eye Institute).

10. The Investigator will tell you about new information that may affect your decision to participate.

11. The investigator may withdraw you from the study if necessary.
This research is not meant to diagnose or treat 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 chance to ask questions. I will also be given a signed copy of this consent form for my records. I authorize the use of my PHI and give my permission to participate in the research described above, titled:

<table>
<thead>
<tr>
<th>Participant’s Signature</th>
<th>Date</th>
<th>Signature of person providing Informed Consent</th>
<th>Date</th>
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</table>

(If designee, see guideline [Who May Obtain Consent](#))

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.

The Notice of Privacy Practices (a separate document) describes the procedures used by WUMC to protect your information. If you have not already received the Notice of Privacy Practices, the research team will make one available to you.

---

I have been offered a copy of the WUMC Notice of Privacy Practices.

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This form is valid only if the Human Studies Committee’s current stamp of approval is shown below.
Ocular Hypertension Treatment Study (OHTS)

Transition to OHTS II

Observation Patient

- Consent
  - Agree to Treatment
    - Yes → One-Eyed Trial → FV
    - No → FV
  - Decline to Participate
    - Medical Withdrawal
    - Lost to Follow-Up

Medication Patient

- Consent
  - Agree to Treatment
    - No → FV
    - Yes
      - Goal Met?
        - Yes → FV
        - No → One-Eyed Trial → FV
      - Decline to Participate
        - Medical Withdrawal
        - Lost to Follow-Up
5. **Schedule of Visits and Form Completion**

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>5-2</td>
</tr>
<tr>
<td>5.2</td>
<td>OHTS II Transition</td>
<td>5-2</td>
</tr>
<tr>
<td>5.3</td>
<td>IOP Confirmation Visit</td>
<td>5-2</td>
</tr>
<tr>
<td>5.4</td>
<td>Follow-up Visits</td>
<td>5-3</td>
</tr>
<tr>
<td>5.4.1</td>
<td>Semi-Annual (6-Month) Follow-up Visit</td>
<td>5-4</td>
</tr>
<tr>
<td>5.4.2</td>
<td>Annual (12-Month) Follow-up Visit</td>
<td>5-5</td>
</tr>
<tr>
<td>5.5</td>
<td>Visual Field Abnormality Confirmation Visit</td>
<td>5-6</td>
</tr>
<tr>
<td>5.6</td>
<td>Optic Disc Deterioration Confirmation Visit</td>
<td>5-6</td>
</tr>
<tr>
<td>5.7</td>
<td>Unscheduled Visits</td>
<td>5-7</td>
</tr>
<tr>
<td>5.8</td>
<td>Adverse Events (AE)</td>
<td>5-7</td>
</tr>
<tr>
<td>5.9</td>
<td>Participant Retention</td>
<td>5-8</td>
</tr>
<tr>
<td>5.10</td>
<td>Participant Transfer</td>
<td>5-8</td>
</tr>
<tr>
<td>5.11</td>
<td>Participant Death</td>
<td>5-9</td>
</tr>
<tr>
<td>5.12</td>
<td>Missed Visit</td>
<td>5-9</td>
</tr>
<tr>
<td>5.13</td>
<td>Inactive Participants</td>
<td>5-9</td>
</tr>
<tr>
<td>5.14</td>
<td>Tests and Measures for Each Visit Type</td>
<td>5-10</td>
</tr>
<tr>
<td>5.15</td>
<td>Forms Required by Visit Type</td>
<td>5-11</td>
</tr>
<tr>
<td>5.16</td>
<td>Forms Required by Event</td>
<td>5-12</td>
</tr>
<tr>
<td>5.17</td>
<td>OHTS II Forms and Current Version Number</td>
<td>5-13</td>
</tr>
</tbody>
</table>
5.1 Introduction

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

5.2 OHTS II Transition

Participants are informed of the OHTS I results and are encouraged to continue in OHTS II. All participants need to sign an informed consent for participation in OHTS II.

Participants originally assigned to the observation group in OHTS I are started on medication in a 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. The IOP confirmation visit determines the safety of the medication and whether the IOP goal has been met.

5.3 IOP Confirmation Visit

An IOP confirmation visit is scheduled in 4 ± 2 weeks at approximately the same time of the day to minimize the effect of diurnal IOP fluctuation:

a) After starting a medication.
   b) After any change in medical therapy including adding or dropping a drug, substituting a drug, increasing or decreasing a drug concentration, or changing the number of daily doses.
   c) After a participant does not meet the IOP treatment goals in 1 or both eyes to confirm whether the IOP goal is met.
   d) After drug-induced side effects require a change in treatment.

The IOP confirmation visits continue until therapeutic goals are met or until the participant’s IOP does not meet the treatment goal 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 include the following:

- 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 Visit 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 in an eye during 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 agonist), 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 IOP Confirmation Visit [CF] form), or schedule another IOP confirmation visit in 4 ± 2 weeks at approximately the same time of the day.

2) If time limits have not been exceeded, medical therapy should be altered as outlined in the medical regimen (see Chapter 7, Treatment 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.

5.4 Follow-up Visits

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

Ideally, follow-up visits should occur ± one month of the scheduled target date. However, follow-up visits ± three months of the target date are acceptable. Regularly scheduled follow-up visits should be at least 60 days apart. If a regularly scheduled visit is not completed within ± three months of the target date, the visit is defined as a “missed visit.” 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 the Coordinating Center. This includes visual 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 6-month follow-up visit, and the 12-month follow-up visit.
5.4.1 Semi-Annual (6-Month) Follow-up Visit

Semi-Annual Follow-up Visit The first 6-month follow-up visit occurred six months after randomization and will be repeated every 12 months thereafter — i.e., at 78, 90, 102, 114, 126, 138, etc. months after randomization.

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

- Prior to examination, all participants, complete the Symptom Checklist form (SY).
- Update Patient Tracking form (TR). 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.
- Blood Pressure measurement.
- 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.
- Gonioscopy is performed once every two years at 6-month visits.
- Dispensing of medication to treated participants.
- Completion of Follow-up Visit form (FV).

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

If the IOP treatment goals for a participant are not reached on this visit, there are three 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 agonist), 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.) If the IOP goal is reached, continue the usual schedule of visits. If the IOP goal is not reached, go to options 2 or 3.

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 the IOP treatment goal 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.
If the participant’s IOP is $\leq 18$ mm Hg, medication is not required but may be prescribed at the clinician’s discretion.

### 5.4.2 Annual (12-Month) Follow-up Visit

**Annual Follow-up Visit** The first 12-month follow-up visit occurred 12 months after randomization and will be repeated every 12 months thereafter; i.e., 84, 96, 108, etc. months after randomization.

Data collected and procedures required at 12-month follow-up visits include the following:

- Prior to examination, all participants complete the Symptom Checklist form (SY).
- Update Patient Tracking form (TR). 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.
- Blood pressure measurement.
- 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.
- Dilated fundus examination and indirect ophthalmoscopy.
- Lens opacification assessment.
- Stereoscopic optic disc photographs.
- Dispensing of medication to treated participants.
- Completion of Follow-up Visit form (FV).

If the IOP treatment goals for a participant are not reached on this visit, there are three 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 agonists), 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 form [IP] and send with the Follow-up Visit form [FV].) If the IOP goal is reached, continue the regular schedule of visits. If the IOP goal is not met, go to option 2 or 3.

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.
5.5 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 visual field abnormal, the VFRC calls the Clinical Center to make sure a repeat (third) visual field 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 normal, the third confirming visual field test is canceled.

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

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

The VFRC reviews the confirmatory set of visual fields. If the abnormality is not confirmed by the confirming visual field test, the VFRC sends a letter of their decision to the Clinical Center. The participant returns to the routine schedule of follow-up. 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.

5.6 Optic Disc Deterioration Confirmation Visit

If the Optic Disc Reading Center (ODRC) detects optic disc deterioration, the ODRC requests a confirming set of photographs of the suspected eye to be taken in 4 ± 2 weeks. In some cases, the optic disc deterioration will have been detected by the 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 deterioration confirming visit include the following:

- Completion of the Unscheduled Visit form (UN).
- Stereoscopic optic disc photographs of the suspected eye only.

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

### 5.7 Unscheduled Visits

The Unscheduled Visit form (UN) is used for a variety of reasons:

- Eye problems not related to the study (i.e., conjunctivitis).
- To repeat unreliable visual fields.
- To confirm a suspected visual field abnormality.
- To repeat ungradable optic photographs.
- To confirm suspected optic disc deterioration.
- To dispense medications.
- For participant initiated visits.
- To transition a participant to OHTS II.
- To transmit data from a non-OHTS II visit.
- To change medication by telephone or by mail. If the change in medication is due to intolerance, an Adverse Event form (AE) should also be completed. The participant should return in $4 \pm 2$ 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.

### 5.8 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 form (AE) must be completed for each symptom complex.** It is important to complete adverse event forms without bias for participants receiving topical medication and for those who are not.
5.9 Participant Retention

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

Approximately one month before scheduled visits, the clinic coordinator will contact the participant to remind the participant of the upcoming examination. If the participant cannot attend the scheduled appointment, another appointment within the time window is arranged. Approximately one week before the scheduled appointment, the participant receives a letter or phone reminder from the clinic coordinator. Some participants may require additional calls or assistance to arrange transportation. 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 OHTS II 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 II, general and ocular health. The Study Chairman’s Office will continue a recognition program for continued participation in the study.

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 Clinical Center; these forms should not be sent to the Coordinating Center.

5.10 Participant Transfer

If a participant moves from one OHTS II clinic area and wishes to be seen at another OHTS II clinic, the top half of the Patient Transfer form (PX) is completed by the original Clinical Center. 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 II file is sent to the new Clinical Center. The original Clinical Center 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 his or her original five-digit study code and abbreviated suffix, but will use the treating site code as the prefix.

### 5.11 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 the form to the Coordinating Center.

### 5.12 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.

### 5.13 Inactive Participants

A participant is considered inactive if two consecutive follow-up visits are missed. The next missed visit will require another Missed Visit form (MV). The Clinical Center should continue to submit Missed Visit forms (MV) for each visit window missed until the participant returns.
## 5.14 Tests and Measures for Each Visit Type

<table>
<thead>
<tr>
<th>Symptom Checklist</th>
<th>Semi-Annual Follow-up Visit*</th>
<th>Annual Follow-up Visit*</th>
<th>IOP Confirming Visit</th>
<th>Visual Field Confirming Visit</th>
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* Semi-annual follow-up visits occur at 6, 18...78, 90, 102, 114, 126, 138 months, etc.

** Annual follow-up visits occur at 12, 24...84, 96, 108 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.

****** Pachymetry performed once during years 2003-2004 at either semi-annual or annual visit.
### 5.15 Forms Required by Visit Type

<table>
<thead>
<tr>
<th>Forms and Documents Required</th>
<th>Semi-Annual Follow-up Visit</th>
<th>Annual Follow-up Visit</th>
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* NEI VFQ administered every 2 years, starting with the 84 month visit

** Pachymetry measurement taken once during years 2003-2004 at either the semi-annual or annual visit
### 5.16 Forms Required by Event

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* Only during transition to OHTS II.
### OHTS II Forms and Current Version Number

**OHTS FORMS & CURRENT VERSION NUMBER**

Current as of 5/4/05

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*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. Current Forms can be viewed and/or printed from the OHTS website @https://vrcc.wustl.edu/ohts*
6. **Clinical Tests and Examinations**

6.1 Introduction ............................................................................................................... 6-2
6.2 Refraction .................................................................................................................. 6-2
6.2.1 Refraction Technique .......................................................................................... 6-2
6.3 Visual Acuity ............................................................................................................. 6-5
6.3.1 Snellen Visual Acuity Technique ..................................................................... 6-5
6.3.2 Snellen Visual Acuity Scoring ......................................................................... 6-5
6.3.3 ETDRS Visual Acuity Technique ..................................................................... 6-6
6.3.4 ETDRS Visual Acuity Scoring ......................................................................... 6-7
6.3.5 ETDRS Visual Acuity Testing Discontinuation ............................................... 6-7
6.3.6 ETDRS Visual Acuity Certification ................................................................. 6-7
6.4 Slit-Lamp Examination ......................................................................................... 6-7
6.5 Tonometry ................................................................................................................ 6-8
6.5.1 Tonometry technique ........................................................................................ 6-8
6.6 Gonioscopy .............................................................................................................. 6-10
6.7 Ophthalmoscopy ..................................................................................................... 6-10
6.8 Blood Pressure ........................................................................................................ 6-10
6.9 Pachymetry ............................................................................................................. 6-12
6.9.1 Overview of Pachymetry Measurements ......................................................... 6-13
6.9.2 Troubleshooting Pachymeter .......................................................................... 6-14
6.9.3 General Description of DGH-500 Pachymeter ............................................... 6-15
6.9.4 Power-up Sequence of Pachymeter ................................................................ 6-16
6.9.5 Calibration of Pachymeter .............................................................................. 6-16
6.9.6 Pachymetry Measurement Procedure ............................................................. 6-17
6.10 Visual Fields ........................................................................................................... 6-18
6.11 Stereoscopic Optic Disc Photography ................................................................. 6-18
6.12 Additional Measures (AM) ................................................................................... 6-19
6.13 NEI Vision Function Questionnaire (VQ) ........................................................... 6-19
6.14 Genetics Testing .................................................................................................... 6-19
6.1 **Introduction**

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

6.2 **Refraction**

Refraction is required semiannually for visual field testing. Refraction may be performed by any certified OHTS II 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.

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

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

**Determination of cylindrical refraction:** For purposes of this discussion, only plus cylinder techniques are presented.

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

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

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

**Example:** Starting refraction: -2.50 + 0.25 axis 37 degrees. Use of the cross-cylinder to check cylinder axis indicates that the participant prefers the 37-degree axis. If on using the cross-cylinder to check cylinder power, one finds that the participant wants the 0.25 cylinder removed, rotate the cylinder to 127 degrees and test for cylinder power once again. If additional power is preferred, add it.
If the preference is to remove the 0.25 cylinder, this should be done. If 0.50 or more diopters of cylinder have been added, the cylinder axis should be refined, if possible, by using the cross-cylinder as described above.

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

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

### 6.3 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. Any OHTS II certified personnel can perform Snellen visual acuity. 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 6.3.6).

#### 6.3.1 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 II. 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.

#### 6.3.2 Snellen Visual Acuity Scoring

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

6.3.3 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 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 320cd/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. After careful instruction, refraction and the placement of the proper lenses in the trial frame, the left eye is occluded and testing begins with the right eye.

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

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

When the participant says he or she cannot read a letter, he or she should be encouraged to guess. 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.

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

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

### 6.3.4 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 participant makes no guesses with an “x” or a line. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. The total score for each eye and the distance used for testing is recorded on the OHTS form for that visit.

### 6.3.5 ETDRS Visual Acuity Testing Discontinuation

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

### 6.3.6 ETDRS Visual Acuity Certification

All study personnel performing an ETDRS visual acuity test must be certified as to technique and scoring by the Coordinating Center. Certification consists of completing a brief 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.

### 6.4 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 follow-up examinations it is important to detect drug reactions such as allergic blepharoconjunctivitis, conjunctival hyperemia and follicular conjunctival reaction. It is also important to detect secondary causes of glaucoma that may occur during follow-up such as exfoliation syndrome, iritis, and neovascularization.

6.5 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. Two collaborators, an operator and a reader, both of whom are certified for the procedure, perform the IOP measurement. Both eyes are tested, with the right eye preceding the left eye. The measurement must be made on an eye that has not received pupil-dilating medications. Clean the prism tip according to your institutional infection control policy. Whenever possible, IOP should be checked at about the same time of day 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 least one but not more than six hours after the last glaucoma medication prescribed to be taken four times a day.
- At least one but not more than eight hours after the last glaucoma medication prescribed to be taken three times a day.
- At least one but not more than 12 hours after the last glaucoma medication prescribed to be taken twice a day.
- At least one but not more than 24 hours after the last glaucoma medication prescribed to be taken once a day.
- At least four but not more than 24 hours after use of pilocarpine 4% ointment.
- At least 10 hours but not more than 6 days after change of a pilocarpine Ocusert.

6.5.1 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 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. Tight-fitting neckwear is loosened. The participant is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the operator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The participant is cautioned not to hold his breath.

• The investigator looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well focused, centered horizontally, and positioned vertically so 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.
6.6 Gonioscopy

Gonioscopy is performed by a study-certified clinician. The test is repeated at least every 2 years.

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

The angle is graded according to the standard Shaffer system:

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

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

6.7 Ophthalmoscopy

Ophthalmoscopy is performed by a study-certified clinician.

The clinical morphology of the optic disc is assessed by direct ophthalmoscopy as well as a stereoscopic examination after pupil dilation with appropriate mydriatics. This examination is carried out at the slit lamp with a Hruby lens, contact lens, or Volk 78 or 90-diopter lens. The retinal periphery is examined with a head-mounted indirect ophthalmoscope and a hand-held condensing lens (a 14D, 20D, or 28D Nikon aspheric lens is recommended).

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).

6.8 Blood Pressure

Blood pressure measurements are performed at each annual and semi-annual visit. The blood pressure measurements should precede the IOP measurement and ocular examination.
All OHTS personnel measuring blood pressure must be certified for blood pressure measurement by passing a test administered by the Coordinating Center. Two non-study participants must be measured prior to taking this test and receiving certification.

OMRON Model HEM-780 IntelliSense™ Automatic Blood Pressure Monitor (http://quickmedical.com/omron/) provides non-invasive determination of systolic blood pressure, diastolic blood pressure, and pulse rate. Several studies suggest that blood pressure may be a risk factor for glaucoma.

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

1. In a quiet room, the participant should be seated for 5 minutes in a comfortable chair with feet on the floor.

2. Loosen tight fitting clothing from the upper left arm. All blood pressure measurements should be taken on the left arm unless there is a medical contraindication.

3. Check that the air plug is securely inserted into the left side of the monitor.

4. The left arm should rest comfortably on a table or arm of a chair (do not rest the arm on lap) so that the blood pressure cuff is at the same level as the heart.

5. Place the velcro cloth of the cuff on the upper arm with the lower edge of the cuff approximately ½ inch – 1 inch above the elbow.

6. Align the green marker on the cuff over the brachial artery. The cuff tube should run down the center of the arm in alignment with the participant’s middle finger.

7. Wrap the cuff snugly around the upper arm and secure with the Velcro.

8. Instruct the participant to keep the left arm still during blood pressure measurements.

9. Press ON/OFF button on the upper right corner of the monitor.

10. Monitor is ready when the heart symbol appears on the display.

11. Press START button on lower right corner of the monitor. Cuff automatically inflates to the ideal level and then stops.

12. When the blood pressure measurement is completed, the cuff automatically deflates. The systolic blood pressure, diastolic blood pressure and pulse are displayed.

13. Record systolic and diastolic blood pressures and pulse.

14. Take second blood pressure measurement after 2-3 minutes.

Record the sets of two readings for systolic blood pressure, diastolic blood pressure and pulse rate. OHTS considers valid ranges for blood pressure measurements as follows:
Systolic = >90 – 280 and Diastolic = >50 – 120. If the coordinator enters readings that are outside these ranges, the Vista entry system will ask the coordinator to confirm the values are correct. The Coordinator has the option of correcting the values or overriding the alert.

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

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

**Examples of problems:**

**Cuff size too small:** Cuff fits arm circumferences from 6 inches to 17 inches. If measurement cannot be taken due to cuff size, check "cuff too small" on the form as the reason for missing data.

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

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

**Blood Pressure above 220 mmHg:** Blood pressure measurement range is 0 to 280 mmHg. If systolic blood pressure is known to be greater than 280 mmHg, report “blood pressure greater than 280” mmHg as the cause for missing data. If systolic blood pressure is known to be more than 220 mmHg, press the START button continuously until the monitor inflates to 250-260 mmHg. The monitor will not inflate above 280 mmHg.

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

**EE in display:** Cuff is under-inflated. Remove arm cuff. Wait 2-3 minutes. Reapply cuff. Inflate cuff 40 mmHg higher than previous inflation by holding down the START button.

**E in display:** Movement during measurement or no pulse or no blood pressure reading due to very weak artery pulse. Remove arm cuff. Wait 2-3 minutes. Reapply cuff. Inflate cuff 40 mmHg higher than previous inflation by holding down the START button.

### 6.9 Pachymetry

A measurement of central corneal thickness will be performed for each participant during OHTS II using a DGH Technologies 500 ultrasonic pachymeter provided by the study.
The thickness of the central cornea affects the IOP measured by the Goldman applanation tonometer. When the central cornea is thick, the true IOP may be lower than the IOP that is measured. When the central cornea is thin, the true IOP may be higher than the IOP that is measured. In addition, thickness of the central corneal thickness may be related to other structural or functional factors associated with the susceptibility to glaucoma damage.

### 6.9.1 Overview of Pachymetry Measurements

- All examinations must be performed by OHTS II certified personnel.
- Certification of personnel will be carried out by telephone by Dr. James Brandt, University of California, Davis, and/or his designees; field personnel trained by DGH Technologies may be able to visit Clinical Centers to provide an in-service if necessary.
- 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 at the University of California, Davis so that a repair or replacement instrument can be arranged.
- 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 participant visit.
- The Coordinating Center will monitor data collection and provide clinic coordinators on a monthly basis with a printout of those OHTS participants 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 reports, the Coordinating Center will provide the investigators group with an update on the proportion of the OHTS II cohort who have had their corneal thickness measurements made.
6.9.2 Troubleshooting Pachymeter

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.            Ingrid Clark
(916) 734-6969 office/voice mail     (916) 734-6316 office/voice mail
(916) 762-6826 pager               (916) 762-3068 pager
jbrandt@ucdavis.edu             ijclark@ucdavis.edu
6.9.3 General Description of DGH-500 Pachymeter

Operation of DGH-500 Pachymeter (Pachette™)

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 Pachette™ on. Pressing “0” side of switch turns Pachette™ 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 II ancillary study

“” OR “¯” ROCKER SWITCH - Used to program options and numerical values presented on displays

### 6.9.4 Power-up Sequence of Pachymeter

1) Plug AC cord into three prong outlet.
2) Verify Probe is connected to front panel.
3) Turn on unit.
4) The Pachette™ 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.

### 6.9.5 Calibration of Pachymeter

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 Pachette™ 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±5 µM. 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.

### 6.9.6 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.](image)

5) With the participant in sitting position and visualizing a fixation spot on the wall, 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. 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.

### 6.10 Visual Fields

Visual fields are crucial for this study since they are used to determine 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 15, the visual Field Reading Center Manual of Procedures, for complete visual field protocol.*

### 6.11 Stereoscopic Optic Disc Photography

Optic disc photographs are crucial for this study since they are used to determine possible endpoints. All personnel must be familiar with the protocol for photography.
See Chapter 14, the Optic Disc Reading Center Manual of Procedures, for complete optic disc photography protocol.

6.12 Additional Measures (AM)

A one-time coordinator administered questionnaire is performed for each participant to assess smoking and exercise history, as well as update family history of glaucoma and racial classification.

6.13 NEI Vision Function Questionnaire (VQ)

A participant completed questionnaire will be performed for each participant during OHTS II.

6.14 Genetics Testing

The genetics ancillary study to the OHTS II is being conducted to bank bloods for genetic studies of ocular hypertension, glaucoma and/or related conditions. The ancillary study will obtain one vacutainer (10cc) of blood from each voluntary OHTS II participant. Bloods will be shipped to the University of Iowa for storage until genes have been identified for testing. Participants in OHTS II are not required to participate in the genetics testing.

See Chapter 16, Ancillary Studies, for complete genetics protocol.
## 7. Treatment Regimen

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>Introduction</td>
<td>7-2</td>
</tr>
<tr>
<td>7.2</td>
<td>Goals of Treatment</td>
<td>7-2</td>
</tr>
<tr>
<td>7.3</td>
<td>Medical Regimen</td>
<td>7-2</td>
</tr>
<tr>
<td>7.3.1</td>
<td>Treatment in OHTS II</td>
<td>7-3</td>
</tr>
<tr>
<td>7.4</td>
<td>Compliance</td>
<td>7-4</td>
</tr>
<tr>
<td>7.5</td>
<td>Deviation from Treatment Protocol</td>
<td>7-5</td>
</tr>
<tr>
<td>7.6</td>
<td>Confirmed POAG Group</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7</td>
<td>Drug Supplies</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7.1</td>
<td>Inventory and Distribution</td>
<td>7-6</td>
</tr>
<tr>
<td>7.7.2</td>
<td>Reporting</td>
<td>7-7</td>
</tr>
<tr>
<td>7.8</td>
<td>Adverse Events (AE)</td>
<td>7-8</td>
</tr>
</tbody>
</table>

### Appendix

<table>
<thead>
<tr>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Regimen</td>
<td>7-10</td>
</tr>
<tr>
<td>Adverse Event Form</td>
<td>7-11</td>
</tr>
</tbody>
</table>
7.1 Introduction

In OHTS II, all participants are offered medication. 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. As new medications become commercially available, the Executive/Steering Committee will consider them for use in OHTS II.

7.2 Goals of Treatment

The treatment goals for both eyes:

(1) Intraocular pressure ≤ 24 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 ≤ 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 therapy continue to be followed in the trial. 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.

7.3 Medical Regimen

Percentage reductions in IOP are computed from the "treatment baseline," which is the average of the 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 medical regimen that applies to all participants. Certain general rules are followed:

- All new treatments begin with a therapeutic trial in one eye. One-eyed trials should start with the eye with the higher intraocular pressure. 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.
• If a drug is moderately effective (IOP reduction 10%-20% from the treatment baseline) the investigator may choose to substitute or add another drug.

• If IOP is < 18 mm Hg, medications are not required and are prescribed at the clinician’s discretion.

See medical regimen flow chart in the Appendix.

### 7.3.1 Treatment in OHTS II

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

- **β-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 S 0.25%

- **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 P 0.15%

- **topical carbonic anhydrase inhibitor**
  - Trusopt 2%
  - Azopt 1%

- **prostaglandin analogue**
  - Xalatan 0.005%
  - Lumigan 0.03%
  - Rescula 0.15%
  - Travatan 0.004%
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 the first visit without an intervening IOP check.

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.

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 the Appendix.

7.4 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 including the following:

- **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. 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 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.

### 7.5 Deviation from Treatment Protocol

- **IOP ≥ 35 mm Hg in one or both eyes on two consecutive visits with maximum tolerated topical medical therapy.** Treatment may be altered 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 for one or both eyes. The Medical Monitor completes a Treatment Change form (TC).

- **Participant choice.** If a participant chooses to stop medication, the clinician should discuss the study, ocular hypertension, glaucoma, and the available treatment options. Record the participant refusal of medication on the examination form. The participant should be encouraged to start treatment again on subsequent visits.

- **Medication Intolerance.** If a participant is not tolerating any of the medications prescribed, the clinician should complete an Adverse Event form (AE). Record participant intolerance to medication on the examination form. The clinician should consider medication without preservatives such as preservative-free Timoptic or medications with different preservatives such as Pilagan.

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.
7.6 Confirmed POAG Group

Participants are moved to the Confirmed POAG Group of the trial if any of the following occur:

- **Confirmed optic disc deterioration 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 receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors, argon laser trabeculoplasty or filtering surgery.

- **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 receiving maximum tolerated topical medication, the clinician can suggest systemic carbonic anhydrase inhibitors, argon laser trabeculoplasty or filtering surgery.

As long as visual fields are testable and/or photographs obtainable, the Endpoint Committee will recommend continued routine follow-up testing but discontinue accelerated confirmation testing for visual fields and/or optic disc photos for the affected 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.

7.7 Drug Supplies

The OHTS Planning Committee determined that medication should be provided to participants without charge. Medication is distributed from the Central Pharmacy located in the Chairman’s Office. Free study medication may increase compliance with the treatment regimen. Study medications have been donated to the study by Alcon Laboratories, Allergan Pharmaceuticals, Bausch and Lomb, Ciba Vision, Merck Sharp & Dohme, Novartis, Otsuka America Pharmaceutical, and Pharmacia & Upjohn as listed in section 7.3.1 “Treatment in OHTS II.”

7.7.1 Inventory and Distribution

**From Central Pharmacy 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 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 7.6.2), 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 including empty or opened bottles are disposed at the Clinical Center.

Expired 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 or participant-returned study medications limits the possibility of study participants receiving contaminated medications.

**7.7.2 Reporting**

OHTS II Clinical Centers are accountable to the Central Pharmacy in 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 II. 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 II 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, participant 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.

### 7.8 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.*
Appendix
Ocular Hypertension Treatment Study (OHTS)

Treatment Regimen

Begin one-eyed trial

Return appointment in 4 to 6 weeks

Is IOP goal reached?

No

Medication at PI discretion

Yes

Continue or Begin Rx OU

Patient returns for next regularly scheduled follow-up visit

Is IOP ≥ 18 mmHg?

Yes

Begin one-eyed trial

Return appointment in 4 to 6 weeks

Is IOP goal reached?

No

Change or add Rx in one-eyed trial

Return appointment in 4 to 6 weeks

Is IOP goal reached?

No

Yes

Continue or Begin Rx OU

Patient returns for next regularly scheduled follow-up visit

Is IOP goal reached?

Yes

No

Patient returns for next regularly scheduled follow-up visit

Is patient compliant (or was Rx instilled and IOP checked at 1 hr)?

No

Yes

Instill Rx and check IOP in 1 hour

Is IOP goal reached?

No

No change or option to change

Yes

Is IOP goal reached?
OHTS Adverse Event: AE

1. Describe the adverse event:

______________________________________________________________________________________

______________________________________________________________________________________

______________________________________________________________________________________

2. Diagnosis, if known:

______________________________________________________________________________________

3. Date of onset (approximate):

   mm / dd / yy

4. Severity: Check only one.
   □ 1 Patient not aware of condition
   □ 2 Awareness of system cluster symptom—but easily tolerated
   □ 3 Discomfort causing interference of usual activity
   □ 4 Incapacitating with inability to work or do usual activity
   □ 5 Patient death (Complete “Confirmation of Death: DT” Form)

5. Check organ system(s) affected by sign/symptom (cluster):
   □ 1 Ocular
   □ 2 General constitutional symptoms
   □ 3 Skin, Hair & Nails
   □ 4 Musculo-Skeletal
   □ 5 Head & Neck
   □ 6 Endocrine
   □ 7 Respiratory
   □ 8 Cardiovascular
   □ 9 Blood & Immune system
   □10 Gastro-Intestinal
   □11 Genito-Urinary
   □12 Neurologic
   □13 Psychiatric
   □14 Other ____________________________

6. Description: Check all that apply.
   □ 1 Condition requiring medical attention
   □ 2 Condition requiring ocular surgery
   □ 3 Condition requiring surgery excluding ocular surgery
   □ 4 Substantial or permanent disability
   □ 5 Outpatient hospitalization (≤ 23 hour stay)
   □ 6 Inpatient hospitalization (>23 hour stay)
     (Send masked hospital discharge summary with ICD-9 code to Coordinating Center)
   □ 7 Prolongation of existing hospitalization
   □ 8 Life threatening (patient in immediate risk of dying from event as it occurred)
   □ 9 Cancer
   □10 Overdose
   □11 Other ____________________________
   □12 None of the above

Complete an AE form for each Adverse Event symptom cluster
OHTS Adverse Event: AE

1. Outcome of event (Leave blank if patient is deceased):
   - □ 1 No longer present/no residual effects
   - □ 2 No longer present/residual effects
   - □ 3 Ongoing
   - □ 4 Undetermined

2. If patient is not currently taking study medication, check here □ 1; otherwise, complete remainder of form.

3. List drug name and %:
   - [Drug #1]
   - [Drug #2]
   - [Drug #3]

4. Relation to study drug(s):
   - Not related □ 1
   - Possibly related □ 2
   - Probably related □ 3
   - Definitely related □ 4

5. Action being taken regarding study drug(s) due to reported AE:
   (Leave blank if patient is deceased)
   - No change □ 1
   - Reduced □ 2
   - Discontinued temporarily □ 3
   - Discontinued permanently □ 4

Investigator Signature (required) Date

Form Completed By (PI or CC): □□□

Coordinating Center use only
Received ................................................................. Entered.................................................................
Copy to: Director......................................................... Central Coordinator............................................ Rx Co........
□ OK Chairman’s initials/date: .................................................................
□ Not OK: disagree/more info-follow-up Chairman’s initials/date: .................................................................
8. Site Visits, Training, Certification, and Performance Monitoring

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>Introduction</td>
<td>8-2</td>
</tr>
<tr>
<td>8.2</td>
<td>Clinic Site Visit</td>
<td>8-2</td>
</tr>
<tr>
<td>8.3</td>
<td>Clinic Investigators</td>
<td>8-2</td>
</tr>
<tr>
<td>8.4</td>
<td>Clinic Coordinators</td>
<td>8-3</td>
</tr>
<tr>
<td>8.5</td>
<td>Photographers</td>
<td>8-3</td>
</tr>
<tr>
<td>8.6</td>
<td>Visual Field Technicians</td>
<td>8-3</td>
</tr>
<tr>
<td>8.7</td>
<td>Clinical Centers</td>
<td>8-4</td>
</tr>
<tr>
<td>8.8</td>
<td>Performance Monitoring</td>
<td>8-4</td>
</tr>
<tr>
<td>8.9</td>
<td>New Personnel</td>
<td>8-5</td>
</tr>
<tr>
<td>8.10</td>
<td>Cross-Training</td>
<td>8-5</td>
</tr>
</tbody>
</table>
8.1 Introduction

It is important that all study personnel are familiar with the OHTS II protocol and proper study procedures. The initial step in this process is the proper training and certification of all study personnel.

8.2 Clinic Site Visit

In the first two years of OHTS II, all participating Clinical Centers will be site-visited by members of the Coordinating Center and possibly by members of the Executive/Steering Committee and National Eye Institute Project Office. In subsequent years, Clinical Centers will be site-visited every two years, or more often as deemed necessary for specific clinics by the Study Chairman, Coordinating Center, Optic Disc Reading Center (ODRC), Visual Field Reading Center (VFRC), the National Eye Institute (NEI) and/or Data and Safety Monitoring Committee (DSMC).

Routine site visits are conducted to:

a. verify accuracy of consent forms.

b. clarify the protocol to clinic personnel.

c. conduct a random audit of primary source documents including study participant charts, visual fields and optic disc photographs.

d. confirm adherence to study protocol.

e. insure the Clinical Center has adequate resources for the proper conduct of the study including for example, desk space for the coordinator, computer with high speed internet access, phone, fax and copier, secure cabinets for storage of study charts and medication, photography equipment, HFAII Humphrey Visual Field Analyzer. The study should also have adequate time allocated for study personnel.

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

8.3 Clinic Investigators

Principal investigators certified for OHTS I will need to obtain additional certification for classification of lens opacities in OHTS II.

New clinic investigators are furnished with a copy of the Manual of Procedures (MOP) which is also available at www.vrcc.wustl.edu. Principal investigators must demonstrate knowledge of
the study protocol to be certified. Certification will be performed via telephone by a central coordinator at the Coordinating Center. The telephone certification will include, but not be limited to, knowledge of the OHTS II protocol for examination procedures, visual acuity measurement, IOP measurement, lens opacities classification system, the treatment regimen and study endpoints. The review may include participant-based examples so that the principal investigators can think through the protocol in participant-oriented terms.

Telephone certification will also be performed for new backup investigators.

### 8.4 Clinic Coordinators

Clinic Coordinators certified for OHTS I are certified for OHTS II. Coordinators and technicians responsible for testing will need to obtain certification for blood pressure measurements.

New clinic coordinators are furnished with the MOP and must be familiar with all aspects of the study. Central coordinators from the Coordinating Center will review the protocol with clinic coordinators by telephone. Clinic coordinators must demonstrate knowledge of the study protocol to be certified. Telephone certification will include, but not be limited to, knowledge of the OHTS II protocol for examination procedures, visual acuity measurement, IOP measurement, blood pressure measurements, the treatment regimen, study endpoints, and scheduling of visits. The review may include participant-based examples so that the clinic coordinators can think through the protocol in participant-oriented terms.

Telephone certification will also be performed for new backup clinic coordinators.

### 8.5 Photographers

Photographers certified for OHTS I are certified for OHTS II.

The certification of new photographers is supervised by the director of the Optic Disc Reading Center (ODRC). This process is detailed in Chapter 14, Optic Disc Photography. Briefly, all new photographers and new backups are supplied with the ODRC chapter of the MOP. They read this material and review the protocol with the ODRC coordinator. The educational material covers photographic technique, proper developing, and the handling, labeling and shipping of photographs.

The new 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.

### 8.6 Visual Field Technicians

Technicians certified for OHTS I are certified for OHTS II.
Certification of new technicians to perform visual field testing is supervised by the coordinator of the Visual Field Reading Center (VFRC). This process is detailed in Chapter 15, Visual Field Reading Center. Briefly, new visual field technicians and new backups are supplied with the VFRC chapter of the MOP. The technician reads this material and reviews the protocol with the VFRC coordinator. The technician submits visual fields from two non-study patients to the VFRC. If these visual fields meet quality standards, the coordinator of the VFRC certifies the technician.

### 8.7 Clinical Centers

The physical facilities of the Clinical Center 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 (HFA II). The make, model and serial number of the fundus camera is provided to the ODRC.

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.** Certification code is recorded on the case report form for study examinations and measures requiring certification.

### 8.8 Performance Monitoring

The Coordinating Center, VFRC, and ODRC continuously monitor the quality of data coming from each Clinical Center. If problems arise, the resource center contacts the clinic coordinator, the clinic principal investigator, Coordinating Center and if necessary, the Study Chairman and Executive/Steering Committee. 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. The site visit generates a plan of action with a specific timetable.

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

1. completion of scheduled follow-up visits (goal ≥90% of scheduled visits).
2. attaining IOP goal in both eyes (goal ≥85% of the participants).
3. obtain useable and reliable visual fields in both eyes per protocol (goal ≥99% of scheduled tests).
4. obtain useable optic disc photographs in both eyes (goal ≥95% of scheduled tests).
In addition to the above, secondary indices of performance are monitored by each resource center as follows:

**Coordinating Center:** Forms received within 14 days of visit (goal ≥ 75%)  
Queries resolved within 10 days of date of query (goal ≥ 75%)  
Forms are query free (goal ≥ 80%)

**Optic Disc Reading Center:** Photos received within 21 days of photography date (goal ≥ 90%)  
Retakes requested (goal ≤ 15%)  
Gradeable photos taken at patient visit (goal 100%)  
Gradeable photos taken and received at ODRC (goal 100%)  
Retakes received within 6 weeks (goal ≤ 2 late retakes)

**Visual Field Reading Center:** Test Parameters (goal ≥ 98% with ≤ 5 error points)  
Patient Data (goal ≥ 80% with ≤ 5 error points)  
Fields Received within 21 days (goal ≥ 90%)  
Reliability (goal ≥ 95%)

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

### 8.9 New Personnel

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

### 8.10 Cross-Training

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

9.1 Introduction ....................................................................................................... 9-2
9.1.1 Clinical Centers................................................................................................. 9-2
9.1.2 Coordinating Center .......................................................................................... 9-2
9.1.3 Visual Field Reading Center (VFRC) ............................................................... 9-3
9.1.4 Optic Disc Reading Center (ODRC)................................................................. 9-3
9.1.5 Study Chairman’s Office ................................................................................... 9-4
9.1.6 NEI Program Office .......................................................................................... 9-4
9.1.7 Confocal Scanning Laser Ophthalmoscopy Reading Center (CSLO).............. 9-4
9.1.8 Short Wave-Length Perimetry Reading Center (SWAP).................................. 9-5
9.1.9 Genetics Center ................................................................................................. 9-5
9.2 Committees and Groups .................................................................................... 9-5
9.3 Executive/Steering Committee ........................................................................... 9-6
9.3.1 Executive/Steering Committee Membership .................................................... 9-6
9.3.2 Executive/Steering Committee Functions......................................................... 9-7
9.3.3 Executive/Steering Committee Meetings.......................................................... 9-7
9.4 Data and Safety Monitoring Committee (DSMC) ............................................ 9-7
9.4.1 DSMC Membership .......................................................................................... 9-8
9.4.2 DSMC Functions............................................................................................... 9-8
9.4.3 DSMC Meetings................................................................................................ 9-9
9.5 Full Investigative Group ................................................................................... 9-9
9.5.1 Full Investigative Group Membership .............................................................. 9-9
9.5.2 Full Investigative Group Functions ................................................................... 9-9
9.5.3 Full Investigative Group Meetings.................................................................... 9-10
9.6 Coordinators Group ............................................................................................ 9-10
9.6.1 Coordinators Group Functions ........................................................................ 9-10
9.6.2 Coordinators Group Membership.................................................................... 9-10
9.6.3 Coordinators Group Meetings ......................................................................... 9-10
9.7 Endpoint Committee ....................................................................................... 9-10
9.7.1 Endpoint Committee Membership .................................................................. 9-10
9.7.2 Endpoint Committee Function ....................................................................... 9-11
9.7.3 Endpoint Committee Meetings........................................................................ 9-11
9.8 Genetics Advisory Committee ........................................................................ 9-11
9.8.1 Genetics Advisory Committee Membership ................................................... 9-11
9.8.2 Genetics Advisory Committee Function ......................................................... 9-12
9.1 Introduction

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

- Clinical Centers
- 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)
- Genetics Center
- Study Chairman's Office
- National Eye Institute (NEI) Project Office

9.1.1 Clinical Centers

Each Clinical Center is responsible for following participants according to the protocol until the termination of the trial. Each Clinical Center has at least one OHTS II 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 NEI (see chapter 11, Clinical Center Procedures, for details on the operations of the Clinical Centers).

9.1.2 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.
- organizing meetings of the DSMC.
- assisting in the organization of the Executive/Steering Committee, Full Investigative Group, and Clinic Coordinators’ Group.
- certifying via telephone principal and backup investigators, clinic coordinators and backup coordinators on the OHTS protocol.
- certifying clinic personnel for visual acuity, IOP and blood pressure measurement.
The Coordinating Center personnel include a director, co-director, central coordinators, systems analysts, programmers, and a project manager (see chapter 13, Coordinating Center, for details on the operations of the Coordinating Center).

9.1.3 Visual Field Reading Center (VFRC)

The VFRC is a joint effort of the Department of Ophthalmology at the 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 (Chapter 15).
- determining when visual fields meet the criteria for abnormality.
- maintaining records of visual field data.
- transmitting visual field data and grading results to the Coordinating Center.
- training and certifying study technicians.
- monitoring and insuring the quality of the data.
- contributing to the understanding and interpretation of visual fields.

The VFRC personnel include a director, associate director, reading center coordinator, analysts, a technician and a programmer analyst.

9.1.4 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 the criteria described in the ODRC MOP (Chapter 14).
- determining when disc photographs meet criteria for deterioration.
- determining whether disc photographs meet criteria for confirmation of deterioration.
- maintaining records of optic disc data.
- transmitting optic disc data and grading results to the Coordinating Center.
- training and certifying study photographers.
- monitoring and insuring the quality of the photographs.
- contributing to the understanding and interpretation of optic disc stereo photography.

The ODRC personnel include a director, associate director, assistant director, reading center coordinator, statisticians, readers, and a research assistant.
9.1.5 **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 and dissemination of information to health professionals and the public.
- participant relations, education and retention.
- maintaining a Central Pharmacy which is responsible for distribution of study medication to clinics.
- quality control and troubleshooting.
- organizing meetings of the Executive/Steering Committee, Full Investigative Group and Clinic Coordinator’s Group.

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

9.1.6 **NEI Program Office**

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

9.1.7 **Confocal Scanning Laser Ophthalmoscopy Reading Center (CSLO)**

The CSLO Reading Center is located in the Department of Ophthalmology, University of California, San Diego. The CSLO Reading Center is responsible for:

- Receiving all CSLO data.
- Grading the CSLO images according to criteria described in the CSLO MOP (Chapter 16).
- Maintaining records of CSLO data.
- Transmitting CSLO data and grading results to the Coordinating Center.
- Training and certifying study technicians.
- Monitoring and insuring the quality of the data.
- Contributing to the understanding and interpretation of CSLO images.

The CSLO Reading Center personnel include a director, co-director, coordinator and readers.
9.1.8 Short Wave-Length Perimetry Reading Center (SWAP)

The SWAP Reading Center is located in the Devers Eye Institute, Legacy Portland Hospitals. The SWAP Reading Center is responsible for:

- Receiving all SWAP data.
- Grading the SWAP visual fields according to criteria described in the SWAP MOP (Chapter 16).
- Maintaining records of SWAP data.
- Transmitting SWAP data and grading results to the Coordinating Center.
- Training and certifying study technicians.
- Monitoring and insuring the quality of the data.
- Contributing to the understanding and interpretation of SWAP visual fields.

The SWAP Reading Center personnel include a director, coordinator and readers.

9.1.9 Genetics Center

The Genetics Center is located in the Department of Ophthalmology, University of Iowa. The Genetics Center is responsible for:

- Receiving blood on OHTS participants.
- Notifying the Clinical Center and Coordinating Center that an adequate blood sample was received.
- Preparing blood for storage.
- Storing blood for future analysis.
- Releasing blood samples to investigators as approved by the Genetics Advisory Committee.

9.2 Committees and Groups

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

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

These committees are expected to function throughout the lifetime of OHTS.
9.3 Executive/Steering Committee

The Executive/Steering Committee has overall responsibility for directing OHTS II 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.

9.3.1 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 Coordinating Center
- Chris Johnson, Ph.D., Co-Director of the VFRC
- 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)
- Ann K. Wilder, B.S.N., C.C.R.C., Central Coordinator (non-voting)
- Two members elected from Full Investigative Group, who serve staggered two-year terms
- One member elected from the Coordinators Group, who serves a two year term
- M. Roy Wilson, M.D., Study Advisor

*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. 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 potential conflict of interest.
9.3.2 Executive/Steering Committee Functions

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

- To direct all activities of OHTS II.
- To formulate all policy decisions related to the design and conduct of OHTS II, 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 recommend to the NEI, Full Investigative Group, and the DSMC 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, SWAP and Genetics) on operational matters.
- To resolve problems brought to attention by the directors of the VFRC, ODRC, Coordinating Center, CSLO, SWAP and Genetics Center, 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 by the study investigators.
- To establish writing committees for principal papers, to review all written and oral reports for publication and presentation, including those from the ancillary studies.
- To appoint subcommittees as required for special study functions.
- To dissolve subcommittees and technical committees when their functions have been fulfilled.

9.3.3 Executive/Steering Committee Meetings

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

9.4 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 II 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 reports to Paul Sieving, M.D., Ph.D., Director of the NEI.
9.4.1 DSMC Membership

The voting members of the DSMC include:

- 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 for renewable five-year terms of office, with the advice and consent of the OHTS II Executive/Steering Committee. 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 potential conflict of interest.

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

- Michael A. Kass, M.D., Study Chairperson
- Mae O. Gordon, Ph.D., Director of the Coordinating Center
- Donald Everett, M.A., NEI Representative

The chairman of the DSMC may invite other individuals to attend meetings as needed to advise on the study design, procedures, and proper interpretation of the data.

9.4.2 DSMC Functions

The specific functions of the DSMC are as follows:

- To review the design and methods, as well as data collection procedures.
- To review site visit reports and protocol violations by clinic.
- To evaluate the accumulating data at regular intervals for evidence of adverse or beneficial effects.
- To monitor participant retention, and data quality.
- 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 II should be released to the study investigators, study participants, the medical community, and the public.
- To recommend changes in study protocol to the Executive/Steering Committee 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 questions and specific aims of the study.
• To approve all ancillary studies.
• To monitor performance of Clinical Centers and to advise the NEI on the continuation of their funding.

9.4.3 DSMC Meetings

The DSMC meets twice yearly. One meeting is a face-to-face meeting, and the other meeting, can be a conference call or a face-to-face meeting, as necessary. Additional meetings are scheduled as necessary.

9.5 Full Investigative Group

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

9.5.1 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
• Patricia Morris, Central Coordinator
• Principal Investigator of each Clinic
• Coordinator of each Clinic, VFRC, and ODRC.

Other staff members of OHTS II centers are encouraged to attend Full Investigative Group meetings as non-voting members.

9.5.2 Full Investigative Group Functions

The OHTS II Full Investigative Group is responsible for:

• Implementing the OHTS II protocol at the Clinical Center.
• Notifying the Executive/Steering Committee when changes in procedures are required.
• Implementing changes in the protocol approved by the Executive/Steering Committee, Full Investigative Group and Data and Safety Monitoring Committee.
• Suggesting new studies or analyses.

9.5.3 Full Investigative Group Meetings

The Full Investigative Group meets once a year in conjunction with the Coordinators Group. Two investigators, elected from the Full Investigative Group, serve staggered two year terms on the Executive/Steering Committee.

9.6 Coordinators Group

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

9.6.1 Coordinators Group Functions

The primary responsibility of the Coordinators Group is to provide information to the Full Investigative Group on logistical aspects of the study, particularly at the working level of individual Clinical Centers. Recommendations from the Coordinators Group can be made to any standing or ad hoc committee of the study.

9.6.2 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 of the Coordinating Center

9.6.3 Coordinators Group Meetings

The Coordinators Group meets once a year in conjunction with the Full Investigative Group. One clinic 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.)

9.7 Endpoint Committee

When a participant develops a reproducible visual field abnormality or a reproducible optic disc deterioration, it is important to determine if the change is actually present, if it clinically significant (optic disc deterioration only) and if it was caused by POAG. The Endpoint Committee, masked as to original randomization status, reviews the clinical data from both eyes
of all participants who develop a reproducible visual field abnormality or a reproducible optic
disc deterioration to make this determination.

9.7.1 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).

9.7.2 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 study treatment. If a POAG endpoint is confirmed, the
Endpoint Committee notifies the Coordinating Center, which notifies the Clinical Center.

9.7.3 Endpoint Committee Meetings

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

9.8 Genetics Advisory Committee

The Genetics Advisory Committee reviews proposals to utilize banked blood from OHTS II
participants.

9.8.1 Genetics Advisory Committee Membership

The following individuals are voting members of the Genetics Advisory Committee:

- Lee Alward, M.D.
- Mae O. Gordon, Ph.D.
- George A. (Jack) Cioffi, M.D.
- Michael A. Kass, M.D.
- Edwin Stone, M.D., Ph.D.
- Donald Zack, M.D., Ph.D.
9.8.2 Genetics Advisory Committee Function

The Genetics Advisory Committee reviews requests to utilize banked blood samples from OHTS II participants. The Committee considers the scientific merit of the proposal, the track record of the investigator in previous studies and the suitability of the OHTS population for the question posed. If the request is approved, the Genetics Center will release masked blood samples to the requesting investigator.
10. Policy Matters

10.1 IRB Approval ..................................................................................................10-2
10.2 Participant Consent .........................................................................................10-2
10.3 Publicity ..........................................................................................................10-2
10.3.1 Publications and Presentations Policy.............................................................10-2
10.4 Editorial Policy................................................................................................10-3
10.4.1 Publication of Trial Design, Methods, and Findings ......................................10-3
10.4.2 Presentations .................................................................................................10-4
10.4.3 Publications from Ancillary Studies .............................................................10-4
10.4.4 Publications Concerning Methods ................................................................10-5
10.5 Ancillary Studies.............................................................................................10-5
10.5.1 Definition of an Ancillary Study.................................................................10-5
10.5.2 Rationale for the Approval Process.............................................................10-5
10.5.3 Preparation of a Request for Approval of an Ancillary Study .....................10-6
10.5.4 Procedures for Obtaining Ancillary Study Approval...................................10-6
10.5.5 Funding of Ancillary Studies ......................................................................10-6
10.5.6 Publication of Ancillary Study Results .......................................................10-7
10.5.7 Progress Reports...........................................................................................10-7
10.6 Access to Study Information .........................................................................10-7
10.6.1 Study Documents ........................................................................................10-7
10.6.2 Study Data ....................................................................................................10-7
10.7 Participation of Women and Minority Groups ................................................10-8
10.8 Protection of Human Subjects Certification ..................................................10-8

Appendix ..................................................................................................................10-9
Publications and Presentation Policy .................................................................10-11
Manuscript Checklist for Authors ......................................................................10-12
Abstract Checklist for Authors ...........................................................................10-13
Manuscript Review Form .......................................................................................10-14
10.1 IRB Approval

The principal investigator of each Clinical Center is responsible for obtaining local IRB approval for OHTS II and its informed consent form. A copy of each Clinical Center's approved informed consent form and documentation of IRB approval must be submitted to the Coordinating Center before participants are enrolled in OHTS II. Current Clinical Center IRB approval is kept on file at the Coordinating Center. The Chairman’s Office and resource centers must also have approval from their local IRBs.

10.2 Participant Consent

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

10.3 Publicity

All publicity and press releases for OHTS I & II must have prior approval of the Executive/Steering Committee, Data and Safety Monitoring Committee (DSMC), and the Information Office of the National Eye Institute (NEI).

When individual investigators speak to local or national press, they should speak as an individual and not as an official representative of OHTS II. 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, DSMC and the Information Office of the NEI. 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.

10.3.1 Publications and Presentations Policy

All publications and presentations of unpublished data relating to the OHTS I & II and its Ancillary Studies must have prior approval by the Executive/Steering Committee. Data related to primary specific aims and outcomes must be approved by the DSMC. 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.
10.4 Editorial Policy

10.4.1 Publication of Trial Design, Methods, and Findings

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

The lead author should submit an abstract to the Study Chair including a short description of the proposed paper, possible co-authors, data to be reported and timeline for drafts and submission (Appendix). The Executive/Steering Committee is responsible for reviewing the scientific merit of the proposed paper and deciding if it should be an OHTS study publication. This review process is intended to ensure the quality of study publications and may require refinement of the proposal. The Executive/Steering Committee is responsible 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. A list of approved study publications will be distributed to all OHTS II investigators on a regular basis. Interested OHTS II investigators are invited to contact the lead author to participate in the writing group.

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

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

The lead author is responsible for coordinating all activities related to the writing and submission of papers and abstracts. This includes arranging conference calls, discussing analytic plans with the Coordinating Center, assigning writing responsibilities to co-authors, maintaining timeliness, determining the order of authorship and circulating drafts to co-authors. The Coordinating Center is responsible for circulating final drafts to the Executive/Steering Committee and as needed, to the DSMC. Upon circulation of the draft, there will be up to a two-week period during which committee members can make comments about the paper.
If the focus of the paper changes as it moves from the abstract to the manuscript stage, the lead author will notify the Study Chairman in writing. The Study Chairman will be responsible for insuring that the revised proposal receives appropriate review.

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

Each publication must acknowledge the following supporting entities of OHTS:

“This study was supported by grants from the National Eye Institute, and the Office of Research on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD, Research to Prevent Blindness NY, NY, Merck Research Laboratories, White House Station, NJ.”

Copies of major papers from OHTS II are sent (before publication) to all principal investigators, to all members of the Executive/Steering Committee, and to the DSMC. Reprints of major 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 DSMC prior to submission to any professional journal or meeting program committee.

10.4.2 Presentations

Oral presentations and abstracts to be printed must be approved 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 DSMC. Study results include all data collected for OHTS II, whether descriptive or comparative in nature. The above restrictions do not apply to local presentations on the design of OHTS II, provided these presentations contain no unpublished study results.

10.4.3 Publications from Ancillary Studies

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

**10.4.4 Publications Concerning Methods**

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 II 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 II centers and investigators and the NEI must be recognized. Review and approval by the Executive/Steering Committee are required before manuscripts concerning methods are submitted for publication. The Coordinating Center is responsible for distributing copies of methodological publications to the Executive/Steering Committee and other OHTS II investigators. Ten reprints of such publications should be sent to the Coordinating Center for the OHTS library.

**10.5 Ancillary Studies**

Ancillary studies will greatly enhance the value of OHTS II 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 DSMC prior to inception, whether or not they involve the need for supplementary funds. OHTS II participants cannot be enrolled in other ocular studies without authorization from the DSMC and the Executive/Steering Committee. Furthermore, OHTS data may not be used for any other study that has not been approved by the DSMC.

**10.5.1 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 II 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.

**10.5.2 Rationale for the Approval Process**

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

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

10.5.3 Preparation of a Request for Approval of an 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 II participants, such as laboratory tests, 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 II study data are required, the investigator must specify what data are needed, for whom it is needed, and the timetable for access to such data. Access to study data require approval by the DSMC.

10.5.4 Procedures for Obtaining Ancillary Study Approval

The investigator proposing an ancillary study should send a written request to the Study Chairman of OHTS II. 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 DSMC, which is responsible for final approval of ancillary studies.

10.5.5 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 the DSMC. 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 DSMC.

### 10.5.6 Publication of Ancillary Study Results

All manuscripts or presentations based on ancillary study data must be reviewed and approved by the OHTS II Executive/Steering Committee before publication or presentation. Such review pertains to impact on OHTS II 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.

### 10.5.7 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 Committee and the DSMC at each meeting.

### 10.6 Access to Study Information

#### 10.6.1 Study Documents

The Manual of Procedures and copies of the data collection forms used in OHTS II 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. 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 II 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 II Research Group:

- minutes of study meetings.
- performance monitoring reports for OHTS II Clinical Centers and Resource Centers.
- DSMC reports.

#### 10.6.2 Study Data

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

10.7 Participation of Women and Minority Groups

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

10.8 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. This includes all investigators and coordinators at clinics, satellites, resource centers, and ancillary studies. Verification that study personnel have completed the certification process is done by the IRB at the local level.
Appendix
OHTS Publication and Presentation Form: PP

- Complete and fax to the Coordinating Center at 314-362-0231.
- Request will be reviewed by the OHTD Executive/Steering Committee.
- The Chairman’s Office will notify you of the Executive/Steering Committee decision.

1. Today’s Date:   /   /   

Check type of presentation or publication:

2.  □ Presentation
   2.1 Provide Title: __________________________________________________________
       __________________________________________________________
   2.2 Name of organization: _________________________________________________
   2.3 Date of presentation: _________________________________________________
   2.4 City __________________    State ___________

3. Publication Type
   □ Article
   □ Book Chapter
   □ Abstract
   □ Technical Report

   3.1 Keywords: (Enter up to 15 keywords for this document)____________________
                 __________________________________________________________

   3.2 Principal Author:____________________________________________________

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

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

3.5 □ Single Clinic    □ Multi-Clinic

3.6 PROPOSED TIMETABLE

   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 and Steering Committee
      
   4. Proposed submission/presentation date
      
   □   /   
   □   /   
   □   /   
   □   /   

Version 4.0  3/10/03
Publications and Presentation Policy

As recorded in Chapter 10.3.1 of the OHTS II 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/Steering Committee. Any material relating to OHTS II 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 and Health Disparities, National Institutes of Health, Bethesda, MD, a grant from Merck Research Laboratories, White House Station, NJ, and unrestricted grants from Research to Prevent Blindness, NY, NY.”

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**

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<td>1.</td>
<td>Contact Dr. Michael Kass, Study Chair, with idea for manuscript</td>
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<td>2.</td>
<td>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, 4 and proceed to step 5.)</td>
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<td>3.</td>
<td>DSMC approves/disapproves release of data</td>
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<td>4.</td>
<td>If DSMC disapproves of release of data, author is notified by Study Chair</td>
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<td>5.</td>
<td>Executive/Steering Committee approves/disapproves</td>
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<td>6.</td>
<td>Chair appoints writing committee</td>
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<td>7.</td>
<td>Coordinating Center holds conference call to discuss statistical needs</td>
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<td>First author circulates draft of manuscript to writing committee members</td>
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<td>Writing committee makes revisions</td>
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<td>Author sends draft sent to Coordinating Center</td>
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<td>Coordinating Center makes revisions and returns to author</td>
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<td>Author returns draft with revisions made to Coordinating Center</td>
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<td>Coordinating Center routes to Executive/Steering Committee for Scientific Review</td>
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<td>Author and Coordinating Center revises manuscript per Executive/Steering Committee, or appeals revisions to Study Chair</td>
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<td>Study Chair signs off on submission of manuscript</td>
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<td>Manuscript submitted to journal/organization</td>
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## Ocular Hypertension Treatment Study
### Abstract Checklist for Authors
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<th>Action</th>
<th>Date Completed</th>
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<tr>
<td>1.</td>
<td>Contact Dr. Michael Kass, Study Chair, with idea for abstract</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>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.)</td>
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<tr>
<td>3.</td>
<td>DSMC approves/disapproves release of data</td>
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<td>4.</td>
<td>If DSMC disapproves of release of data, author is notified by Study Chair</td>
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<tr>
<td>5.</td>
<td>Executive/Steering Committee approves/disapproves</td>
<td></td>
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<tr>
<td>6.</td>
<td>Chair appoints writing committee</td>
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<tr>
<td>7.</td>
<td>Coordinating Center holds conference call to discuss statistical needs</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>First Lead author circulates draft of abstract to writing committee members</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Writing committee makes revisions</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Author sends draft sent to Coordinating Center</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Coordinating Center makes revisions and returns to author</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Author returns draft with revisions made to Coordinating Center</td>
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</tr>
<tr>
<td>13.</td>
<td>Coordinating Center routes to Executive/Steering Committee for Scientific Review</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Author and Coordinating Center revises manuscript per Executive/Steering Committee, or appeals revisions to Study Chair</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Abstract submitted to organization</td>
<td></td>
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MANUSCRIPT REVIEW FORM

Date Sent for Review: ________________________________

Deadline for Return of Review to Coordinating Center: ________________________________

Proposed Manuscript Title: ________________________________

Proposed Journal: ________________________________

Authors: ________________________________

RECOMMENDATION

☐ Accept as is
☐ Accept after minor revisions
☐ Accept after major revisions
☐ Reject

TECHNICAL ASPECTS

YES NO UNCERTAIN

Writing clear and grammatical? ☐ ☐ ☐
Methodology adequate? ☐ ☐ ☐
Number of cases and follow-up adequate? ☐ ☐ ☐
Conclusions follow from data? ☐ ☐ ☐
Literature references adequate? ☐ ☐ ☐

3. Is the title adequately descriptive? ☐ Yes ☐ No
If no, recommend title change to: ____________________________________________________
_______________________________________________________________________________

4. Is the abstract adequately descriptive and detailed? ☐ Yes ☐ No
Reviewed by: ___________________________________/___________________________________

Signature Today's Date

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

11.1 Clinical Center Responsibilities.......................................................... 11-2
11.2 Clinical Center Personnel ................................................................. 11-3
11.2.1 Responsibilities of the Principal Investigator ..................................... 11-3
11.2.2 Responsibilities of the Clinic Coordinator ....................................... 11-3
11.2.3 Responsibilities of the Technician .................................................... 11-4
11.2.4 Responsibilities of the Photographer ............................................... 11-5
11.3 Study Documents............................................................................... 11-5
11.4 Scheduling and Coordination of Participant Visits............................. 11-6
11.4.1 Schedule of Visits .......................................................................... 11-6
11.4.2 Clinic Tracking Report .................................................................... 11-6
11.5 Checking Completed Examination Forms ........................................ 11-7
11.5.1 Completeness .................................................................................. 11-7
11.5.2 Legibility ......................................................................................... 11-7
11.5.3 Edits and Corrections ....................................................................... 11-7
11.6 Assuring Completeness of Follow-up................................................. 11-8
11.7 Preparing for Return Visits ................................................................. 11-8
11.8 Recording Medication Taken by Participant ....................................... 11-9
11.8.1 Drug List ......................................................................................... 11-10
11.9 Reports and Services on Web ............................................................. 11-21

Appendix
Application for Web Access ........................................................................ 11-25
11.1 Clinical Center Responsibilities

The responsibilities of OHTS II Clinical Centers include the following:

- To provide each participant with OHTS II educational materials.
- To enroll participants in OHTS II through written informed consent.
- To manage each participant in accord with the instructions in the MOP.
- To examine each participant enrolled in OHTS II using the study protocol and the schedule.
- To complete the proper forms and obtain visual fields and optic disc photographs required at each visit.
- To transmit 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 II in an easily accessible but confidential manner.
- To maintain complete and current residency and employment information on each OHTS II participant.
- To maintain current informed consent documents that meet OHTS II standards and the standards of the local Institutional Review Board.
- To maintain all equipment, supplies and drugs required for OHTS II.
- To promote participant satisfaction, commitment, and retention to OHTS II through reminder systems, good rapport, newsletters, recognition awards and regular reports on their examinations.
- To help train new study personnel as needed.
- To provide representation at all meetings of the Full Investigative Group and Clinic Coordinators Group.
11.2 **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 and new personnel are certified as needed.

11.2.1 **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 provide participant education, enroll participants in OHTS II after informed consent and provide follow-up care for participants in OHTS II.
- To supervise all Clinical Center personnel who perform tests and measures.
- To examine the participants according to OHTS II procedures.
- To determine the therapy for each participant.
- To attend Full Investigative Group meetings.
- To aid participant retention through good rapport, reminder systems and recognition awards.
- To submit and maintain current IRB approval and consent from the clinic’s local IRB office.
- To perform clinical measures including IOP measurement, refraction, slit lamp examination, gonioscopy and ophthalmoscopy.

11.2.2 **Responsibilities of the Clinic Coordinator**

The responsibilities of the clinic coordinator include the following:

- To coordinate the Clinical Center activities related to OHTS II.
- To have a thorough understanding of OHTS II 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 study protocol.

• To schedule participant visits and arrange participant transportation.

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

• To maintain study documentation including a current MOP, appointment notebooks, participant log book, copies of current study forms, log books of visual fields and 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 Coordinating Center and the Reading Centers.

• To photocopy all forms for Clinical Center records and to send original forms to the Coordinating Center on a timely basis.

• To assure that copies of all forms are retained in the OHTS II files at the Clinical Center.

• To respond to queries from the Coordinating Center and the Reading Centers.

• To notify the Coordinating Center about personnel changes.

• To inform the principal investigator and the Coordinating Center of any problems evaluating, treating, or following OHTS II participants.

• To attend meetings of the Full Investigative Group and Clinic Coordinators Group.

• To ensure that the Clinical Center 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, refractions, and blood pressure measurements as specified by the protocol.

11.2.3 Responsibilities of the Technician

The OHTS technician's responsibilities include the following:

• To learn correct OHTS II 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.

• In some centers, the technician may also take blood pressure measurements.

11.2.4 Responsibilities of the Photographer

The OHTS II photographer's responsibilities include the following:

• To learn correct OHTS II photography protocol, 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.

11.3 Study Documents

Each Clinical Center must have available the following:

• A current copy of the OHTS II Manual of Procedures.

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

• Copies of the OHTS II study forms for data collection, clinic management and study management.

• Batch edits received at the Clinical Center requiring data corrections should be filed in the appropriated OHTS II participant file. Log books for participant visual field test and optic disc photographs.

• An address directory of OHTS II 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 e-mail from the
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.

11.4 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.

11.4.1 Schedule of Visits

The schedule of visits is given in Chapter 5. The clinic coordinator must be familiar with this schedule to ensure timely visits. It is best if all regularly scheduled visits (semi-annual and annual) occur within one month of the target date (± 1 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 of the target date (± 2 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 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 approximately one week in advance 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.

11.4.2 Clinic Tracking Report

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

- Participants who are due to have follow-up visits.
- Participants with late or missed visits.
- Participants for whom a Transition Visit Status form (TV) is needed.
- Participants with pending retake or confirmation photos and photos pending ≥21 days.
Participants with pending retest or confirmation visual fields and visual fields not received as reported on case report forms received at the Coordinating Center.

Participants for whom a Vision Function Questionnaire form (VQ) is needed.

Participants for whom an Additional Measures form (AM) is needed.

Participants who need pachymetry testing.

Participants who need sign an informed consent and/or have blood drawn for the Genetics Ancillary Study.

Forms with outstanding edit queries for ≥ 21 days.

11.5 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.

11.5.1 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 or email.

11.5.2 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.

11.5.3 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 II 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 may 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 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.**

### 11.6 Assuring Completeness of Follow-up

One of the most important duties of the Clinical Center is maintaining good rapport with all OHTS II participants to ensure that each participant remains in the study. The clinic coordinator should be thoroughly familiar with the materials in Chapter 5 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.

### 11.7 Preparing for Return Visits

The following tasks 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 II file.

- Place the participant's OHTS II 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 as needed.
- 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 II Patient Tracking Information form (TR), in the folder as a reminder to review and update the information.

### 11.8 Recording Medication Taken by Participant

Use of all medications, systemic and ocular, is recorded at each regularly scheduled follow up visit (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 (11.8.1) to determine if the medication is an antidepressant, beta-adrenergic blocking agent, calcium channel blocking agent, corticosteroid (either ophthalmic, systemic, nasal or bronchial inhaled steroid), estrogen or progesterone for hormone replacement therapy. If the medication is in one of these eight categories, the clinic coordinator checks (✔️) the category that applies on the visit form.

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

<table>
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<tr>
<th>Drug Name</th>
<th>Class</th>
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<tr>
<td>Acebutolol</td>
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**ANTIDEPRESSANTS**
- BETA-ADRENERGIC BLOCKING AGENT - Beta-Blocker
- CALCIUM CHANNEL BLOCKING AGENTS - Ca+Ch.Blocker
- ESTROGEN/PROGESTINS – Estrogen/Prog
- AND COMBINATION MEDICATIONS i.e.
- ANTIDEPRESSANT COMBINATION – AntidepCombo
- BETA-ADRENERGIC BLOCKING AGENT COMBINATION-B Block Combo
- ESTROGEN/PROGESTIN COMBINATION-EstroProCombo

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<tr>
<th>Drug Name</th>
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CORTICOSTEROIDS

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

COMBINATION MEDICATIONS, i.e.

OPHTHALMIC STEROID COMBINATION - OphSterCombo
INHALED STEROID COMBINATION - InhSterCombo
TOPICAL STEROID COMBINATION - TopSterCombo

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**STATINS**

| Lipitor                 | Atorvastatin  |
| Lescol                  | Fluvastatin   |
| Mevacor                 | Lovastatin    |
| Pravachol               | Pravastatin   |
| Crestor                 | Rosuvastatin  |
| Zorcor                  | Simivastatin  |
11.9 Reports and Services on Web

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 II 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 II personnel at their own clinic. Upon leaving the study, their user ID 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:
# OHTS REPORTS: Clinic A

<table>
<thead>
<tr>
<th>Lists of Forms Received at VRCC</th>
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<td>Follow-up Visit Schedules</td>
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<td>Overall Study: AEs Received By Year</td>
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<td>Changes to Processed Forms</td>
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<td>TV Forms Needed</td>
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<td>Transition Forms With Problems</td>
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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 Requesting Access (Please Print)  Clinic or Reading Center  Applicant’s OHTS Certification Code

Position in OHTS  Email Address

Applicant Signature  Date  Clinic PI Signature  Date

For Coordinating Center Use Only

Userid  Temporary Password  Date Assigned  Date Removed

Comments: __________________________________________

OHTS Web address: http://www.vrcc.wustl.edu/data/ohts/
12. Chairman's Office

12.1 Introduction ..................................................................................................... 12-2
12.1.1 Study Chairman .............................................................................................. 12-2
12.1.2 Vice-Chairs ..................................................................................................... 12-2
12.1.3 Project Managers ............................................................................................ 12-3
12.1.4 Medical Monitor ............................................................................................. 12-3
12.1 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 include:

- **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** — Washington OHTS Center
- **Deborah Dunn, Project Manager and Central Pharmacy Administrator** — Washington University School of Medicine
- **Ellen Long, Project Manager** — Washington University School of Medicine

### 12.1.1 Study Chairman

The study chairman is responsible for the overall scientific conduct of OHTS II 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 (DSMC), 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 Project 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 the Reading Centers, the Coordinating Center and Clinical Centers as needed.

### 12.1.2 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, Coordinating Center 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.
12.1.3 Project Managers

Responsibilities of the Project Manager include the following:

- to prepare the annual budget for continuation for the Study Chairman’s Office, Reading Centers and Vice-Chair’s.
- monitor expenditures made by the Chairman, Vice-Chairs, Visual Field Reading Center and Optic Disc Reading Center.
- to organize and to prepare minutes for meetings of the Executive/Steering Committee and Full Investigative Group and Clinic Coordinators meeting.
- to schedule and to prepare minutes (as necessary) for conference calls of the Executive/Steering Committee, standing study committees, ad hoc study committees, and also calls to Clinical Centers once or twice a year.
- to prepare and distribute informational materials for the purpose of public relations.
- to develop and implement a program for participant education and retention.
- to organize and maintain the Central Pharmacy. The project manager serves as a liaison with pharmaceutical companies for supplying study medication. The project manager maintains and distributes study medication to Clinical Centers, as well as monitors Clinical Center use of study medication.
- to act as the study chairman’s representative.
- to assist clinical centers in the preparation of grant renewals and IRB approvals.

12.1.4 Medical Monitor

The medical monitor is appointed by the Study Chairman and reviews all treatment change requests, requests for protocol exemptions, medical withdrawals and requests for expedited visual field confirmation testing.
# 13. Coordinating Center

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>13.2</td>
<td>Personnel</td>
</tr>
<tr>
<td>13.3</td>
<td>Protocol Development and Modifications</td>
</tr>
<tr>
<td>13.4</td>
<td>Follow-up</td>
</tr>
<tr>
<td>13.5</td>
<td>Participant and Resource Center Close-out</td>
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<tr>
<td>13.6</td>
<td>Study Close-out</td>
</tr>
<tr>
<td>13.7</td>
<td>Quality Assurance at Clinics</td>
</tr>
<tr>
<td>13.8</td>
<td>Data Security and Protection of Confidentiality</td>
</tr>
<tr>
<td>13.9.1</td>
<td>Records Flow Within the Coordinating Center</td>
</tr>
<tr>
<td>13.9.1</td>
<td>Reports to Clinical Centers</td>
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<tr>
<td>13.10</td>
<td>Form Design</td>
</tr>
<tr>
<td>13.11</td>
<td>Data Management</td>
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</tbody>
</table>

References: 13-14
13.1 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, Clinic Coordinator’s Group, and the Data and Safety Monitoring Committee (DSMC) in the design and implementation of the Ocular Hypertension Treatment Study (OHTS). The Coordinating Center coordinates the efforts of investigators, monitors protocol adherence, processess, analyzes, and stores study data.

The staff of the Coordinating Center includes the Director, Co-Director/Biostatistician, Assistant Director, Project Manager, two Central Coordinators, three Statistical Data Analysts, two Database Administrators, Project Assistant, and Web Master.

Study data consists of case report forms from Clinical Centers, visual field data from the Visual Field Reading Center and the Short Wavelength Perimetry Reading Center (closed to data collection), optic disc data from the Optic Disc Reading Center and Confocal Scanning Laser Ophthalmoscopy Reading Center.

13.2 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.
- Collaborates with the Study Chairman’s Office in the planning of Executive/Steering Committee Meetings, Clinic Coordinator’s Meetings, Full Investigative Group Meetings, and all Publication Committees.
- Responsible for meetings of the DSMC and serves as an ex-officio member.
- Serves on the Executive/Steering Committee as a voting member.
- Participates in site visits to reading centers and Clinical Centers.
- Chairs weekly staff meetings, sets staff priorities, responsible for personnel decisions and the Coordinating Center budget.
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 DSMC and Publication Committees. Attends meetings of the Executive/Steering Committee, Clinic Coordinator’s Group, Full Investigative Group, Publication Committee, the DSMC and weekly staff meetings.
- Serves as faculty level liaison with the Division of Biostatistics.

Assistant Director  

Steven M. Kymes, Ph.D.
- Provides faculty level input in the preparation of manuscripts, including writing the methods section and conducting analyses.
- Assists with the analyses for the DSMC, Executive/Steering Committee and Full Investigative Group.
- Conducts analyses of the NEI-Vision Function Questionnaire (VFQ) and economic evaluations of ocular hypertensive management strategies.
- Provides back-up to the Director.

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.
- Prepares the annual budget for the Coordinating Center grant and monitors expenditures.
- Serves as study archivist and maintains a computerized catalog and library of study documents including abstracts, reprints, slides and tapes.
- Coordinates the efforts of Coordinating Center staff, attends weekly staff meetings and prepares minutes of those meetings.
- Maintains a performance schedule calendar.
- Assists in organization of local and national meetings and prepares minutes of those meetings.
- Assists Clinical Centers with the preparation of annual continuation renewals and IRB submissions.
- Provides back-up to Director of the Coordinating Center, and to the Project Manager in the Chairman’s Office.
Central Coordinators

Patricia Morris
Teresa Roediger, B.S.

- Each central coordinator works with specific Clinical Centers.
- Reviews case report forms received from Clinical Centers.
- Monitors adherence to the protocol and prepares monthly clinic tracking reports.
- Trains and certifies Clinic Coordinators and clinicians about study protocol, IOP determination, visual acuity, lens opacity classification and blood pressure measurement.
- Conducts troubleshooting calls with Clinic Coordinators and when necessary, conference calls between the clinic and the Study Chairman’s office.
- Responsible for preparation, scheduling, and conducting site visits to Clinic Centers.
- Prepares endpoint charts for review and liaison to Endpoint Committee.
- Serves as liaison to Medical Monitor for Treatment Change.
- Serves as liaison to Study Chairman and Medical Monitor for participant medical withdrawals and protocol exemptions.
- Reviews Adverse Event forms.
- Non-voting members of the Executive/Steering Committee.
- Maintains IRB reminder calendar for clinical centers and verifies Clinical Center IRB coverage.

Statistical Data Analysts

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

- Conducts statistical analyses for study publications/presentations and local and national meetings.
- Develops data cleaning programs and data entry program.
- Develops and maintains web system for static and interactive access to study data.
- Generates recurrent reports for recruitment, data quality, protocol adherence and activity reports for resource centers.
- Generates recurrent and ad hoc reports for monitoring study efficacy and safety outcomes for the DSMC.
Database Administrators

Joel Achtenberg, M.S.W.
Karen Clark, B.A.

- Responsible for oversight of management and processing of study data.
- Responsible for oversight of the writing and maintaining of programs for data entry, editing, management and reporting.
- Maintains study databases, tape archives and comprehensive documentation of variables, formats and program code used in reports.
- Provides oversight of computer systems and direction for future computing needs.
- Chairs weekly Information Systems Group (ISG) meetings and coordinates ISG priorities and tasks.

Project Assistant

Cheryl La Rue

- Responsible for data entry, managing, filing and archiving of case report forms received at the Coordinating Center.
- Conducts data editing and auditing.
- Coordinates the data entry subcontractor and the courier company.
- Updates archive of conflict of interest and publication/presentation agreement forms.
- Responsible for data entry changes to master data base.
- Provides backup to the project manager.

Web Master

Elizabeth Hornbeck, B.S.

- Develops and maintains web system.
- Develops and maintains on-line reference library of study manuscripts.
- Prepares semi-annual participant newsletter
- Provides back-up for Project Assistant.

13.3 Protocol Development and Modifications

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.
- Developing 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 DSMC.

• Developing, maintaining, and distributing a detailed Manual of Procedures.

• Developing procedures for training and certifying Clinic Coordinators, technicians, photographers, principal investigators, and reading center personnel.

• Monitoring Institutional Review Board approval.

13.4 Follow-up

Follow-up in OHTS II is projected to take at least five years. This phase includes the time from the participant providing informed consent to participate in OHTS II to completion of follow-up visits. Coordinating Center responsibilities during this phase include the following:

• Providing scientific and operational support to Clinical Centers, the Visual Field Reading Center (VFRC), and the Optic Disc Reading Center (ODRC).

• Initiating steps necessary 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 in OHTS I. Monthly monitoring reports summarize timeliness of visits and subsequent data processing.)

• Assisting Clinical Center staff with interpreting the Manual of Procedures and study protocol.

• 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 retention and follow-up, and protocol adherence.

• At six-month intervals and upon request, the Coordinating Center generates monitoring reports for the Executive/Steering Committee and the DSMC. Closed reports for the DSMC include safety and efficacy monitoring. Open reports include protocol violations by clinic, participant retention, achievement of IOP goals, and prescription of medication.

• Analyzing data for presentations and publications.
13.5 **Participant and Resource Center Close-out**

Participant and resource center close-out includes:

- Developing and monitoring procedures for participant close-out.
- Assisting in the preparation of manuscripts.
- Final data editing, preparation of de-identified datasets, and archival storage.
- Close-out of Clinical Centers, the VFRC, the ODRC, and the Coordinating Center.
- Final disposition of data files.

13.6 **Study Close-out**

During study close-out 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.

13.7 **Quality Assurance at Clinics**

- The Central Coordinators train and certify Clinical Center personnel (coordinators, principal investigators and their backups) on the protocol, IOP measurement, visual acuity testing, examination procedures, forms completion, and data entry/editing at annual meetings and/or by telephone. Certification of clinic personnel for Short Wave Length Perimetry, Confocal Scanning Laser Ophthalmoscopy, pachymetry, visual field testing and optic disc photography are performed by their respective reading centers.
- The Coordinating Center generates quality control reports on the performance of Clinical Centers.
- Central Coordinators conduct troubleshooting calls and e-mails with Clinical Centers as needed, typically at least once per week.
- 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 date of written informed consent for participation in OHTS II and/or Decline to Participate forms for OHTS II.
  b. Observe a demonstration of OHTS IOP measurement protocol with a volunteer.
c. Review a 25% sample of participants study charts for detailed comparison of the source document to data printouts from the Coordinating Center. Verification includes:

- Comparison of IOP readings recorded at each visit.
- Comparison of visual fields from clinic Humphrey Visual Field Perimeter printout and listing of visual fields received at the Visual Field Reading Center.
- Comparison of photographs in the participant chart with photographs received at the Optic Disc Reading Center.
- Comparison of topical medications on printouts from the Coordinating Center with the primary source document.

d. Assist clinic coordinators with any backlog of outstanding forms.

e. Perform 100% audit of the medication status of participants who have been reviewed by the Endpoint Committee or have been approved for treatment change.

f. Check inventory of study medication and storage security.

g. Check storage security of OHTS case report forms and informed consent forms.

h. Verify serial number of cameras for optic disc photography.

i. To identify and resolve other problems as necessary.

### 13.8 Data Security and Protection of Confidentiality

As the central repository of information for the study, the Coordinating Center has particular responsibilities towards data security. The Coordinating Center has responsibility to protect the data from all hazards, including disasters and unauthorized access. OHTS data and programs are stored on a Unix drive in the Division of Biostatistics. The computer room in the Division of Biostatistics is protected by fire and heat sensors and is only accessible by card access. The Division of Biostatistics and the OHTS Coordinating Center are located in a building with after hours entry by card access only. Each night, the Data Control Coordinator performs tape back-ups of all OHTS files (suspend datasets, master datasets, programs, archive datasets) on a tape drive in the Coordinating Center secure suite. Daily back-ups are retained for a week, weekly back-ups are retained for a month, monthly back-ups are retained for a year, and annual back-ups are retained indefinitely. Each night, the Biostatistics system administrator performs a separate tape back-up of the entire system. The monthly tape back-ups performed by the Biostatistics system administrator are stored in an off-site facility. In addition, OHTS programs automatically create back-ups of each active dataset whenever a change is made to the dataset. The four most recently aged datasets are stored on disk and are immediately retrievable.

All OHTS datasets (active and snapshot) are stored on a Unix server that limits access to authorized personnel via approved passwords. Unix controls read/write/execute privileges via userid and password. We have four levels of access privilege in the OHTS data management system that is built on SAS. The four levels are: supervisor, programmer, Central Coordinator
and Data Control Coordinator. Each individual’s access level is maintained in a security dataset and is associated with that individual’s unique userid and password. In addition, access to analysis (“snapshot”) datasets generated monthly are controlled by passwords unique to the snapshot datasets and provided only to those authorized to perform analyses and reporting.

OHTS datasets and programs used in the preparation of publications are stored in a separate Unix directory. Every publication is annotated so that each number in the publication is linked to a specific program and dataset from which it was generated. These referenced datasets and programs are stored in this directory.

The Coordinating Center is in full compliance with Health Insurance Portability and Accountability Act (HIPAA). Our institution requires a two key standard for both electronic and hardcopy protected health information (PHI). We have exceeded this standard utilizing the following barriers to electronic PHI: 1) password protected workstations that are locked when not in use; 2) password protected access to data and; 3) the system is on a secure network behind the Division of Biostatistics’ firewall. The firewall is configured to allow only authorized IP addresses and the number of open ports is restricted. PHI on hardcopy are stored in locked file cabinets in a card-controlled suite that records date and time of user entry. Only study and security personnel have card entry to this suite. Custodial staff are permitted entry only when study personnel are present. Business Associate Agreements are in place for off-site storage of case report forms, remote data entry and ICD-9 coding of hospital discharge summaries.

The Coordinating Center generates reports containing limited PHI (dates, 3 character ID code) that are run daily and monthly, many of which are available on our secure web site. Each authorized user is assigned a unique ID and password, which designates level of access to the web site. Clinical Center personnel are permitted access only to information specific to their Clinical Center. Reading center personnel are permitted access only to information specific to their reading center. The Database Administrator and Web Master review log reports of web access for failed log-in attempts and utilization.

### 13.9 Records Flow Within the Coordinating Center

Each day, Central Coordinators date stamp the case report forms that are received at the Coordinating Center and remove administrative forms and correspondence. This starts the clock for tracking internal processing of forms within the Coordinating Center. The Central Coordinator takes the case report forms to the Data Control Coordinator. Within one working day (defined as before 3:30 pm) of the day of receipt, the Data Control Coordinator performs the following manual checks:

- compares the information on the Transmittal Log with the form type, form version number, participant ID, and visit date fields on each case report form sent with the Transmittal Log.
- checks that the same IDs and dates are recorded on each page of the case report form.
- checks that the case report form has the correct number of pages.
The Data Control Coordinator reports discrepancies identified above using a problem report which is referred to the Central Coordinator. These Transmittal Logs cannot be entered until the problem report is resolved. The Data Control Coordinator enters the error-free Transmittal Log and the entry program validates the visit date, form version, and consistency of name code with the numeric ID, and also checks whether the participant’s consent status is current. The Data Control Coordinator prints out the computer generated log and manually checks accuracy of data entry against the Transmittal Log. The Data Control Coordinator then returns the case report forms to the Central Coordinators for a manual scan for missing or erroneous data.

The Central Coordinators review case report forms and the problem reports to determine if the case report form is ready for data entry. Central Coordinators resolve the problem report or contact the Clinical Center for resolution e.g. incorrect ID, dates or forms. Case report forms with serious problems are not sent to data entry pending resolution of the problem. The Central Coordinator assumes responsibility for the resolution of the problem or is authorized to permit a variance. The Central Coordinator is responsible for bringing issues to the attention of the Director of the Coordinating Center as needed for possible discussion with the Study Chairman and Executive/Steering Committee about possible protocol changes. The Central Coordinator returns the case report forms that are ready for data entry to the Data Control Coordinator. The Data Control Coordinator stamps a unique batch number on each page of the case report form, stamps the batch number on a computer generated batch inventory log and then bundles them by form type and form version for remote key data entry.

Key to disk entry of data is performed off-site by a commercial data entry service. The batch of case report forms are picked up from the Coordinating Center by courier three days per week. Two different key operators, with the second operator performing verification, key data to disk. 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 and version 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 and version 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 levels of edits. The first level checks for consistency of form type within a file, the number of pages for each form, and correctness of participant ID codes. The Data Control Coordinator is notified at this stage of discrepancies or errors that need to be corrected prior to running the form-specific edits. The second level consists of core edits that are conducted for all case report forms and those that are form-specific (unique to that case report form type). The core edits include:

- identification of missing values.
- out-of-range values.
- illegal characters.
• valid clinic codes.
• valid certifications.

The form-specific edits include:
• correctness of IOP computation.
• completion of appropriate tests and measures required for the f/up visit (semi-annual versus annual).
• appropriateness of treatment follow-up (need to schedule IOP confirmation visit).
• omission of treatment for participants in the medication group.

After completion of form-specific batch edits, the third level of editing checks across forms to identify duplicate forms, unnecessary forms, and completion of an Adverse Events Form when required by the protocol (Chapter 2).

Central Coordinators fax edit queries to Clinic Coordinators. The edit query 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, missing forms etc. Records with errors or questionable items are flagged 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.

Case report forms whose data have been transferred to the central database are then routed for free-text entry (if an endpoint patient) and then filed in the participant’s study file in a locked filing cabinet.

Case report forms for the most recent visit windows are kept at the Coordinating Center in locked file cabinets. Participant charts with all other case report forms are kept at Iron Mountain Records Storage. Both the Coordinating Center and Iron Mountain are in compliance with HIPAA regulations for appropriate care and storage of participant medical records. Charts created for the purposes of endpoint determination are kept in their entirety at the Coordinating Center.

Some case report forms (Adverse Events, Hospital Discharge Summary, POAG Endpoint Forms, Protocol Exemption Forms, Medical Withdrawal, and Treatment Change Form) are entered by the Data Control Coordinators using SAS full screen entry programs. These forms are entered in-house because of their complexity (free text), time urgency (Adverse Event Forms and POAG Endpoint Forms) or low volume. Edit checks of these data include verification of visit date, ID number and name code, range and variable format checks. A manual comparison of the entered data with hard copy of the case report form is completed to confirm accuracy.
13.9.1 Reports to Clinical Centers

In order to track transactions with the Clinical Centers, the Coordinating Center generates daily and monthly reports. Every 24 hours, the Coordinating Center generates web-based reports (https://vrcc.wustl.edu) available to authorized users.

The daily generated web-based reports provide listings of:

- Participants with follow-up visits at 1, 2, and 3 months prior to target visit date.
- Late/Missed follow-up visits (1, 2, and 3 months past target visit date or window has closed).
- Participants whose consent form is outstanding (OHTS II, genetics, CSLO).
- Edit queries outstanding over 21 days.
- Outstanding one-time measures (pachymetry, blood draws, diabetes history).
- Participants who have reached a POAG endpoint.
- Forms received & logged at the Coordinating Center by ID or form type.
- Deaths.
- Participants who have completed blood draws for genetic ancillary study.
- Gender and race table for their clinic.
- List of current participants.
- Staff certifications.
- Listing of changes to forms already in master datasets giving form type, date of form, variables changed, change date and comments.

The monthly generated web-based reports provide listings of:

- Participants whose target visit date occurs in two months.
- Participants with late or missed visits (Missed Visit Report needs to be submitted).
- Outstanding one-time measures (pachymetry, blood draws, diabetes history).
- Participants whose consent form is outstanding.
- Transition Visit status.

The monthly reports are also printed and mailed to clinics along with reports from the Reading Centers. The paper report from the Optic Disc Reading Center lists participants requiring repeat photography due to poor quality or confirmation of suspected change, and photographs not received > 21 days after completion of follow-up visit. The paper report from Visual Field Reading Center lists participants with visual fields reported as completed but not received, and
participants who need to be retested due to unreliable visual fields or to confirm suspected abnormality.

### 13.10 Form Design

The Coordinating Center distributes master forms to Clinical Centers and the clinic coordinator is responsible for photocopying forms as needed. Master case report forms are also available for printing on the OHTS web site (www.vrcc.wustl.edu). 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 instructions 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 that 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 by certification code along with relevant dates of processing.
- Forms may be revised to reflect protocol modifications and corrections suggested on trouble reports, etc. Revised forms are identified by a unique form version number and date printed on each page.

### 13.11 Data Management

The SAS system is used for virtually all computer processing within the Coordinating Center. SAS has flexibility across hardware platforms that 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 PCs 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 that 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 programs are written on a regular or as needed basis for accessing this library for the production of those management reports that the Executive/Steering Committee, Coordinating Center and DSMC develop jointly. Other programs extract analysis subsets for interim analyses and quality control monitoring.
Each observation in a given dataset has an “edit date” and “move date” that indicates the stage of processing for that form. These dates also provide a mechanism to track forms flow and to identify any delays in processing. When new or revised data is received from the clinical center, the Data Control Coordinator 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 and logs all changes to a dataset.

References:


14. Optic Disc Photography

14.1 ODRC Objective ................................................................. 14-2
14.1.1 Personnel ................................................................. 14-2
14.1.2 Responsibilities of ODRC ............................................. 14-3
14.2 Optic Disc Reading Center Procedures ............................... 14-3
14.2.1 Reader Pre-requisite .................................................... 14-3
14.2.2 Training and Certification of Optic Disc Readers ............ 14-3
14.2.3 Logging in Photographs from Clinical Centers ............... 14-4
14.2.4 Storage of Optic Disc Photographs ............................... 14-5
14.2.5 Evaluation of Stereo and Clarity ................................. 14-5
14.2.6 When Readers Disagree on Technical Quality or Progression Criteria 14-6
14.2.7 Disc Progression Assessment: Change from Baseline ....... 14-6
14.2.8 Masked Rereading of Change ..................................... 14-6
14.2.9 Confirmatory Change Photographs ............................... 14-6
14.3 Quality Control Procedures ............................................. 14-7
14.4 Communications to Clinical Center ................................... 14-8
14.4.1 Communications to the Clinical Coordinators ............... 14-8
14.4.2 Communications to Clinical Center Principal Investigators 14-9
14.4.3 Transmission of Data from ODRC to Coordinating Center 14-9
14.4.4 Data Entry ............................................................. 14-9
14.4.5 Report Generation .................................................... 14-10
14.5 Transmission of Data from Coordinating Center to ODRC .... 14-10
14.6 When to take Optic Disc Photographs ............................... 14-11
14.6.1 Who must be certified for Photography ......................... 14-12
14.6.2 Certification for Photography .................................... 14-12
14.6.3 Certification Code .................................................... 14-12
14.6.4 Continuation of Certification as an OHTS Photographer .... 14-13
14.6.5 OHTS Cameras & Procedures .................................... 14-13
14.7 Optic Disc Photography Protocol ..................................... 14-14
14.7.1 Determine Eyepiece Setting ....................................... 14-14
14.7.2 Film .......................................................................... 14-14
14.7.3 Dilation ..................................................................... 14-14
14.7.4 Photography Instruction .......................................... 14-14
14.7.5 Developing Film ....................................................... 14-15
14.7.6 Labeling Slides ........................................................ 14-15
14.7.7 Mailing Slides to ODRC .......................................... 14-16
Appendix .............................................................................. 14-17

ODRC Disc Hemorrhage Definition ......................................... 14-18
Figure 1 Placement of Masked Slides for Readers .................... 14-20
Figure 2 Proper Slide Arrangement for Submission for Photographer Certification ........................................ 14-20
Figure 3 Proper Labeling for OHTS Study Slides .................... 14-21
Figure 4 Correct Placement of OD and OS Slides for Mailing .... 14-22
14.1 ODRC Objective

Optic disc (nerve) stereo photography will be used to evaluate endpoint criteria in OHTS II. Optic disc stereo photography will be performed annually after initial randomization in OHTS to determine if glaucomatous damage has occurred. Treatment assignment is not provided to the ODRC personnel.

14.1.1 Personnel

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14.1.2 Responsibilities of ODRC

- 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 study photographers and back up study photographers.
- Receives, processes, and archives all photographs and associated data.
- Assesses photographic quality and notifies Clinical Centers when photographs must be repeated.
- Determines if progressive optic nerve damage has occurred.
- Enters and manages optic disc related data.
- Transmits data to the Coordinating Center and the Clinical Centers in a timely fashion.
- Generates reports for the Steering Committee, Executive Committee, and Data and Safety Monitoring Committee. (per 14.4.5)
- Provides statistical analyses requested by the Coordinating Center.

14.2 Optic Disc Reading Center Procedures

14.2.1 Reader Pre-requisite

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

14.2.2 Training and Certification of Optic Disc Readers

The Director of the Optic Disc Reading Center developed training and test sets for reader certification for grading eligibility and for progression. Certification occurs at three levels. Certification for eligibility reading consists of two parts: the first for recognition of exclusion entities (Part I), and the second for recognition of asymmetry and quantifying cup/disc ratio (Part II), and certification for reading progression has one part (Part III).

Part I. Recognition of exclusion entities (e.g., giant drusen of the disc).

Training: A teaching set contains at least one example of the exclusion entities: 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 consists of two test sets. The test set includes at least one example of each exclusion criteria. Special attention is paid to localized thinning of the neuroretinal rim. For
testing, an equal number of eligible disc photographs (with a variety of cup/disc ratios) are mixed with ineligible photographs. Competent readers should have no trouble detecting obvious exclusion entities such as drusen, that would not likely be submitted by the investigator. The most important test is to verify that the prospective reader recognizes a thinned neuroretinal rim. Two test sets are available so that if the prospective reader fails the first test (100% correct identification expected), the second set is used after further training. If the prospective reader passes on the first attempt, the second set is reviewed for additional experience.

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

Training: The Associate Director or Assistant Director of the ODRC (Senior Readers) reads slides with the trainees simultaneously. Grading the slides side by side with an experienced Senior Reader has been demonstrated to be an effective method of training new readers.

Testing: When the Senior Reader believes the trainee is sufficiently competent, the trainee will no longer read the slides together with a teacher, but independently. The trainee’s results will not be used for study purposes, but will be compared with the readings of the two independent previously trained readers or the Associate or Assistant Director. On 50 consecutive sets, the horizontal C/D ratio must be within 0.1 of at least one of the two readers. For example, the candidate reader may designate 0.3 in one eye and 0.5 in the other. This would be an acceptable match with 0.4 and 0.6 readings of the readers, or with 0.2 and 0.6 readings of the readers, but would not be a match with 0.4 and 0.7 readings. If the trainee fails to correctly grade 50 consecutive correct readings, the count for 50 consecutive correct readings begins again and continues until 50 consecutive correct responses are given.

Part III. Judgment of progression.

Training: The candidate readers will grade pairs side by side with the Associate Director or Assistant Director until the candidate readers are deemed ready to be tested.

Testing: As in Part II, successful match with the reading of the Associate or Assistant Director in 50 consecutive sets of discs read with at least 3 demonstrating progression are required for certification of judging progression. One false positive reading of progression in the set of 50 is permitted. If the set of 50 did not contain 3 true positive cases, the series continues until 3 positive cases are identified correctly with no more than 1 false reading of progression.

The trainee is certified as a reader to judge eligibility and progression after successfully completing parts I, II, and III.

14.2.3 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 are detected.
• The Research Assistant, who does not read the optic disc photographs, assigns a unique tracking number (two alpha and three numeric characters) to the set of slides for the right eye and another unique tracking number for the left eye, and completes a report on adequacy of labeling.

• The Research Assistant masks the readers to the information on the slides by placing an opaque label on the plastic slide sheet or the slide frame itself.

• The Research Assistant validates photographer ID, visit code, participant ID, and camera model and serial number.

• The Research Assistant logs photographs received in the "Daily Photo Receipt Log Sheet".

### 14.2.4 Storage of Optic Disc Photographs

All photos are stored in single 8 1/2 x 11" plastic sheets that are filed by clinic and participant ID number. Ungraded slides are stored in separate plastic sheets in the same participant file. Files must be easily accessible and kept in locked metal file cabinets on site.

In the future, all photos will be scanned and digitized for more compact storage and longevity.

### 14.2.5 Evaluation of Stereo and Clarity

• Only technically acceptable photographs will be evaluated for change.

• The Research Assistant selects the best stereo pairs and arranges the slides in masked grading sheets.

• Two 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, 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 Associate Director or Assistant Director (Senior Readers).

• If one reader grades an "unacceptable," retake photos will automatically be requested. The reader does no further grading of a stereo pair judged "unacceptable."

• A final 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 quality, the ODRC coordinator contacts the Clinical Center coordinator to request that photographs be retaken within four weeks and discusses the reason for additional photographs.
14.2.6 When Readers Disagree on Technical Quality or Progression Criteria

When readers disagree, the Associate Director or Assistant Director (Senior Readers) will reread the set and remain masked to the first round of grading results. This process is called adjudication.

When the Senior Reader who serves as the adjudicator agrees with one of the previous readers, those results will represent the ODRC results.

When the Senior Reader disagrees with both readers, the set is discussed in conference with the readers and the final ODRC result is determined by the Associate Director or Assistant Director (Senior Readers).

14.2.7 Disc Progression 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 for change or optic disc progression only if the temporal order is judged correctly.

Progressive optic nerve damage is defined for OHTS II, as in OHTS, as a visually detectable decrease in neural rim surface, as either generalized or localized thinning of the optic disc rim. Excavation of localized areas of rim tissue, a change in position of the blood vessels, or development of a notch, are evidence of change. The development of an optic nerve hemorrhage or a visible nerve fiber layer defect is not an endpoint for optic nerve progression.

The ODRC Coordinator will e-mail the Clinic Coordinator within one working day of suspected optic disc progression and request confirmation photos.

14.2.8 Masked Rereading of Change

To minimize false positives and to assure uniform reading, the Associate Director or Assistant Director (Senior Readers) will reread any set in which either reader reports a change.

14.2.9 Confirmatory Change Photographs

ODRC Coordinator will notify the Clinical Center coordinator by e-mail to schedule the patient for a confirmatory photograph after a progression finding is confirmed by a Senior Reader. The principal investigator at the Clinical Center is 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 this letter
is sent to the coordinator at the Clinical Center and to the Coordinating Center. Confirmatory photographs must be taken as soon as possible (within 4 weeks of the ODRC request) unless the participant has previously reached a photographic or visual field endpoint as determined by the OHTS Endpoint Committee, in which case the confirmatory photographs may be obtained at the next regularly scheduled study visit.

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 progression, 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, and mails them by Federal Express to the Coordinating Center.

If the confirmatory photos graded by the two readers and Senior Reader do not show progression, then the principal investigator at the Clinical Center, clinic coordinator, and the Coordinating Center are notified in writing that progression has not been confirmed. The participant continues the regular follow-up visit schedule.

14.3 Quality Control Procedures

I. Quality control procedures seek to ensure that disc progression from baseline, as described in section 14.2.7, are reproducible over time. This process involves inserting masked photos into the stream of current study photos given to the two readers for evaluation. The research assistant inserts the quality control photographs that are provided by the biostatisticians and they appear no different that other photographs to be read.

II. All usual ODRC procedures are followed for each pair of test photographs until a determination of change or no change from baseline has been made.

- Two sets of photos are used for Quality Control purposes. Set 1 consists of 50 normal stereo optic nerve photographs, which were randomly selected from the photos of patients who have not demonstrated optic disc progression as confirmed by the Endpoint Committee. The readers compare stereo follow-up photos and baseline photos. Quality control readings of Set 1, the normal photos without change, are considered in agreement with the original determination if both readers score them as no progression; or, should the photos go to a Senior Reader, if the Senior Reader scores them as no progression. The readings are considered not in agreement with the original determination if a Senior Reader scores them as demonstrating progression, even though no confirmation photo was obtained.

- Set 2 consists of 72 stereo photographic pairs (36 annual and 36 confirmation photos) which the Endpoint Committee determined to have shown optic disc progression due to primary open angle glaucoma. Readings of progression photos are considered in agreement with the original determination if the readers send the...
annual photos to a Senior Reader who also then scores them as showing progression. The confirmation photos must also be judged by the Senior Reader as showing progression from baseline. Any other outcome is not considered in agreement. For example, if the Senior Reader does not agree that progression has occurred even though both readers graded the photographs as demonstrating change, then repeat ODRC reading was not in agreement with the previous assessment.

- All Quality Control photos are copies of stereo photographs that are masked to appear as ordinary study photos. The readers and Senior Reader are unaware that these photographs are part of Quality Control Sets 1 and 2.
- Agreement between the original study readings and the quality control readings of these photos are tabulated and reported to the DSMC annually. Agreement of the total grading process for the ODRC is also quantified with the kappa statistic.

III. Another quality control check is incorporated to the process at the ODRC. New annual study photos are taken after a patient has been determined by the Endpoint Committee to have optic disc progression due to glaucoma. Subsequent regularly scheduled annual photos which are judged as “no progression” by the ODRC are reported to the DSMC. Disagreement between the initial grading that demonstrated progression and repeat grading are considered false negatives.

14.4 Communications to Clinical Center

The ODRC will notify the Clinical Centers of the suspicion of change, the need for retake or confirmation photographs, and any protocol violations or edits.

14.4.1 Communications to the Clinical Coordinators

1. The clinic coordinators will be notified within two working days, by e-mail, of the need for:

   - Retake photographs due to poor photo quality
   - Confirmation photographs due to suspected optic disc progression

2. As soon as the ODRC has completed the evaluation process, the clinic coordinators will receive by mail:

   - Copies of letters informing the Principal Investigators of any optic disc or retinal hemorrhages identified by the ODRC
   - Copies of letters to the Principal Investigators indicating suspected optic disc progression
• Copies of memos to the Principal Investigators indicating that suspected optic disc progression was not confirmed
• Copies of the checklists that accompanied the photographs indicating the date received at the ODRC
• Protocol violation and edit forms

Protocol violations include, but are not limited to: Any follow-up photographs not submitted (annual photos, retake photos, confirmation photos, red reflex or macula photos), photographs taken by a non-certified photographer, photographs not received at the ODRC within 21 days of being taken.

Edits include, but are not limited to: Errors in labeling the slides, incomplete or incorrect checklists, incomplete set of photos, when follow-up and QA photos do not match.

14.4.2 Communications to Clinical Center Principal Investigators

The Principal Investigators will be notified by letter of any suspected optic disc progression, suspected progression that is not confirmed with confirmation photographs, and of any disc or retinal hemorrhages identified by the ODRC.

14.4.3 Transmission of Data from ODRC to Coordinating Center

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

Daily:
- Suspected progression
- Confirmed progression

Monthly:
- Data logs including: participant ID, photographer ID, visit code, photo date, date of follow-up visit, date photos received at ODRC, reader ID and date photos read, senior reader ID and date photos reviewed (if applicable), retake reason and date requested (if applicable).

Ad hoc basis:
- Any problem with a clinic with regard to labeling, photo quality, retakes, or timeliness of photographs.

14.4.4 Data Entry

The ODRC coordinator, readers, and research assistant are trained to enter data and verify submissions. Follow-up data will be entered to computer files from the paper forms completed
by the two readers. The log will be data entered and 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. All data will be submitted to edits to ensure completeness and accuracy.

### 14.4.5 Report Generation

The ODRC will produce reports for Steering Committee and Data and Safety Monitoring Committee meetings. These reports 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 and equipment
   2. Number of units/participants:
      a. Logged in by month, total to date
      b. Under review
      c. Completed review

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

II. Technical Quality/Performance at Clinic
   1. Number and percentage (n,%) failing technical criteria for clarity or stereo and requiring retake photographs
   2. Tabulation by clinic/photographer with regard to ranking of photos for clarity, stereo, percentage re-take required, and protocol violations.

III. Technical Quality at Optic Disc Reading Center
   1. Intergrader Agreement

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 completion of the evaluation process.
   3. Number of days from date of photos to transmission of data to Coordinating Center.

### 14.5 Transmission of Data from Coordinating Center to ODRC

Transmission occurs by E-mail or File Transfer Protocol

- Valid participant ID numbers
14.6 When to take Optic Disc Photographs

- Follow-up:
  12 month intervals after initial OHTS randomization, (12, 24-, 36-, 48-, 60-, 72-, 84-, 96-, 108-, 120-, 132-, 144- months). Photographs must be received at the ODRC within 21 days of the date of the photographs.

- Retakes:
  When technical quality is poor or unacceptable, retake photographs are requested by the ODRC. Repeat photos must be taken within 28 days of the ODRC request and must be received at the ODRC within 21 days of the date of the photographs.

- Confirmation of Progression:
  To confirm progressive optic nerve damage, confirming photos are requested by the ODRC. Confirming photos must be taken within 28 days of the ODRC request and must be received at the ODRC within 21 days of the date of the photographs. Patients who previously reached an endpoint as determined by the Endpoint Committee may have their confirmation photographs taken at the next regularly scheduled study visit.

- Fundus Red Reflex Photograph:
  A red reflex photograph of each eye to document the presence of either lens or corneal opacities is taken at every regularly scheduled annual visit. The study photographer pulls the fundus camera away from the participant and centers the image on the iris with the focusing knob at the maximum plus position. The iris should fill a 30° field. If necessary, the joystick or the focusing knob may be used to ensure that the focus is crisp. An exposure is made at the same camera power setting used for fundus photographs.

- Macula Photos:
  A single non stereo photograph of the macula area in both eyes is taken at each regularly scheduled annual visit with the camera set at the lowest magnification. The study photographer centers 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 - ¼ disc diameter nasal to the center of macula.

- Unscheduled Photos:
  At the discretion of the Principal Investigator of the Clinical Center additional sets of optic disc stereo photographs may be taken.

All optic disc stereo photographs taken for either OHTS or non-OHTS related visits (excluding fluorescein angiograms) must be mailed to the ODRC for review and filing. If the participant is determined to show progression, then all photos received by the ODRC will be forwarded to the Coordinating Center.
14.6.1 Who must be certified for Photography

Stereoscopic optic disc photographs must be taken by certified OHTS photographers. Photographs used for photographer certification may not be used for OHTS related protocol study visits.

14.6.2 Certification for Photography

- Clinic Coordinator notifies ODRC Coordinator that a photographer requires certification.
- Photographer takes two full stereo sets, two pairs for each eye, of two participants plus a single non-stereo red reflex and macula view for each eye (24 total slides – Patient 1: right eye - two stereo pairs = 4 slides, red reflex and macula = 2 slides, left eye – two stereo pairs = 4 slides, red reflex and macula = 2 slides and Patient 2: right eye - two stereo pairs = 4 slides, red reflex and macula = 2 slides, left eye – two stereo pairs = 4 slides, red reflex and macula = 2 slides) (See MOP Appendix, Figure 2), completes the photography checklist, labels the slides, and sends them to the ODRC. Once received by the ODRC, the slides become ODRC property and cannot be returned to the clinic.
- Model and serial number of fundus camera designated for OHTS is reported to the ODRC by the clinical coordinator or by the photographer.
- 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 14.6.3 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 submitted are acceptable and the photographer is certified.
- ODRC contacts the Coordinating Center with the new photographer certification information including photographer initials.

14.6.3 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.
14.6.4 Continuation of Certification as an OHTS Photographer

- Once certified, a photographer remains certified if performance and the quality of the disc photographs are judged acceptable by the ODRC Ophthalmic Photographer consultant.
- Certification may be rescinded if the ODRC determines that the photographer's performance is unacceptable and does not improve after consultation and review by the ODRC Ophthalmic Photographer Consultant.

14.6.5 OHTS Cameras & Procedures

- Each study center will designate one camera for OHTS. Acceptable fundus cameras include Zeiss, Topcon, Nidek, Nikon, and Kowa.
- Study photographers should select the 2X or 1.6X magnification lens for the Zeiss fundus camera.
- For all other fundus cameras, the highest magnification available should be used.
- Study photographers must 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 in writing prior to changing the equipment. The replacement camera’s make, model, and serial number must be reported to the ODRC.

If a camera is being replaced for the purpose of obtaining better quality photographs, but the original camera is useable, the original camera should be kept for continued use in participants already randomized into the study.

Whenever possible, the original camera should be used until all participants have been photographed with that camera at their next annual visit. 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 initial visit, then the photos taken with the new camera will become the baseline photos against which all future follow-up photos will be compared.

If the replacement camera is a different make than the original camera, all study photographers must be certified with the new camera following the procedures set in section 14.6.2.

Once certified, study photographers may begin using the new camera to photograph participants for the remainder of the Study.
14.7 Optic Disc Photography Protocol

14.7.1 Determine Eyepiece Setting

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

14.7.2 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.

14.7.3 Dilation

Pupils must be dilated before photography. Participants should be instructed to remain with eyes closed at least 20 - 30 minutes prior to photography to minimize corneal epithelial changes and to maintain a clear view.

14.7.4 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 number that is written on a piece of plain white paper.
• 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 eye.

• 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 retinal pigment epithelium peripillary crescent, if present, and take the first right stereo photograph, focusing at the junction of the RPE and the neuroretinal rim. After taking this photograph, tilt the joystick left to the 9 o'clock position outside the peripillary crescent, if present, focusing at the junction of the RPE and the neuroretinal rim and take the first left stereo photograph.

• 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 camera is used, set the magnification at the highest available level.

• Set the appropriate flash settings and use the same settings that give the best results for all photographs.

• 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).

### 14.7.5 Developing Film

The study photographer or clinical coordinator must send film for processing within two working days after the photographs are taken. Clinics should develop film immediately after each visit. Waiting until the end of a roll is reached could cause the clinic to miss the two-week submission deadline.

### 14.7.6 Labeling Slides

Follow labeling instructions (see MOP Appendix, Figure 3). 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.
14.7.7 Mailing Slides to ODRC

- All study slides must be received by the ODRC within 21 days of the date taken.
- Place slides in side-loading 8 1/2 x 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 MOP Appendix, Figure 4).
- 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
**ODRC Disc Hemorrhage Definition.**

Hemorrhages occur on the anterior portion of the optic nerve and adjacent retina (namely among the axons and within the axonal layer of the retina) for various reasons. They can occur as the result of an accident; a retinal disease, such as a central or branch vein occlusion; diabetic retinopathy; hypertensive retinopathy; anterior ischemic optic neuropathy; in association with glaucomatous optic neuropathy, and ocular hypertension without observable glaucomatous optic disc damage. Although disc hemorrhages do not meet the defined criteria for the development of POAG in OHTS or OHTS II, they may be associated with ocular hypertension or may be a risk factor for the development of POAG. For this reason, only optic disc hemorrhages classified as “glaucomatous disc hemorrhages” will be considered disc hemorrhages in OHTS II. Examples of disc hemorrhages, including a “glaucomatous disc hemorrhage”, can be found on the OHTS website (www.vrcc.wustl.edu).

**Concept:** A "disc hemorrhage" of the type we wish to identify in OHTS II refers to visible extravascular blood sometimes seen in the anterior optic nerve that are about to have prior to or during the development of glaucomatous damage to a bundle of axons, or are in the process of undergoing glaucomatous damage. The disc hemorrhage may occur either as the a first observable event or in addition to visible signs of glaucomatous optic damage that might already exist, such as focal narrowing of the neuroretinal rim or generalized increase in cupping.

**Description:** In the most typical form, disc hemorrhages are elongated extravascular accumulations of blood that occupy the spaces between axons of the retinal nerve-fiber layer as they turn to assemble into the lateral borders of the anterior optic nerve. These glaucoma-relevant hemorrhages are generally described as flame-shaped or splinter-shaped, depending on their breadth, and are radially oriented, perpendicular to the circumferential disc margin. Disc hemorrhages, often show feathered edges, unless they are narrow enough in which case they are seen as a single sliver.

**Confounding hemorrhages:** Similar elongated splinter hemorrhages may occur in the retinal nerve fiber layer near or far from the optic disc in certain retinopathies, and are most often associated with exudates, vascular changes, deeper retinal hemorrhages without an elongated component, or other signs of the disease specific retinopathy. These hemorrhages are would be recognized as not glaucoma-relevant, being strictly retinal (that is, beyond the peripapillary crescent) or being associated with multiple hemorrhages of several types or with vascular changes and exudates indicating a retinopathy. Disc hemorrhages may occur in diabetes or retinal vascular diseases, including central retinal vein occlusion, which may occur in the context of ocular hypertension or glaucoma, but are not pathogenetically related to simple splinter hemorrhages in an unknown way related to the pathogenic process of glaucomatous optic nerve damage.

**Criteria for recognition in this study:**

**Inclusion:** The glaucoma-relevant disc hemorrhages generally may extend from within the optic nerve head to the adjacent retina, crossing any peripapillary zone of absent or
disrupted retinal pigment epithelium (forming a peripapillary crescent or halo), but need not occupy the entire length of this typical position. In this study OHTS II the hemorrhage is considered glaucoma-relevant if it has a portion of its length within the disc, the peripapillary zone of abnormal retinal pigment epithelium, or both, whether or not it extends into the retina. At times, a presumed resolving splinter disc hemorrhage will break up into blotches within the disc or at its margin, and will still be considered a glaucoma-relevant disc hemorrhage (despite the lack of a elongated element to its shape), unless it is accompanied by multiple nearby blotchy hemorrhages suggestive of a specific retinopathy, for example from such as retinal vein occlusion or diabetes. Quite infrequently, it may be difficult to tell whether an isolated narrow red line is a small hemorrhage or a small short blood vessel (for example, a small segment of a dilated capillary shunt), and the reader will exercise judgment.

**Exclusion:** If located strictly completely within the retina beyond the peripapillary zone, a splinter-shaped hemorrhage is usually considered a hemorrhage due to retinal disease, not relevant to the present context, unless possibly it is an isolated hemorrhage very, very near the disc margin with no other signs of retinopathy to explain the presence of a hemorrhage. Hemorrhages of any shape in the optic nerve head will not be considered relevant to the present purpose if in the company of multiple nearby retinal hemorrhages and other signs of disease of the retina or its vessels. A splinter hemorrhage on the disc will also be considered not to be a disc hemorrhage relevant to ocular hypertension or glaucoma if the optic disc is swollen or otherwise obviously abnormal from acute anterior ischemic optic neuropathy, papillitis, or other non-glaucomatous optic disc disease.
Figure 1  Placement of Masked Slides for Readers

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Figure 2  Proper Slide Arrangement for Submission for Photographer Certification

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Figure 3  Proper Labeling for OHTS Study Slides

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Figure 4  Correct Placement of OD and OS Slides for Mailing

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## Figure 4  Correct Placement of OD and OS Slides for Mailing

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## 15. Visual Field Reading Center Procedures

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<tr>
<td>15.2</td>
<td>VFRC Objectives</td>
<td>15-6</td>
</tr>
<tr>
<td>15.3</td>
<td>VFRC Daily Operations and Procedures</td>
<td>15-6</td>
</tr>
<tr>
<td>15.3.1</td>
<td>Visual Field Shipments from the Clinical Centers</td>
<td>15-7</td>
</tr>
<tr>
<td>15.3.2</td>
<td>Filing, Back-up, and Review Systems</td>
<td>15-7</td>
</tr>
<tr>
<td>15.3.3</td>
<td>Management of Humphrey Field Data</td>
<td>15-8</td>
</tr>
<tr>
<td>15.3.3.1</td>
<td>Humphrey Field Data Files</td>
<td>15-8</td>
</tr>
<tr>
<td>15.3.3.2</td>
<td>Conversion of the Humphrey Disk Format</td>
<td>15-9</td>
</tr>
<tr>
<td>15.3.3.3</td>
<td>Handling of Missing or &quot;Not Tested&quot; Data</td>
<td>15-9</td>
</tr>
<tr>
<td>15.3.3.4</td>
<td>Conversion of Data into a Format for Analysis</td>
<td>15-9</td>
</tr>
<tr>
<td>15.3.3.5</td>
<td>Visual Field Quality Control Data</td>
<td>15-11</td>
</tr>
<tr>
<td>15.3.3.6</td>
<td>Data File Transfers to the Coordinating Center</td>
<td>15-12</td>
</tr>
<tr>
<td>15.3.4</td>
<td>Visual Field POAG Confirmation</td>
<td>15-12</td>
</tr>
<tr>
<td>15.3.5</td>
<td>Additional Visual Field Data Considerations</td>
<td>15-13</td>
</tr>
<tr>
<td>15.4</td>
<td>Quality Control Functions</td>
<td>15-14</td>
</tr>
<tr>
<td>15.4.1</td>
<td>Visual Field Quality Control</td>
<td>15-14</td>
</tr>
<tr>
<td>15.4.2</td>
<td>Turnaround Time Reporting System</td>
<td>15-15</td>
</tr>
<tr>
<td>15.4.3</td>
<td>Internal Quality Control System</td>
<td>15-15</td>
</tr>
<tr>
<td>15.4.4</td>
<td>Certification of Visual Field Technicians</td>
<td>15-15</td>
</tr>
<tr>
<td>15.5</td>
<td>Training and Certification of Technicians</td>
<td>15-16</td>
</tr>
<tr>
<td>15.5.1</td>
<td>Training on the Humphrey Field Analyzer</td>
<td>15-16</td>
</tr>
<tr>
<td>15.5.2</td>
<td>Certification Procedures</td>
<td>15-16</td>
</tr>
<tr>
<td>15.6</td>
<td>Archival Function of the VFRC</td>
<td>15-17</td>
</tr>
<tr>
<td>15.7</td>
<td>Visual Field Abnormality Classification</td>
<td>15-18</td>
</tr>
</tbody>
</table>

### Perimetry Protocol

- Introduction                                         15-21
- Visual Field Testing Procedures                       15-23
- Transmission of the Visual Field to the VFRC         15-29
- Technician Certification Procedures                   15-30
- Visual Field Abnormality Classification               15-34
15.1 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 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, 4 part-time Analysts, a part-time Computer Programmer, and a part-time Visual Field Technician.

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15.1.2 Responsibilities of VFRC Personnel

**John L. Keltner, M.D.,** serves as the Principal Investigator and Director of the Ocular Hypertension Treatment Study II (OHTS II) Visual Field Reading Center (VFRC) and will devote 25% effort to the study. The research will be carried out at the University of California, Davis Medical Center site, located in Sacramento, CA. As PI, Dr. Keltner will be responsible for determining visual field outcomes, assuring communication among study members, maintaining the VFRC organization as an effective collaborating group, and organizing monthly meetings or conferences with Dr. Chris Johnson, Co–PI of the study. In addition, 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, and (f) determining when visual field change signifying glaucomatous damage has occurred. He will be responsible for the overall budget and decisions pertaining to any reallocation that may serve the best interests of the project. Dr. Keltner has been Chair of the Department of Ophthalmology (a relatively large academic department with 14 faculty members) for 26 years.

**Chris A. Johnson, Ph.D.,** serves as the Co-Principal Investigator and Associate Director of the OHTS II VFRC and will devote 25% effort to the study. He currently resides in Portland, Oregon and serves as a Senior Scientist and Director of Diagnostic Research at Discoveries in Sight Research Labs, Devers Eye Institute. He attends monthly VFRC meetings in Sacramento, California and is in constant communication via e-mail and phone with the P.I. and VFRC staff on an as-needed basis. He is responsible for assisting the P.I. with managing all aspects of the research, which include the following: (a) guiding the development of the computer programs used by the VFRC, (b) assisting with visual field data analysis and interpretation for abstracts, posters, presentations and/or manuscripts, (c) monitoring the quality of the visual field information, (d) helping to provide direction for technician training and certification, and (e) determining when visual field change signifying glaucomatous damage has occurred.

**Kimberly E. Cello, B.S.,** serves as the Coordinator of the VFRC and will devote 100% effort to the study. She will be 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.

**Shannan E. Bandermann, MA.,** serves as both an assistant to the Coordinator and an assistant to the VFRC and will devote 50% effort to the study. She is responsible for assisting the VFRC coordinator with various projects/reports, training new VFRC Assistants, and performing daily VFRC activities. Her responsibilities include: (a) receiving and processing of visual field data,
(b) monitoring, tracking and updating the VFRC abnormality/unreliability log, (c) certifying OHTS visual field technicians, (d) preparing reports on various visual field topics, (e) contributing to visual field data analyses, and (f) assisting with the preparation and development of VFRC manuscripts. She has officially been certified as VFRC Personnel and a Certified Visual Field Reader.

**Daniel Redline, B.S.,** serves as an Assistant to the VFRC and will devote 60% effort to the study. He is responsible for assisting the VFRC coordinator with various projects/reports and performing the daily activities in the center. His responsibilities include: (a) contributing to visual field data analyses, (b) assisting with the preparation and development of VFRC manuscripts, (c) receiving and processing of visual field data, (d) tracking and updating the VFRC abnormality/unreliability log, (e) monitors abnormality and unreliability faxes for the clinical sites, and (f) certifying the visual field technicians of each clinical center.

**Eunice Olson, B.A.,** serves as an Assistant to the VFRC and will devote 50% effort to the study. Her responsibilities include: (a) assisting with the editing, preparation and development of VFRC manuscripts, (b) receiving and processing of visual field data, (c) tracking and updating the VFRC abnormality/unreliability log, (d) monitors abnormality and unreliability faxes for the clinical sites, and (e) certifying the visual field technicians of each clinical center.

**Rodel Pena, B.S.,** serves as an Assistant to the VFRC and will devote 50% effort to the study. His responsibilities include: (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 clinical sites, and (d) certifying the visual field technicians of each clinical center.

**Bhupinder Dhillon, B.S.,** serves as the Computer Programmer and will devote 20% effort to the study. His responsibilities include: (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.

**Marilyn Sponzo, COA,** the VFRC Visual Field Technician, is responsible for retrieving requested visual field data from participants who have reached reproducible Optic Disc progression and sending that data to the OHTS Coordinating Center.

**Biostatistician Consultants:**

**Richard Levine, Ph.D. and Juanjuan Fan, Ph.D.**

The OHTS has recently transitioned into an intensive data analysis, presentation, and publication phase, thus we are requesting funding for a part-time (50%) Senior Statistical Data Analyst to assist Dr. Keltner at the Visual Field Reading Center. The statistical data analyst(s) will assist with analysis of outcome visual field data, manuscript preparation, and implementation of a transition phase from a close-out of randomized trial to an open follow-on study. Dr. Richard Levine, Ph.D. and Juanjuan Fan, Ph.D., will share this position and devote 25% (each) effort to the study. The VFRC currently has ten projects requiring data analysis, consequently this effort


will include analyses for current projects as well as any upcoming projects/manuscripts as requested by the Data Safety and Monitoring Committee (DSMC). In addition, analyses will include collaboration with the OHTS Data Coordinating Center (St. Louis, Missouri) to ensure data quality and consistency.

### 15.2 VFRC Objectives

The objectives of the VFRC with respect to the OHTS II 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 perform the following quality control functions (Section 15.4):
   - (a) establish visual field reliability criteria for the clinical centers,
   - (b) report on the adherence to the OHTS protocol in the performance of visual fields;
   - (c) report on the turnaround time for transmission of fields and data from clinical centers to VFRC to Coordinating Center,
   - (d) maintain an internal quality control system,
   - (e) respond to an external quality control system,
   - (f) maintain perimetry certification at the clinical centers with the assistance of VFRC visual field technicians;
3. To process all visual field data from the Humphrey tests performed on OHTS II participants using the VFRC computers, to convert the visual field data into the appropriate format, and to transmit the resulting data files (monthly) to the Coordinating Center;
4. To provide training and certification of technicians who will be performing the Humphrey visual field examinations for the OHTS II (Section 15.5);
5. To store, archive, and document all visual field information associated with the OHTS II (Section 15.6);
6. Present and publish appropriate data in the form of abstracts, posters, presentations, and manuscripts

### 15.3 VFRC Daily Operations and Procedures

The VFRC will receive all of the visual fields from the OHTS II clinical centers, process the data, and prepare the data files for the Coordinating Center in a form suitable for analysis. There will be approximately over 75,000 Humphrey follow-up visual fields processed over the span of
the study from the OHTS II participants, as well as an additional 7,256 Humphrey fields performed on ineligible individuals.

15.3.1 Visual Field Shipments from the Clinical Centers

All OHTS II visual fields, including abnormal and unreliable ones, must be mailed to the VFRC within 21 days of testing. In addition, you must also immediately fax all abnormal and/or unreliable follow-up fields to the VFRC within 7 days of testing, as well as the required retests for these fields, even if they are normal. 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. Each shipment should include one Humphrey disk with the corresponding visual field printouts and a disk directory you have printed out. 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!

Be sure to attach a label to each Humphrey disk you send to the VFRC (see Figure 6). 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.

The HFA disk must be enclosed in a protective disk mailer. Although the VFRC will periodically return disks and disk mailers to you, you will be responsible for purchasing and maintaining your own supply. You may enclose all of the visual field materials in the disk mailer; however, it is preferable to 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.

Finally, you need to keep copies of the OHTS II visual fields (i.e., two sets of floppy disks and one set of visual field 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. 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 checked off on the disk directory).
15.3.2 Filing, Back-up, and Review Systems

The VFRC performs and tracks the completion of the following procedures:

(1) 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 15.3.3.5). Copies of these reports are then sent to the clinical centers as feedback regarding the performance of the technician in following the OHTS II visual field protocol. A computer program, HUMPHREY.COM, which was modified for the OHTS II, 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) The Director and Associate Director review all follow-up visual fields that may show a confirmed abnormality indicating possible glaucomatous damage (see section 15.3.5). They record their comments and abnormality visual field classifications regarding the fields on OHTS Visual Field Review Forms. These observations form the basis for discussions at the VFRC and with other study centers regarding the fields, in addition, they serve as a record of the reviewers evaluations.

15.3.3 Management of Humphrey Field Data

The procedures involved in handling the data from the Humphrey fields are described below.

15.3.3.1 Humphrey Field Data Files

The fields recorded by the Humphrey Field Analyzer II (HFA II) are stored on high density, 3 1/2” 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.
15.3.3.2 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 II.

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 15.3.3.5).

(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.

15.3.3.3 Handling of Missing or "Not Tested" Data

When a Humphrey visual field 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.

15.3.3.4 Conversion of Data into a Format for Analysis

The Humphrey 30-2 Full Threshold 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 global indices 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. **Mean Deviation (MD)** 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. **Pattern Standard Deviation (PSD)** 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. **Short-term Fluctuation (SF)** 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. **Corrected Pattern Standard Deviation (CPSD)** 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. **Glaucoma Hemifield Test (GHT)**, 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.
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.

15.3.3.5 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 reliability indices 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 II, STATPAC 2 will place an "xx" indicating unreliability by any of these indices when there are 33% or more occurrences. In addition, STATPAC 2 will state, “Low Patient Reliability” above the GHT index. These indices include the following:
(a) **Fixation losses.** 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) **False positive errors.** 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) **False negative errors.** 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) **Quality Control Reports** will be produced by the OHTS HUMPHREY.COM program. These reports will be sent to the clinical centers on a monthly basis 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
- (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
- (l) 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) the actual ratios for fixation losses, false positives, and false negatives

### 15.3.3.6 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 the VFRC will send 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.

### 15.3.4 Visual Field POAG Confirmation

Humphrey 30-2 visual fields are done every six months by certified study technicians. A reliable field is considered abnormal if p < 5% for the CPSD or if the GHT is outside normal limits after
review by masked certified readers at the Visual Field Reading Center. Since 86% of the first reliable, abnormal visual fields that occurred in OHTS I were 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 visual field reliable and abnormal, the VFRC calls the Clinical Center to schedule a repeat (third) visual field within 1 to 8 weeks. (If the participant has already developed POAG, then the 3rd set of visual fields can be done at the next regularly scheduled visit). If the third visual field is also reliable and abnormal, the VFRC contacts the Coordinating Center to convene the Endpoint Committee. In some instances, senior readers may accept an abnormal visual field with one or more unreliability index flagged. This exception is recorded, and the abnormal, unreliable visual field is included in the series of three consecutive abnormal visual fields. The abnormalities on the three visual fields must be of the same character and location as determined by the masked readers to trigger an endpoint review. The VFRC sends the Coordinating Center a narrative description of the defect and copies of visual fields of the affected eye and fellow eye from the Qualifying Assessment to date. The protocol for Endpoint Committee review of visual field abnormality is the same as described for optic disc endpoint review.

The Endpoint Committee will make a determination as to whether the visual field abnormality is attributable to POAG or not. If the Endpoint Committee determines that the abnormality is not attributable to POAG, the Coordinating Center notifies the Clinical Center of this decision. The participant continues routine follow-up. If the Endpoint Committee determines that the abnormality is due to POAG, the Coordinating Center notifies the Clinical Center of this decision. Participants who reach a POAG endpoint continue to complete all tests and measures at their regularly scheduled follow-up visits as part of the POAG treatment group.

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, (e.g., with three consecutive visual fields showing the same "new" abnormality.) Non POAG reports are generated on a monthly basis to report any non-POAG eyes that have had 3 consecutive abnormal visual fields post endpoint confirmation. The VFRC sends the Coordinating Center a narrative description of the defect and copies of visual fields of the affected and fellow eye from the Qualifying Assessment to date. These eyes will be reviewed by the Endpoint Committee to determine if a “new” glaucomatous abnormality is present.

### 15.3.5 Additional Visual Field Data Considerations

Follow-up visual fields must be repeated when they are unreliable. 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 unreliable, 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):

<table>
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<td>NU</td>
<td>Adjudicate</td>
</tr>
<tr>
<td>NU</td>
<td>AR or AU</td>
<td>Use 1st VF*</td>
</tr>
<tr>
<td>AU</td>
<td>NR</td>
<td>Use Retest</td>
</tr>
<tr>
<td>AU</td>
<td>NU</td>
<td>Use Retest</td>
</tr>
<tr>
<td>AU</td>
<td>AU</td>
<td>Adjudicate</td>
</tr>
<tr>
<td>AU</td>
<td>AR</td>
<td>Use Retest</td>
</tr>
</tbody>
</table>

*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 six-month 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 to a possible confirmed abnormality.

15.4 Quality Control Functions

The VFRC is responsible for a series of quality control functions which are described below.

15.4.1 Visual Field Quality Control

The guidelines established to assess the quality of the Humphrey fields performed at the clinical centers are described in section 15.3.3.5. Visual Field Quality Control Reports will be produced by the OHTS HUMPHREY.COM program for all visual fields received (see section 15.3.3.5). Copies of these reports will be sent to the clinical centers on a monthly 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.
15.4.2 Turnaround Time Reporting System

Information on the turnaround time of the visual field data is included in the files transmitted to the Coordinating Center. Specifically, there is information regarding the test date, date received, date processed, and the date the files were sent to the Coordinating Center.

15.4.3 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 15.3.3.5). 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 processing of each data file, the information is double-checked before it is translated into the format for the Coordinating Center (see section 15.3.3.2).

15.4.4 Certification of Visual Field Technicians

The VFRC will conduct perimetry certification of the OHTS II visual field technicians by telephone and mail (see section 15.5). Each clinical center must have at least two technicians certified for OHTS II 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 II visual field technicians for following the OHTS II perimetry protocol. In addition, when site visits of the OHTS II 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.
15.5 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 II perimetry, each clinical center is provided with the OHTS II Perimetry Protocol and the OHTS Perimetry Procedures videotape as well as this Manual of Procedures (MOP) chapter. These materials describe the test procedures and data recording methods used in the OHTS II. The Principal Investigator at each clinical center is responsible for ensuring that the appropriate personnel are competent in the OHTS II perimetry protocol.

15.5.1 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 II 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 with 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.

15.5.2 Certification Procedures

In a telephone session with a VFRC assistant, each candidate for certification must demonstrate a complete understanding of the proper techniques for OHTS II visual field testing. Subsequently, the technician will need to perform visual fields according to the OHTS II 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 II 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 participant data;
7. running the Program 30-2;
8. sensitivity to participant fatigue -- allowing the participant to rest during the test;
9. running the STATPAC 2 program and printing the data;
10. making back-up disks.

All certified technicians will need to maintain their certification by performing visual field tests according to OHTS II protocol on a regular basis. Certification will lapse for any technician who does not perform an OHTS II 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 II protocol along with a memo attesting that he or she has re-read the Perimetry Protocol.

### 15.6 Archival Function of the VFRC

The VFRC is responsible for storing the visual field information generated by the OHTS II. 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 disk of the VFRC computer with back-up files on computer Super Disks. 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 II. Effective 6/00, the VFRC has implemented an additional backup system of converting the HFA I 5.25 inch disks to the HFA II 3.5 inch disks due to the discontinuation of HFA I perimeters.
15.7 Visual Field Abnormality Classification

The OHTS visual field abnormality classification system is on-going and is currently being used by the VFRC to classify all abnormal VFs as they are received. VFRC certified visual field readers classify the upper and lower hemifields separately as to the presence of abnormality that met the secondary definition (hemifields were not evaluated for the secondary definition of abnormality unless the visual field first met the OHTS criteria for abnormality). The secondary definition of abnormality is defined as: (a) A single point is worse than the 0.5% probability level on the Total and/or Pattern Deviation plots. (b) Two adjacent points (cluster) are beyond normal limits ($p < 5\%$), and at least one point is worse than the 1% level on the Total and/or Pattern Deviation plot. (A cluster is defined as two or more horizontally- or vertically-contiguous abnormal points with $p < 5\%$) and (c) Three or more clustered points are worse than the 5% level on the Total and/or Pattern Deviation plot and the pattern loss is consistent with ocular pathology. Thus, for a hemifield to be classified as normal, it must not meet any of the above criteria for hemifield abnormality. If the hemifield was classified as “abnormal,” the abnormality was further classified into one of the 17 mutually exclusive categories listed in Table 1. While more than one classification is possible for a hemifield, the most predominant defect was used for the final classification.

The procedures for hemifield classification are as follows: (1) The superior and inferior hemifields of visual fields that meet the OHTS abnormality criteria are evaluated separately, with the superior hemifield being classified first. Hemifield classifications are separated by a slash. If a defect straddles the horizontal midline, only a single designation is given and no slash is presented. (2) In general, the pattern on the deviation plot (“Total” or “Pattern”) showing the greater number of abnormal points is used to determine the appropriate classification for a hemifield abnormality. However, the other deviation plot, as well as the gray scale, is evaluated to confirm the appropriateness of the classification. Abnormal points that are extraneous to the salient pattern are considered less important for the determination of the hemifield classification. Thus, the most predominant pattern is classified.

Agreement between the readers is assessed by reporting whether none, two, or all three readers agreed on the classification of the hemifields. Thus, we report agreement among readers as the percent of hemifield classifications in which there was no agreement, agreement by two of three readers, and agreement by three of three readers. If at least two readers agreed with an abnormality classification, the majority classification was accepted (2 out of 3 readers in agreement). If all three readers disagreed, then the visual fields were adjudicated by group consensus to reach a final classification of the hemifield abnormality.
Table 1. OHTS Abnormality Classifications

<table>
<thead>
<tr>
<th>Nerve Fiber Bundle Abnormalities:</th>
</tr>
</thead>
</table>
| 1. **Altitudinal (Alt)** - Severe visual field loss throughout the entire superior or inferior hemifield that respects the horizontal midline.  
  • The majority of points in the hemifield have a $p < 0.5\%$ value on the total deviation plot.  
  • The entire horizontal midline demonstrates abnormality. |
| 2. **Arcuate (Arc)** - Significant visual field loss in the nerve fiber bundle region.  
  • Extends across contiguous abnormal points from the blind spot to at least one point outside 15 degrees adjacent to the nasal meridian. |
| 3. **Nasal Step (NS)** - Limited field loss adjacent to the nasal horizontal meridian.  
  • Includes at least one abnormal point at or outside 15 degrees on the meridian.  
  • Cannot include more than one significant point (on either plot) in the nerve fiber bundle region on the temporal side. |
| 4. **Paracentral (Pc)** - A relatively small visual field abnormality in the nerve fiber bundle region.  
  • Generally not contiguous with the blind spot or the nasal meridian.  
  • Does not involve points outside 15 degrees that are adjacent to the nasal meridian. |
| 5. **Partial Arcuate (PArc)** - Visual field loss in the nerve fiber bundle region that extends incompletely from the blind spot to the nasal meridian.  
  • The defect is generally contiguous with either the blind spot or the nasal meridian.  
  • Must include at least one abnormal location in the temporal visual field. |
| 6. **Temporal Wedge (TW)** – A small visual field defect that is temporal to the blind spot. |
**Non-Nerve Fiber Bundle Abnormalities:**

7. **Central (C)** - Visual field loss that is predominantly in the macular region.
   - The foveal threshold must have a \( p < 5\% \) value.
   - Can be associated with a single hemi-field and paired with another defect.

8. **Hemianopia (H)** - A visual field defect that respects the vertical meridian.
   - Involves essentially all points in a vertical hemifield.

9. **Inferior Depression (ID)** - Two or more abnormal points in the very inferior region.

10. **Partial Hemianopia (PH)** - A visual field defect that respects the vertical meridian.
    - Greater than one quadrant but less than a complete vertical hemifield.

11. **Partial Peripheral Rim (PPR)** - Generally continuous field loss outside 15 degrees.
    - Not in all quadrants.
    - Must have some curvature.

12. **Peripheral Rim (PR)** - Generally continuous visual field loss outside 15 degrees in all four quadrants.
    - Usually no visual field loss inside 15 degrees on either deviation plot.
    - Must be visual field loss temporal to the blind spot.

13. **Quadrant (Q)** - Significant visual field loss throughout an entire quadrant that respects the vertical and horizontal midlines.
    - Essentially all points must have a \( p < 5\% \) value on the Total Deviation Plot.

14. **Superior Depression (SD)** - Two or more abnormal points in the very superior region.

15. **Total Loss (TL)** - Severe widespread visual field loss (MD \( \leq -20.00 \) dB).

16. **Vertical Step (VS)** - Limited visual field loss that respects the vertical meridian.
    - Includes at least two abnormal points at or outside 15 degrees along the vertical meridian.

17. **Widespread (Wsp)** - Diffuse visual field loss that includes all four quadrants.
    - The GHT may show a General Reduction of Sensitivity or the MD must show \( p < 5\% \).
    - The PSD and CPSD must not show a \( p < 5\% \) value.
    - The majority of abnormal points on the Total Deviation Plot are not abnormal on the Pattern Deviation Plot.
VISUAL FIELD READING CENTER

Perimetry Protocol
for the
Ocular Hypertension Treatment Study II (OHTS II)

September 2002

Department of Ophthalmology
School of Medicine
University of California, Davis
Perimetry Table of Contents

I. INTRODUCTION

Patient Visit Timetable

II. VISUAL FIELD TEST PROCEDURES

General Test Guidelines

Determining the Appropriate Refraction

Preparing the Patient

Performing the Over-Refraction Procedure

Entering Patient Data

Proceeding with the Test

Saving the Results

Repeating Visual Field Tests

III. TRANSMISSION OF THE VISUAL FIELDS TO THE VFRC

IV. CERTIFICATION PROCEDURES

Certification Tests

V. VISUAL FIELD ABNORMALITY CLASSIFICATION
Visual Field Reading Center
PERIMETRY PROTOCOL
for the
OCULAR HYPERTENSION TREATMENT STUDY II (OHTS II)

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. To analyze visual field changes and/or progression, automated static perimetry will be performed on OHTS II participants using the full threshold 30-2 test pattern on the Humphrey Visual Field Analyzer (HFA).

Patient Visit Timetable

Visual field testing will consist of Humphrey tests of the central 30° field of both eyes. These tests will be performed at six-month intervals for the duration of the study.

II. Visual Field Testing Procedures

General Test Guidelines

Reduce the lighting in the room to a moderate level in order for the HFA to adapt to the background luminance. Perform the visual field test on each eye of a patient using the Full threshold 30-2 program and test the patient's right eye first. Use the following test parameters:

- Threshold strategy: Full threshold
- Fixation target: Central
- Stimulus size: III
- Stimulus color: White
- Test speed: Normal
- Foveal threshold: On
- Fluctuation: On
- FASTPAC: Off

Determining the Appropriate Refraction

Depending on the age of the patient, the refraction used at the bowl may be quite different from the patient's best-corrected distance Rx. Take the current distance Rx and add the amount of sphere indicated by Goldmann's Table (use the patient's birthdate to determine the patient's age, not the age on the Humphrey visual field printout). The only exception is if the eye was dilated with 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 required for the test is greater than ±6.00 D, have the patient wear soft contacts, if possible. If a patient 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 "naked eye" correction used for the test (i.e., the combined correction of the contact lens and the trial lens) into the patient data (see Entering Patient Data).

GOLDMANN'S TABLE

<table>
<thead>
<tr>
<th>Age</th>
<th>Add</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 44</td>
<td>+1.50 DS</td>
</tr>
<tr>
<td>45 - 49</td>
<td>+2.00 DS</td>
</tr>
<tr>
<td>50 - 54</td>
<td>+2.50 DS</td>
</tr>
<tr>
<td>55 and older</td>
<td>+3.00 DS</td>
</tr>
</tbody>
</table>

Examples:

1. Best-corrected distance Rx (41-year-old): OD -2.00 +2.00 x 120  
   OS -3.25 +0.75 x 090  
   Use: OD -0.50 +2.00 x 120  
   OS -1.50 DS

   2. Best-corrected distance Rx (53-year-old): OD +1.00 DS +0.25 +065  
      OS Plano +1.50 x 090  
      Use: OD +3.50 DS  
      OS +2.50 +1.50 x 090

Preparing the Patient

Measure the patient'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. If using a cycloplegic, use the full near correction (see Determining the Appropriate Refraction) and enter the letter N (for Neosynephrine) or C (for a cycloplegic) into the ID field after the Visit Code in the patient data screen (see Entering Patient Data below). If a patient 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 tested. If the brow is heavy or the upper lid is drooping, tape accordingly. Allow the patient to adapt to the bowl luminance for three minutes. During this time, familiarize the patient with the testing procedure (see Figure 1).
HUMPHREY PATIENT INSTRUCTIONS
- keep at your perimeter -

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

Figure 1

Adjust the chin rest and table height to align the pupil in the center of the eye monitor. Make sure the patient's forehead is against the head rest and that he or she is comfortable. Move the trial lens holder close to the patient's eye; however, make sure the patient's lashes do not touch the lens. Check again to see that the pupil is at the center of the lens. It is extremely important to reduce the possibility of trial lens rim artifact by having the lens as close to the patient's eye as possible (see Figure 2) and by aligning the pupil in the center of the lens (see Figure 3).

Proper Trial Lens Position
Figure 2
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. Place the trial lens (es) in the lens holder. Offer the patient a choice of half Diopter PLUS then offer a choice of half Diopter MINUS over the calculated spherical correction. Ask the patient 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 patient's responses, determine the proper lens correction.

Entering Patient Data

Load a pre-formatted floppy disk into the disk drive of the HFA. (Please do NOT use Imation™ brand disks as they are not compatible with the VFRC’s processing software.) Enter patient data as follows (see Figure 4):

<table>
<thead>
<tr>
<th>Humphrey Screen</th>
<th>Information Entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID ..................</td>
<td>Leave Blank</td>
</tr>
<tr>
<td>BIRTHDATE ........</td>
<td>MM-DD-YYYY</td>
</tr>
<tr>
<td>PUPIL DIAMETER...</td>
<td>RE: e.g., 4 mm</td>
</tr>
<tr>
<td>NAME ................</td>
<td></td>
</tr>
<tr>
<td>VISUAL ACUITY....</td>
<td>RE: e.g., 20/20</td>
</tr>
<tr>
<td>RX USED............</td>
<td>RE: (+ or -) ___ ___ DS (+ or -) ___ ___ DCX ___ ___ DEG</td>
</tr>
<tr>
<td>COMMENTS..........</td>
<td>Site Code, Tech Initials, Visit Code, Dilation</td>
</tr>
</tbody>
</table>
Your Site Code has two characters. It should be followed immediately by your (i.e., the technician's) initials and the code for the patient'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 84-month visit is 084, the 90-month visit code is 090, 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 G1JNS096 would be entered at clinical center G1 by technician John N. Smith at the patient's 096-month visit.

The Patient ID has eight characters: the first five are a unique number given by your clinical center to each potential study patient and the other three are the patient's initials (as for the technician's initials, three and three only). Be sure to distinguish between zeros and letter O's appropriately. The Patient 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 P0.00 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 Patient Data (unless it is the same as for the right eye). Example: 06007KEC-1.50P1.25X075

Enter three digits for each, 0.00 for plano.
Proceeding with the Test

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

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

![Initializing Gaze Failed Menu](image)

**Initializing Gaze Failed 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 and remind the patient to fixate at the target. If excessive fixation losses are again detected after the second try to locate the blind spot, just allow the patient to continue through to the end of the testing program.

The patient should be given 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. (Reminder: Imation™ brand 3.5” disks should not be used.) 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 test results at the completion of each test, and make a copy of each printout.

Repeating Visual Field Tests

After printing the visual fields, 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 patient 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 or sooner (if indicated by the VFRC) in order to test within the same visit window. An unreliable follow-up field should be repeated only once, even if the re-test is also unreliable. If the re-test is abnormal, whether reliable or not, and the first test was normal but unreliable, it will be considered an abnormal field, and you should wait until the next follow-up window to repeat the test. (see below)

If a reliable 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 reliable and 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 will decide if the abnormality is glaucomatous or non-glaucomatous and if the eye has reached a confirmed visual field abnormality. In some instances, senior readers may accept an abnormal visual field with one or more unreliability index flagged. This exception is recorded, and the abnormal, unreliable visual field is included in the series of three consecutive abnormal visual fields.

III. Transmission of the Visual Field to the VFRC

All OHTS II visual fields, including abnormal and unreliable ones, must be mailed to the VFRC within 21 days of testing. In addition, you must also immediately fax all abnormal and/or unreliable follow-up fields to the VFRC within 7 days of testing, as well as the required retests for these fields, even if they are normal. 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. Each shipment should include one Humphrey disk with the corresponding visual field printouts and a disk directory you have printed out. 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!

Be sure to attach a label to each Humphrey disk you send to the VFRC (see Figure 6). 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**

<table>
<thead>
<tr>
<th>HUMPHREY DISK</th>
<th>CLINICAL CENTER: _____</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAILING DATE:  / /</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 6**

The HFA disk must be enclosed in a protective disk mailer. Although the VFRC will periodically return disks and disk mailers to you, you will be responsible for purchasing and maintaining your own supply. You may enclose all of the visual field materials in the disk mailer; however, it is preferable to 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.

Finally, you need to keep copies of the OHTS II visual fields (i.e., two sets of floppy disks and one set of visual field 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. Technician Certification Procedures**

Each clinical center must have at least two visual field technicians certified for OHTS II perimetry. It is the responsibility of the P.I. at each clinical center to ensure that the appropriate personnel are competent in the OHTS II perimetry protocol. To obtain certification, a technician must demonstrate an understanding of the correct procedures for all aspects of the OHTS II visual field testing (see Figures 7a and 7b). The certification process involves a telephone session with a VFRC staff member after which the candidate must submit two sets of practice visual fields to the VFRC. The candidate for certification is recommended to study this manual and review the *OHTS II 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, 6077, or 6085.
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 staff member. After a satisfactory telephone session, the candidate must submit visual fields performed on both eyes of two subjects according to OHTS II 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 II 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 II 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 patient, such as the head and chin rest and chair;
- calculating the proper lens power from the distance refraction;
- adjusting the fixation monitor and resetting the fixation monitor later during the test;
- selecting the proper test parameters and entering patient data;
- running Program 30-2;
- being sensitive to patient fatigue -- allowing the patient to rest during the test;
- saving and printing the test data;
- making a back-up disk and copying visual field files onto another disk.
HUMPHREY FIELD ANALYZER
OHTS II CERTIFICATION EXAM

TECHNICIAN NAME: ___________________________________

CLINICAL CENTER: ________________________CODE:____

1. Initialize floppy disks

   YES  NO
   □    □

2. Measure pupil size

   YES  NO
   □    □

3. Adjust lens holder properly and align patient

   YES  NO
   □    □

4. Calculate lens correction

   YES  NO
   □    □

5. Perform refraction at the bowl

   YES  NO
   □    □

6. Select proper test parameters and enter patient data

   YES  NO
   □    □

7. Run 30-2 program with foveal threshold

   YES  NO
   □    □

8. Change gaze tracking initialization

   YES  NO
   □    □

9. Edit distance Rx in Name field between tests

   YES  NO
   □    □

10. Save test data on disk

    YES  NO
    □    □

11. Printout visual fields

    YES  NO
    □    □

12. Copy test data onto disk #3

    YES  NO
    □    □

13. Solve lens correction problems (Figure 7b)

    YES  NO
    □    □

Figure 7a
OHTS II CERTIFICATION EXAM
LENS CORRECTION CALCULATIONS

TECHNICIAN NAME: ___________________________________

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 +0.25 X120
   OS -0.75 +1.00 x 070

Calculated correction:
   OD: ____________________________
   OS: ____________________________

Figure 7b
V. Visual Field Abnormality Classification

The OHTS visual field abnormality classification system is on-going and is currently being used by the VFRC to classify all abnormal VFs as they are received. VFRC certified visual field readers classify the upper and lower hemifields separately as to the presence of abnormality that met the secondary definition (hemifields were not evaluated for the secondary definition of abnormality unless the visual field first met the OHTS criteria for abnormality). The secondary definition of abnormality is defined as: (a) A single point is worse than the 0.5% probability level on the Total and/or Pattern Deviation plots. (b) Two adjacent points (cluster) are beyond normal limits ($p < 5\%$), and at least one point is worse than the 1% level on the Total and/or Pattern Deviation plot. (A cluster is defined as two or more horizontally- or vertically-contiguous abnormal points with $p < 5\%$) and (c) Three or more clustered points are worse than the 5% level on the Total and/or Pattern Deviation plot and the pattern loss is consistent with ocular pathology. Thus, for a hemifield to be classified as normal, it must not meet any of the above criteria for hemifield abnormality. If the hemifield was classified as “abnormal,” the abnormality was further classified into one of the 17 mutually exclusive categories listed in Table 1. While more than one classification is possible for a hemifield, the most predominant defect was used for the final classification.

The procedures for hemifield classification are as follows: (1) The superior and inferior hemifields of visual fields that meet the OHTS abnormality criteria are evaluated separately, with the superior hemifield being classified first. Hemifield classifications are separated by a slash. If a defect straddles the horizontal midline, only a single designation is given and no slash is presented. (2) In general, the pattern on the deviation plot (“Total” or “Pattern”) showing the greater number of abnormal points is used to determine the appropriate classification for a hemifield abnormality. However, the other deviation plot, as well as the gray scale, is evaluated to confirm the appropriateness of the classification. Abnormal points that are extraneous to the salient pattern are considered less important for the determination of the hemifield classification. Thus, the most predominant pattern is classified.

Agreement between the readers is assessed by reporting whether none, two, or all three readers agreed on the classification of the hemifields. Thus, we report agreement among readers as the percent of hemifield classifications in which there was no agreement, agreement by two of three readers, and agreement by three of three readers. If at least two readers agreed with an abnormality classification, the majority classification was accepted (2 out of 3 readers in agreement). If all three readers disagreed, then the visual fields were adjudicated by group consensus to reach a final classification of the hemifield abnormality.
Table 1. OHTS Abnormality Classifications

<table>
<thead>
<tr>
<th>Nerve Fiber Bundle Abnormalities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Altitudinal (Alt) - Severe visual field loss throughout the entire superior or inferior hemifield that respects the horizontal midline.</td>
</tr>
<tr>
<td>• The majority of points in the hemifield have a $p &lt; 0.5%$ value on the total deviation plot.</td>
</tr>
<tr>
<td>• The entire horizontal midline demonstrates abnormality.</td>
</tr>
<tr>
<td>2. Arcuate (Arc) - Significant visual field loss in the nerve fiber bundle region.</td>
</tr>
<tr>
<td>• Extends across contiguous abnormal points from the blind spot to at least one point outside 15 degrees adjacent to the nasal meridian.</td>
</tr>
<tr>
<td>3. Nasal Step (NS) - Limited field loss adjacent to the nasal horizontal meridian.</td>
</tr>
<tr>
<td>• Includes at least one abnormal point at or outside 15 degrees on the meridian.</td>
</tr>
<tr>
<td>• Cannot include more than one significant point (on either plot) in the nerve fiber bundle region on the temporal side.</td>
</tr>
<tr>
<td>4. Paracentral (Pc) - A relatively small visual field abnormality in the nerve fiber bundle region.</td>
</tr>
<tr>
<td>• Generally not contiguous with the blind spot or the nasal meridian.</td>
</tr>
<tr>
<td>• Does not involve points outside 15 degrees that are adjacent to the nasal meridian.</td>
</tr>
<tr>
<td>5. Partial Arcuate (PArc) - Visual field loss in the nerve fiber bundle region that extends incompletely from the blind spot to the nasal meridian.</td>
</tr>
<tr>
<td>• The defect is generally contiguous with either the blind spot or the nasal meridian.</td>
</tr>
<tr>
<td>• Must include at least one abnormal location in the temporal visual field.</td>
</tr>
<tr>
<td>6. Temporal Wedge (TW) – A small visual field defect that is temporal to the blind spot.</td>
</tr>
</tbody>
</table>
### Non-Nerve Fiber Bundle Abnormalities:

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td><strong>Central (C)</strong> - Visual field loss that is predominantly in the macular region.</td>
<td>- The foveal threshold must have a $p &lt; 5%$ value.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Can be associated with a single hemi-field and paired with another defect.</td>
</tr>
<tr>
<td>8.</td>
<td><strong>Hemianopia (H)</strong> - A visual field defect that respects the vertical meridian.</td>
<td>- Involves essentially all points in a vertical hemifield.</td>
</tr>
<tr>
<td>9.</td>
<td><strong>Inferior Depression (ID)</strong> - Two or more abnormal points in the very inferior region.</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td><strong>Partial Hemianopia (PH)</strong> - A visual field defect that respects the vertical meridian.</td>
<td>- Greater than one quadrant but less than a complete vertical hemifield.</td>
</tr>
<tr>
<td>11.</td>
<td><strong>Partial Peripheral Rim (PPR)</strong> - Generally continuous field loss outside 15 degrees.</td>
<td>- Not in all quadrants.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Must have some curvature.</td>
</tr>
<tr>
<td>12.</td>
<td><strong>Peripheral Rim (PR)</strong> - Generally continuous visual field loss outside 15 degrees in all four quadrants.</td>
<td>- Usually no visual field loss inside 15 degrees on either deviation plot.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Must be visual field loss temporal to the blind spot.</td>
</tr>
<tr>
<td>13.</td>
<td><strong>Quadrant (Q)</strong> - Significant visual field loss throughout an entire quadrant that respects the vertical and horizontal midlines.</td>
<td>- Essentially all points must have a $p &lt; 5%$ value on the Total Deviation Plot.</td>
</tr>
<tr>
<td>14.</td>
<td><strong>Superior Depression (SD)</strong> - Two or more abnormal points in the very superior region.</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td><strong>Total Loss (TL)</strong> - Severe widespread visual field loss (MD ≤ -20.00 dB).</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td><strong>Vertical Step (VS)</strong> - Limited visual field loss that respects the vertical meridian.</td>
<td>- Includes at least two abnormal points at or outside 15 degrees along the vertical meridian.</td>
</tr>
<tr>
<td>17.</td>
<td><strong>Widespread (Wsp)</strong> - Diffuse visual field loss that includes all four quadrants.</td>
<td>- The GHT may show a General Reduction of Sensitivity or the MD must show $p &lt; 5%$.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The PSD and CPSD must not show a $p &lt; 5%$ value.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The majority of abnormal points on the Total Deviation Plot are not abnormal on the Pattern Deviation Plot.</td>
</tr>
</tbody>
</table>
16. Ancillary studies

Confocal Scanning Laser Ophthalmoscope (CSLO) .................................................. 16-2
CSLO HRT HEYEX Software Update ................................................................. 16-25
Short Wavelength Automated Perimetry (SWAP) ........................................ 16-51
Genetics Ancillary Testing .............................................................................. 16-59

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 II

Version 4

February 28, 2003

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# TABLE OF CONTENTS

1.0 INTRODUCTION ...................................................................................................... 16-4

2.0 USE OF TOPOGRAPHIC INFORMATION.......................................................... 16-4

3.0 INFORMED CONSENT AT THE RANDOMIZATION VISIT ......................... 16-5

4.0 PATIENT VISIT TIMETABLE .............................................................................. 16-5

5.0 INSTALLATION OF HRT SOFTWARE ............................................................... 16-5

5.1 HRT SOFTWARE VERSION 2.01 .......................................................................... 16-5

5.2 HRT HEYEX SOFTWARE VERSION 3.0.4 .......................................................... 16-5

6.0 OVERVIEW OF HRT OHTS II IMAGE ACQUISITION PROTOCOL ............ 16-5

7.0 IMAGE ACQUISITION PROTOCOL .................................................................... 16-7

7.1 PREPARATION ......................................................................................................... 16-7

7.1.1 PREPARING THE SYSTEM...........................................................................................16-7

7.1.2 PREPARING THE PATIENT .........................................................................................16-7

7.1.3 THE INFLUENCE OF PUPIL SIZE ..............................................................................16-7

7.2 CREATION OF A DATABASE ENTRY AND INPUT OF PATIENT DATA... 16-8

7.2.1 CREATING A NEW DATABASE ENTRY WITH NEW PATIENT DATA .......................16-8

7.2.2 DUPLICATING AN EXISTING DATABASE ENTRY FOR ALL OHTS II STUDY FOLLOW-UP VISITS ..................................................................................................................................................16-11

7.2.3 ADJUSTING THE CAMERA TO THE EYE BEING EXAMINED ..............................................16-11

7.3 IMAGE ACQUISITION AND MONITORING.................................................... 16-12

8.0 ARCHIVING ............................................................................................................ 16-13

8.1 ARCHIVING MEDIA.............................................................................................. 16-14

8.2 BACKUP COPY OF THE DATABASE .................................................................... 16-14

8.3 ARCHIVING IMAGES ........................................................................................... 16-15

8.4 DELETING ARCHIVED IMAGES FROM THE HARD DRIVE ...................... 16-15

8.5 RETRIEVING ARCHIVED IMAGES ONTO THE HARD DRIVE .................. 16-16

9.0 TRANSFER OF EXAMINATIONS TO THE CSLORC .............................. 16-16

9.1 PRINT LIST FOR CHECKING DATA COMPLETENESS AT THE CSLORC 16-16

9.2 EXPORTING IMAGES FOR TRANSFER TO THE CSLORC .................. 16-17

10.0 CERTIFICATION PROCEDURES....................................................................... 16-18

APPENDIX A - INSPECTION OF IMAGE SERIES FOR QUALITY CONTROL..... 16-19

A.1 INSPECTION OF THE 3D IMAGE SERIES FOR BRIGHTNESS.............. 16-19

A.2 INSPECTION OF THE 3D IMAGE SERIES FOR AXIAL LOCATION AND SCAN DEPTH ................................................................. 16-20

A.3 INSPECTION OF THE 3D IMAGE SERIES FOR EYE MOVEMENT AND BLINKS................................................................. 16-21

A.4 INSPECTION OF THE 3D IMAGE SERIES FOR FRAMING .................... 16-22

APPENDIX B - LETTER OF AGREEMENT ......................................................... 16-23

APPENDIX C - IMAGE ACQUISITION LOG ......................................................... 16-24
1.0 INTRODUCTION

This manual contains specific information regarding image acquisition and processing for the OHTS II Study. The protocol for CSLO Image Acquisition for OHTS II is the same as completed during OHTS. Changes in the Manual of Procedures reflect computing updates and or revisions to improve clarity.

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 is based on sections of the Heidelberg Retina Tomograph (HRT) Operation Manual (Software Version 2.01) that are relevant to image acquisition, archiving, backing-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. Certified operators should be familiar with all aspects of the HRT Operation Manual provided with the HRT by Heidelberg Engineering. In addition, please refer to the CSLO Reading Center Quality Control Manual (distributed in May 2000). This manual provides suggestions on how to improve image quality at the acquisition phase.

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 II trial by jeopardizing recruitment, retention, and implementation of the primary trial or assessment of the primary findings. Patients can be shown their optic disc images on the video monitor, if they are interested. However, no additional 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 them 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 CSLO Ancillary Study 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 OHTS II 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 II patients, both in written form and verbally, that the HRT procedures are entirely voluntary and are independent of the decision to participate in OHTS II. To insure that there is no confusion between agreeing to participate in OHTS II and agreeing to participate in the ancillary testing, informed consent for HRT imaging is to be obtained after subjects have provided informed consent for OHTS II. 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 II, does not affect their treatment or quality of care, and they can withdraw from the ancillary study at any time without risk to their participation in OHTS II.

4.0 PATIENT VISIT TIMETABLE

Annual examinations will be completed with pupil dilation at the same annual visits when stereophotographs are taken.

5.0 INSTALLATION OF HRT SOFTWARE

All OHTS II images will be processed using HRT Operation Software Release 2.01/OHTS or the HRT HEYEX software 3.0.4 or higher. All sites should continue to use their established OHTS HRT database. If your site is upgrading to the HRT HEYEX software see the HEYEX version of the HRT OHTS II protocol located as an appendix at the end of this chapter.

5.1 HRT SOFTWARE VERSION 2.01

A separate OHTS database in its own directory (C:\OHTS) is used to facilitate maintenance of the integrity of the images and data. An OHTS specific config.sys file was created upon installation of Operation Software Release 2.01/OHTS The HRT CSLO database used for the OHTS study should continue to be used for the OHTS II study.

5.2 HRT HEYEX SOFTWARE VERSION 3.0.4

If your HRT has been upgraded to the HEYEX software 3.0.4 or higher please contact the CSLO Reading Center and see the HEYEX version of the HRT OHTS II protocol located as an appendix at the end of this chapter.

6.0 OVERVIEW OF HRT OHTS II 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.

7. Obtain k-values (keratometry readings) at the baseline visit. If the patient undergoes intraocular surgery, then a new “baseline” k-value should be obtained at least three months post-operatively.

8. 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)

9. Obtain all OHTS II 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 II HRT Image Acquisition Log (Appendix C).

21. Repeat Steps 16 to 20 to obtain 3 good quality images at 15 degrees (at the same scan depth) of the right eye.

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” 3.5 floppy disk) of eligible 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 follow-up examinations of this patient 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.

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. 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 II 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

No new entries need to be made for OHTS II patients as they should already exist in the OHTS database. Follow-up examinations should be completed for all OHTS II patients. Skip to section 7.2.2.

For all OHTS 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 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' field). 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 II 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 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 switch 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

Last Name: _______________ Enter "#" then OHTS Patient ID
First Name: ____________________ Patient initials (3 required)
Date of Birth: ________________ mm/dd/yyyy
Patient Number ________________ Enter OHTS Patient ID (8 digits: 4 digit investigator number + 3 initials)
Sex: ___M ___F Click on appropriate box
Ancestry:____________________ Scroll for appropriate response
Operator: _____________________ Enter your 3 initials
Eye Examined: ___Right ___Left 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
Cylinder: _________________0. dpt. Enter value for last test refraction
Axis: _________________ Enter value for last test refraction
Pupil ∅ (Size): ________________ Record to nearest millimeter
Corrective Lenses:_____________ Scroll for appropriate response
Classification:______________ Enter Code for Patient's Visit
Remarks:_______________________ Leave Blank

1. The OHTS Patient ID ("#" and 5 digits + 3 letters): The five digit Patient ID number assigned by OHTS, followed by the patient's 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 II visit - this will usually be at the yearly 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 II 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 II STUDY FOLLOW-UP VISITS

If the patient has been examined before for OHTS, 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 the information 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 that 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 examination of the patient in each case. The data of the selected previous examination 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, 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 Operation Panel of the patient's previous examination. It is recommended to preset the Operation 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 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 that 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 images 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 headrest 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 (about a thumb’s width). 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 red 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

1. Ask the patient not to blink 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.

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 needs 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.
3. If the quality of the image series is acceptable, 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.

4. In order to examine the images for eye movement, select the 'Display' sub-menu and 'Movie' menu item. All 32 images will be displayed 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 disc 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 or the image moved out of the frame you should repeat image acquisition (continue at Section 7.2.3, Step 3). Halt the display of the images by pressing any key.

5. If the quality of the image series is perfect and no excessive eye movements are present, store the series on the computer's hard drive. To do this, select the 'Save Series' menu item. Continue with Step 7.2.3 until you have stored at least three image series per eye.

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 for future examinations. This procedure is described in Chapter 6 of the Heidelberg Retina Tomograph Operation Manual (version 2.01). It is recommended that HRT operators review these sections of the HRT operation manual.
8.1 ARCHIVING MEDIA

Optical disks are used to archive data from 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 'OK'. 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. The number is assigned per disk side. Write this number on the side of the disk that has just been prepared. This is used to locate the images stored on the disk later on.
4. Now insert the other side of the disk that has just been prepared into the drive, and repeat Steps 1 through 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 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 onto 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 Heidelberg Service Office for your area or contact the CSLORC and they can direct you to the appropriate person.
8.3 ARCHIVING IMAGES

The three-dimensional images, aligned images, topograph images, 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 onto optical or magneto-optical disks. This is accomplished as follows:

1. In the Main Menu, select the 'Database' menu and choose 'Archive Images'.

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 type that you would like to archive. 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. Choose 'Archive' to start the archiving.

5. You are asked to insert an optical disk into the disk drive. Confirm by selecting 'OK'. The archiving process will start. During 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 choose 'Delete'.

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 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 'Delete' 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 'All' in order to delete the displayed image as well as all other images that are marked for deletion but are not archived. Select 'Skip' to keep the displayed image on the hard drive.
8.5  RETRIEVING ARCHIVED IMAGES ONTO 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 onto the computer's hard drive. This is accomplished as follows:

1. In the Main Menu, select 'Database' and choose 'Retrieve Images'.
2. A selection mask appears, as described above under 'Archiving'. Select the type of images and the examinations to be retrieved.
3. Select 'Retrieve' to copy the images onto the hard drive.
4. You are asked to insert an optical disk with a specified number into the disk drive. Confirm by selecting 'OK' after inserting the correct disk. 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 II images will be sent on optical disks by Federal Express, along with the corresponding HRT Image Acquisition Logs, to the CSLORC (Confocal Scanning Laser Ophthalmoscopy 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 a 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 be exported onto an optical disk. Please do not send images until your Print List has been reviewed and you have received confirmation from the CSLORC. Instructions for sending a print list file are as follows:

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 "Database". Choose "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 the desired date in the 'Search Options' found at the bottom of the menu. (e.g. Since: 1/1/1997 Before: 4/1/1997 then select "Search")

   **NOTE:** If there are extra images or images that do not meet OHTS II image quality standards de-select these before hitting "Load". The CSLORC only needs 9 images: 3 OD at 15 degrees, 3 OD at 10 degrees, and 3 OS at 10 degrees.

4. Select "Load".

Version 4.0 3/10/03
5. In the software Main Menu, select "Database". Choose "Print List". A box appears that is labeled, “Print Data”.

6. In the box labeled, ‘File’, type "a:Print" followed by your two-digit investigator ID# (e.g. a:PrintS1). (Caution to DOS users: do not insert a space after the colon.) Make sure the ‘File’ box and the ‘Append’ box are highlighted in red. Then 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. The file name should appear.

7. Send Print List on a 3.5" diskette to the CSLORC for approval. Once the Print List is approved by the CSLORC, images can be exported.

9.2 EXPORTING IMAGES FOR TRANSFER TO THE CSLORC

To transfer OHTS II patient images to an optical diskette, a separate program, ExportOHTS must be used. This transfers complete examinations (patient information, acquired images, measurement results) between databases.

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**EXPORTING IMAGES**

1. In the OHTS HRT database, retrieve all the necessary images onto the hard drive (see section 8.5 for directions on how to retrieve images).

2. For quick results type desired date in the ‘Search Options’ box found at the bottom of ‘Retrieve’ page. (e.g. Since: 3/1/1997 Before: 5/30/1997 then select “Search”)

3. Once all desired images are on the hard drive, quit out of OHTS HRT database.

4. Double click the ‘ExportOHTS’ icon located on your desktop within the "Export Apps" folder. For DOS based users, at the DOS prompt type: “ExportOHTS”.

5. A new main menu will appear with the following headings: Database, Info, Quit - Select “Database” and then choose “Export Entries”.

6. Choose "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 in red - this tells the CSLORC which site the images came from by changing the Patient ID# to the Site ID#.

9. Highlight images, then choose “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 process.
10.0 CERTIFICATION PROCEDURES

All technicians who were certified for OHTS will automatically be certified for OHTS II. 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 II 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 II HRT protocol. To obtain certification, a technician must demonstrate an understanding of the correct procedures for all aspects of HRT image acquisition and processing.

The certification process includes a telephone session with a CSLORC coordinator. The candidate for certification should study the OHTS II 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 be sent), and nine images obtained on each of two non-study patients. For each non-study patient, submit three 15-degree images and three 10-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 II HRT images on a regular basis.

To become certified for OHTS II 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
- identifying image quality problems e.g. framing
- saving the image data, archiving images and making back-ups of the 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 and how to improve image series). Before the telephone interview, make sure your site has a certification CD (contains mock HRT image series) and the images can be viewed on a PC. If the site does not have this CD, contact the CSLORC.

APPENDIX A - INSPECTION OF IMAGE SERIES FOR QUALITY CONTROL

A.1 INSPECTION OF THE 3D IMAGE SERIES 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, images which appear slightly too bright are more acceptable than those appearing too dark.

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:
   • The first four images of the series should appear dark.
   • The last four images of the series should appear dark.
   • All other images should appear more or less bright.
   • In the middle images, the retina should appear bright.

   NOTE: The first and the last images of a series will never appear completely black under normal circumstances. A dark image means that the first/last four images appear obviously darker than the following/preceding images.

2. If there are no images with bright colors either the adjustment of the laser scanning camera was not properly centered in the pupil, or the sensitivity of the light detector was set too low. The series must be recorded again; continue with Section 7.2.3, Step 1.

3. If the series contains images with large solid white fields with read and blue dots, 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 again; continue with Section 7.2.3, Step 1.
**A.2 INSPECTION OF THE 3D IMAGE SERIES 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 focal plane (which determines the axial location of the 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.

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 too negative; 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.

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 too positive; 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.

3. If the image series begins with too many dark images:
   The location of the first focal plane of the image series was too positive; 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.

4. If the image series ends with too many dark images:
   The location of the first focal plane of the image series was too negative; 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.

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.

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 32 image series by approximately 2 images.
- 0.5 mm increase/decrease of the total scan depth compresses/expands the 32 image series by approximately 4 images 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.

<table>
<thead>
<tr>
<th>Series begins with…</th>
<th>Series ends with…</th>
<th>Set focal plane to…</th>
<th>Set scan depth to…</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 4 dark images</td>
<td>= 4 dark images</td>
<td>more negative</td>
<td>higher value</td>
</tr>
<tr>
<td>= 4 dark images</td>
<td>&lt; 4 dark images</td>
<td>more negative</td>
<td>higher value</td>
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<td>more positive</td>
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<td>&lt; 4 dark images</td>
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<td>&lt; 4 dark images</td>
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</tr>
<tr>
<td>&gt; 4 dark images</td>
<td>&gt; 4 dark images</td>
<td>more negative</td>
<td>smaller value</td>
</tr>
</tbody>
</table>

**A.3 INSPECTION OF THE 3D IMAGE SERIES FOR EYE MOVEMENT 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.

1. Display a movie by selecting “Movie” in the Image Acquisition menu. This displays the 32 images of the series one after the other (press any key to stop the movie).

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 image processing. If strong movements of a quarter of the image size or more occur, the series has to be rejected and recorded again; continue with Section 7.2.3, Step 1.

3. If a sudden change in the brightness of the images occurs; the patient blinked during the image acquisition period. The series must be recorded again; continue with Section 7.2.3, Step 1.
A.4 INSPECTION OF THE 3D 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 prevent framing during image acquisition.

1. Framed images should be re-taken after adjustment of the distance and/or alignment of the HRT laser within 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 patient’s 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.

2. Framing is also a common problem when using corrective lenses (glasses or a 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 ACQUISITION LOG

<table>
<thead>
<tr>
<th>OHTS Site ID:</th>
<th>Operator Initials:</th>
</tr>
</thead>
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<tr>
<td>OHTS Patient ID:</td>
<td>Date:</td>
</tr>
<tr>
<td>Visit Code:</td>
<td>Consent Date:</td>
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</tbody>
</table>

### Patient Information

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<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pupil Size</td>
<td>mm</td>
</tr>
<tr>
<td>2</td>
<td>Corrective Lenses Used</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>q Glasses</td>
<td>q Glasses</td>
</tr>
<tr>
<td></td>
<td>q Contacts</td>
<td>q Contacts</td>
</tr>
<tr>
<td></td>
<td>q Trial Lens</td>
<td>q Trial Lens</td>
</tr>
<tr>
<td>3</td>
<td>Clear Media (Lens and Cornea)</td>
<td>YES</td>
</tr>
<tr>
<td>4</td>
<td>Patient Able to Fixate</td>
<td>YES</td>
</tr>
</tbody>
</table>

### Quality Control

<table>
<thead>
<tr>
<th></th>
<th>OD 15º</th>
<th>OD 10º</th>
<th>OS 10º</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Optic Nerve Centered</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>(&lt;1/4 of disc outside of target circle)</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>2</td>
<td>All images obtained at identical and</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>appropriate scan depth</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>3</td>
<td>Movie has minimal movement</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>4</td>
<td>No floaters over optic disk</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>5</td>
<td>Image sharp and clear (appearance of</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>blood vessels, optic disc, and retina)</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>6</td>
<td>Appropriate dark/light/dark pattern</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>of the 32 optical sections</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td>7</td>
<td>Quality control software says &quot;OK&quot;</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>*If not, specify all depths and focuses</td>
<td>1 2 3 1 2 3</td>
<td>1 2 3 1 2 3</td>
</tr>
<tr>
<td></td>
<td>attempted for each eye and angle</td>
<td>Depths Attempted:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Focuses Attempted:</td>
<td></td>
</tr>
</tbody>
</table>

### 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*
HRT HEYEX Software Update for OHTS II

Heidelberg Retina Tomograph Manual of Procedures for OHTS II

Version 2.0

February 28, 2003

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# TABLE OF CONTENTS

1. **INTRODUCTION** ........................................................................................................... 16-27
2. **CHECKING THE INSTALLED HEYEX SOFTWARE** ........................................... 16-27
3. **OVERVIEW OF HRT IMAGE ACQUISITION PROTOCOL** ............................... 16-28
4. CREATING A DATABASE ENTRY AND INPUTTING PATIENT DATA .... 16-29
   4.1 CREATING A NEW DATABASE ENTRY WITH NEW PATIENT DATA.... 16-29
   4.2 ENTERING PATIENT DATA FOR A FOLLOW-UP VISIT ........................ 16-31
5. **IMAGE ACQUISITION** ............................................................................................... 16-32
   5.1 THE INFLUENCE OF PUPIL SIZE ........................................................................... 16-32
   5.2 SITUATING THE PATIENT AND ACQUIRING IMAGES ....................... 16-33
6. **CREATING A BATCH PRINTLIST TO SEND TO THE CSLORC** ................ 16-36
7. **OPTICAL DISKS** ........................................................................................................ 16-38
   7.1 FORMATTING OPTICAL DISKS .............................................................................. 16-38
   7.2 LABELING OPTICAL DISKS .................................................................................... 16-39
8. **ARCHIVING/BACKING UP AND RETRIEVING/DELETING IMAGE SERIES** .......... 16-39
   8.1 ARCHIVING AND BACKING UP IMAGE SERIES ............................................ 16-39
   8.2 DELETING ARCHIVED IMAGES FROM THE HARD DRIVE ....................... 16-40
   8.3 RETRIEVING ARCHIVED IMAGES ONTO THE HARD DRIVE ............... 16-40
   8.3.1 BATCH RETRIEVING ......................................................................................... 16-40
   8.3.2 RETRIEVING A SINGLE IMAGE ....................................................................... 16-42
9. **EXPORTING IMAGES TO THE CSLORC** ............................................................ 16-42
10. **CERTIFICATION PROCEDURES** ........................................................................ 16-44
11. **INSPECTION OF IMAGE SERIES FOR QUALITY CONTROL** .................... 16-46
   11.1 DARK-LIGHT-DARK PATTERN ............................................................................. 16-46
   11.2 FOCUS AND SCAN DEPTH ................................................................................... 16-47
   11.3 EYE MOVEMENT AND BLINKS .......................................................................... 16-49
   11.4 FRAMING .............................................................................................................. 16-49
   11.5 FLOATERS ............................................................................................................. 16-50
   11.6 VESSEL DOUBLING .............................................................................................. 16-50
INTRODUCTION

Confocal Scanning Laser Ophthalmoscopy is a technique that 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 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 OHTS. This manual is based on sections of the Heidelberg Retina Tomograph Operating Instructions (Software Version 3.0.4 or higher) that are relevant to image acquisition, archiving, backing-up, data exporting and transfer. This manual should be used in conjunction with the HEYEX HRT Operating Instructions and Operation Software Release Updates, but should not replace it. Certified operators should be familiar with all aspects of the HRT Operation Manual provided with the HRT by Heidelberg Engineering.

CHECKING THE INSTALLED HEYEX SOFTWARE

After the HEYEX software is correctly installed, under Start-Settings-Control Panel-Add/Remove Programs, the following items should be listed:

- Heidelberg Eye Explorer
- Heidelberg Eye Explorer License Manager
- Heidelberg Retina Tomograph
- PCimage-SG/SGVS

If these titles are not present, contact a Heidelberg representative or the CSLORC.
OVERVIEW OF HRT IMAGE ACQUISITION PROTOCOL

(1) All examinations must be completed by certified personnel.

(2) Ensure that pupil size template is attached to forehead rest.

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

(4) Obtain k-values (keratometry readings) at the **first visit only**. Use this k-value throughout the duration of the study. Only if the patient undergoes intraocular surgery should a new “baseline” k-value be obtained three months post-operatively.

(5) Glasses and contact lenses should be removed for HRT examination unless the patient has astigmatism > 1.0 diopter. If corrective lenses are used for the first visit, they should be used for all follow-up visits.

(6) Obtain all images in the separate OHTS database/directory by **double clicking** the OHTS icon on your desktop.

(7) Enter patient information accurately.

(8) Obtain 3 images using a 15-degree field for the right eye only. Then obtain 3 images of both eyes using a 10-degree field (for a total of 9 images per visit).

(9) Set field of view to 15 degrees for imaging right eye.

(10) Set intensity to maximum.

(11) Record pupil size while laser is focused on pupil.

(12) Obtain image.

(13) Review 32 image series for quality and review movie for eye movement.

(14) Save series image. **(Do NOT do any further processing until SERIES images have been exported and sent to the CSLO Reading Center.)**

(15) Repeat steps 10-14 to obtain 3 good quality images at 15 degrees (at the same scan depth) and 3 good quality images at 10 degrees (at the same scan depth) of the right eye.

(16) Repeat steps 4-14 to obtain 3 good quality images at 10 degrees (at the same scan depth) of the left eye.

(17) Check to make sure the correct number of images has been acquired. Delete any extra series images.
(18) Complete OHTS HRT Image Acquisition Log.

(19) After deleting any extra images, archive/backup image series on optical diskette.

(20) At the beginning of each quarter send printlist, and upon the CSLORC’s request, export 3D-Series images to an optical disk and send to the CSLORC.

**NOTE:** No topographies or means should be computed before creating a printlist or before exporting images to the CSLORC.

**CREATING A DATABASE ENTRY AND INPUTTING PATIENT DATA**

Prior to acquiring the images of a new patient, it is necessary to create a new database entry by entering the data for a new patient and eye.

**CREATING A NEW DATABASE ENTRY WITH NEW PATIENT DATA**

(1) To create a new patient, click on the New Patient symbol in the toolbar or select Record in the main tool bar and choose New Patient. A dialog box will appear. For this study, patient data must be entered according to the OHTS II standard protocol under the Patient Data tab. Fill in the patient information as shown in Figure 4.1. Then select OK.

**NOTE:** The HRT HEYEX software is case sensitive. Make sure the patient initials are ALWAYS in capital letters so no duplicate patient entries are created.

**FIGURE 4.1:** Enter the following in the Patient Data screen:

<table>
<thead>
<tr>
<th>Field</th>
<th>Formula/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last:</td>
<td>Enter “#” + 5 digit ID (2 digit site ID + 3 digit Patient ID) + 3 patient initials¹</td>
</tr>
<tr>
<td>First:</td>
<td>Patient initials (3 characters)¹</td>
</tr>
<tr>
<td>Title:</td>
<td>Leave blank</td>
</tr>
<tr>
<td>Date of Birth:</td>
<td>Mm/dd/yyyy</td>
</tr>
<tr>
<td>Sex:</td>
<td>Click on appropriate box</td>
</tr>
<tr>
<td>Patient ID:</td>
<td>Enter 5 digit ID (2 digit site ID + 3 digit Patient ID) + 3 patient initials¹</td>
</tr>
</tbody>
</table>

¹ If patient has no middle name, use an “X”.
(2) After creating a new patient record, another dialog box will appear to set up a new examination. The box is titled “Examination Data”. Fill in the information for this screen as shown in Figure 4.2 below. Then select OK.

**FIGURE 4.2: Enter the following in the Examination Data screen:**

- **Device type:** Heidelberg Retina Tomograph II ΔV
- **Operator:** ________________ Enter your 3 initials¹
- **Study:** ____________________ Leave blank

¹Operator initials: 3 are required. If there is no middle name, use an “X”.

(3) After filling out the examination data, a new dialog box named “Eye Data” will appear. You may enter parameters for both eyes. Note that a value for corneal curvature is mandatory because it affects the absolute scaling of the data determined from the acquired images. Do not enter negative values for this field. See Figure 4.3 below for inputting data into the “Eye Data” screen. Then select OK.

**FIGURE 4.3: Enter the following in the Eye Data screen:**

- **C-Curve [mm]:** ________________ Enter mean k-value (in millimeters)¹
- **Refraction [dpt]:** ________________ Enter value for last test refraction²
- **Cylinder [dpt]:** ________________ Enter value for last test refraction²
- **Axis [deg]:** ________________ Enter value for last test refraction²
- **Pupil size [mm]:** ________________ Record to nearest millimeter³
- **IOP [mmHg]:** ________________ Leave blank
- **VField Mean:** ________________ Leave blank
- **VField Var:** ________________ Leave blank
- **Corrective Lens Glasses [dpt]:** ______
- **Corrective Lens Astig. Lenses [dpt]:** ______
- **Corrective Lens Contact Lens [dpt]:** ______
- **Contact Lens Type:** ______

¹Use the K-values from the baseline visit. Only if the patient undergoes intraocular surgery should a new k-value be obtained.
²Obtain refraction from current visit - this will usually be at the yearly visit. Enter a ‘+’ or ‘-‘ and three digits for each, 0.00 for plano (e.g. -1.25 Sphere Refraction, +0.50 cylinder, 180 Axis).
³Record pupil size to the nearest millimeter diameter that most closely matches pupil gauge size on template attached to forehead rest.
⁴Corrective lenses should be worn during image acquisition due to astigmatism only when cylinder is > 1 diopter.
ENTERING PATIENT DATA FOR A FOLLOW-UP VISIT

(1) If you want to perform a follow-up examination of a patient that already exists in the database, select the desired patient from the patient list and click on the New Examination tool bar button or right click with the mouse on the highlighted patient and select New Examination from the pop up menu.

(2) A dialog box titled “Examination Data” will appear to set up a new examination. Fill in the information for this screen as shown in Figure 4.4 below. Then select OK.

**FIGURE 4.4: Enter the following in the Examination Data screen:**

| Device type: Heidelberg Retina Tomograph II ΔV | Heidelberg Retina Tomograph is the default |
| Operator: ______________________ | Enter your 3 initials¹ |
| Study: ______________________ | Leave blank |

¹Operator initials: 3 are required. If there is no middle name, use an “X”.

(3) After filling out the examination data, a new dialog box named “Eye Data” will appear. You may enter parameters for the appropriate eye. Note that a value for corneal curvature is mandatory because it affects the absolute scaling of the data determined from the acquired images. Do not enter negative values for this field. See Figure 4.5 below for inputting data into the “Eye Data” screen. Then select OK.
FIGURE 4.5: Enter the following in the Eye Data screen for appropriate study eye:

- C-Curve [mm]: _______________ Enter mean k-value (in millimeters)\(^1\)
- Refraction [dpt]: _______________ Enter value for last test refraction\(^2\)
- Cylinder [dpt]: _______________ Enter value for last test refraction\(^2\)
- Axis [deg]: _______________ Enter value for last test refraction\(^2\)
- Pupil size [mm]: _______________ Record to nearest millimeter\(^3\)
- IOP [mmHg]: _______________ Leave Blank
- VFieldMean: _______________ Leave Blank
- VFieldVar: _______________ Leave Blank
- Corrective Lens Glasses [dpt]: ______
- Astig. Lenses [dpt]: ______ Mark “Astig. Lenses” if Trial Lenses are used.
- Contact Lens [dpt]: ______
- Contact Lens Type: ______ V

\(^1\) Use the k-values from the baseline visit. Only if the patient undergoes intraocular surgery should a new k-value be obtained.
\(^2\) Obtain refraction from current visit - this will usually be at the yearly visit. Enter a ‘+’ or ‘-’ and three digits for each, 0.00 for plano (e.g. -1.25 Sphere Refraction, +0.50 cylinder, 180 Axis).
\(^3\) Record pupil size to the nearest millimeter diameter that most closely matches pupil gauge size on template attached to forehead rest
\(^4\) Corrective lenses should be worn during image acquisition due to astigmatism only when cylinder is > 1 diopter.

IMAGE ACQUISITION

THE INFLUENCE OF PUPIL SIZE

Under normal circumstances, during an examination the pupil of the eye 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, 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 a dilation of the pupil is recommended.

For OHTS II, all images will be obtained with pharmacologically dilated pupils > 3 mm in diameter. Pupil size will be recorded while the laser is focused on the pupil. After all images are
acquired, you must go back and add pupil size by *right clicking* on each series image icon and *choosing change parameters*.

### SITUATING THE PATIENT AND ACQUIRING IMAGES

1. Before situating the patient in the headrest, determine if he/she has astigmatism >1 diopter. If so, the image series should be taken with corrective lenses (trial lenses, glasses or hard contacts). Tilt glasses downward to prevent a reflection on the image screen.

   **NOTE:** If corrective lenses are used for the first visit, they should be used for ALL follow-up visits throughout the study.

2. Select the following settings for acquiring images: focal plane to the refraction of the examined eye (spherical equivalent), and scan depth to 2.5mm. Set the size of the field of view to 15 degrees to obtain images of the 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.

3. Ask the patient to position their head and chin firmly against the headrest 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.

4. 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 center of the pupil to be examined. 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 the optic nerve is visible on the screen.

5. Record pupil size while the laser is focused on the pupil.

6. The distance between the front edge of the objective tube and the examined eye must be no more than 15 mm (about a thumb’s width). 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.

(7) 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 red and blue dots inside the image.

(8) For the fine adjustment of the image, move the camera so that the optic nerve 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. 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.

(9) Ask the patient not to blink 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 acquisition, the 32 images are shown on the screen.

(10) The acquired series of images is automatically monitored for quality. If the position of the focal plane, the scan depth, or the detector sensitivity needs 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. 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 Section 11. Also see the “CSLO Reading Center HRT Image Quality Control Guidelines” for further image quality details.

(11) If the quality of the image series is acceptable, you will receive the quality control message, “Image series ok. Inspect series for eye movements.” If the image needs to be retaken, push the freeze button on the operation panel. When the computer asks if you want to save the image series before taking a new image, click No. After re-setting the relevant parameters as the quality control suggested, note your attempts to obtain a good quality image on the OHTS Image Acquisition Log.
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 Section 11 of this manual 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.

(12) In acquisition mode, to examine the images for eye movement, go to Display and Show Movie. All 32 images will be displayed on the right side and the movie will be displayed on the left. Halt the display of the images by clicking on the button below the movie image. Quite small eye movements of up to one quarter of the disc size are acceptable. (These will be automatically corrected during subsequent processing of the images.) If large or frequent eye movements are present or the image moved out of the frame you should retake the image. If the quality of the image series is acceptable and no excessive eye movements are present, store the series on the computer’s hard drive. To do this, select Save Series.

(13) If an image series is saved and you decide it should be deleted due to poor quality, click on the series image icon to highlight, right click and choose Delete. You will be asked if you are sure you want the image to be deleted, select Yes. Keep in mind images that have been archived cannot be deleted.

Note: Do NOT do any further computing of the series images until they have been exported and sent to the CSLO Reading Center. When asked if you would like to compute topographies now, select NO.

(14) Continue with the above steps until you have stored at least three image series at 15 degrees and 3 series at 10 degrees.

(15) To examine the patient's left eye, select the second eye in the OS/OD selection field on the screen, and repeat the steps above.
(16) After all images are acquired for the patient, you must go back and enter pupil size by right clicking on each series image icon and choosing change parameters.

(17) To quit the acquisition window:

a. Click on File then Exit in the toolbar or click on the x in the top right corner of the screen.

b. The message, “1 image series stored. Would you like to compute the topographies now?” will appear on the screen. Select No.

**NOTE:** At this time it is very important to check that you have acquired the correct number of images and to delete any extra images. All extra images need to be deleted before the images are archived. When you create a batch printlist and batch series export to send to the CSLO Reading Center, you will NOT have the option to choose the 9 best images. All series images archived will be exported. The study protocol states that ONLY 9 SERIES images are to be sent to the CSLORC.

(18) Fill out the OHTS Image Acquisition Log immediately after image acquisition.

(19) Once all extra images have been deleted, archive/backup image series on an optical diskette.

**CREATING A BATCH PRINTLIST TO SEND TO THE CSLORC**

Before transferring images (which is done on a quarterly basis), a printlist needs to be sent to the CSLORC. The printlist should contain all of the patient visit information entered for the quarter. Once the printlist has been reviewed and all requested corrections have been made, the CSLORC will request series images be exported onto an optical disk.

**NOTE:** Do NOT send images until the printlist has been approved and the CSLORC requests them.

The steps for creating a batch printlist are as follows:
(1) Review all patient visits for the quarter. Double check that there are only 9 images per visit per patient.

**NOTE:** When creating a batch printlist you will not have the option to select the images to be included in the printlist. All images saved on your hard drive (series, topographies and means) will be included. For this reason it is very important to delete any extra series images before creating a printlist and to only have series images (no topographies or means) on your hard drive.

(2) Label with your site ID and format a 3.5" floppy diskette. Insert the diskette into the A drive.

(3) In the Main Menu, click on **Database** and **Filter** (or click on the funnel icon to filter).

(4) A dialog box titled “Database Filter” will appear. In the “Examination” portion, click on the radio button, **Between**, and enter the dates for the appropriate quarter. For example, for quarter 4, enter 10/1/2002 and 12/31/2002. See figure 6.1.

**FIGURE 6.1**

![Database filter dialog box](image-url)
(5) Make sure the box is checked next to “Show only examinations within the patients that match to this filter” at the bottom of the dialog box (see figure 6.1). Then click OK. The patient visits you selected should now appear on the left side of the screen.

(6) Load patient visits by clicking on Record in the main menu and then select Load All (or you may also use the first icon with four circles to load all patients). This will add the selected patient visits to the right side of the screen.

(7) Right click on any patient on the right side of the screen. Click on HRT Batch, then Print List.

(8) A “Save As” dialogue box will appear. Save to the A drive and name the file PRNT and your site ID, for example “PRNTD1”. Click Save.

(9) Send the printlist diskette to the CSLORC at the beginning of each new quarter. Once you have received confirmation that all patient data is correct, images can be exported and sent along with the HRT Image Acquisition Logs.

OPTICAL DISKS

Optical disks are used to archive and export data from the HRT. Magneto-optical (MO) disks can be written on multiple times. The CSLORC is able to accept capacities of 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).

FORMATTING OPTICAL DISKS

Before archiving or exporting series images, follow the steps below to format the disk:

(1) Insert a new optical disk into the optical drive.

(2) Right click on the removable drive icon for the optical disk drive on the desktop and choose Format. (You may have to go into My Computer and find your disk drive icon there if it is not on the desktop.)

(3) Choose Full and click on Start.

(4) Choose OK to the warning of the drive being either a large hard disk or a removable disk.

(5) After formatting is complete, select Close and then OK.
(6) **Click** on the X to close out the Windows help screen.

(7) **Click** on Close.

(8) **Click** on the X to close the disk contents screen.

(9) Flip the disk over and repeat steps 2 through 8 for side B.

### LABELING OPTICAL DISKS

1. When a new optical disk is inserted into the HRT for archiving, a window appears that says, “An unknown disk has been inserted. Do you want to use it for archiving?”

2. **Click Yes**.

3. Then a new window appears that says, “Archive Disk name is: “HXD00001”. Label the disk for later usage!”

4. **Write this label number on the appropriate side of the optical disk.** This number will be different every time a new optical is inserted into the HRT. This number is very important and is used to direct the operator to the appropriate disk when retrieving images back to the hard drive.

### ARCHIVING/BACKING UP AND RETRIEVING/DELETING IMAGE SERIES

**ARCHIVING AND BACKING UP IMAGE SERIES**

All image series that have been saved to the hard drive of the HRT must be archived to a designated OHTS optical disk. Each study site should have at least three optical disks: two for archiving images/database backup and a third for exporting and mailing images to the CSLORC. The disks for archiving images and backing-up the database will remain at the study site for the duration of the study. Archiving/backing-up should take place each day after image acquisition is completed and after any extra image series have been deleted.

**NOTE:** Backing up the database is automatically achieved when images are archived to an optical disk. It is not necessary to back up the database separately.
(1) In the main patient list menu, go to **Database** and choose **Archive Images**.

(2) You will be asked to insert an optical disk into the drive.

(3) If there are patients that have been selected prior to the archive session, a message will now appear asking whether to archive selected patients only (which are located on the right side of the screen). If **Yes** is selected, only those selected patients will be archived. If **No** is selected, the HEYEX software will scan the entire database and archive any exams which have not yet been archived. Selecting **No** is recommended so all series images are archived.

**NOTE:** In a case where you need to have access to a database backup copy, please contact the Heidelberg service office for your area or contact the CSLORC and they can direct you to the appropriate person.

DELETING ARCHIVED IMAGES FROM THE HARD DRIVE

Once images have been archived, the entry cannot be permanently deleted. After archiving series images onto optical disks, the software will automatically delete image series from the hard drive (the image icon will still be visible) in order to increase free disk space for new examinations.

RETRIEVING ARCHIVED IMAGES ONTO THE HARD DRIVE

**BATCH RETRIEVING**

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 onto the computer's hard drive. Batch retrieval of images for several visits for one patient or batch retrieval of visits in a specified date range for multiple patients is accomplished as follows:

(1) Choose the patients and visits you are interested in retrieving by using the filter process. In the Main Menu, click on **Database** and **Filter** (or click on the **funnel icon** to filter). A “Database Filter” dialogue box will appear. In the “Examination” portion you can filter by patient and/or a date range or by a date range only.
a. **To retrieve 1 patient’s multiple visits:** Enter patient ID under name and uncheck the “Show only examinations within the patients that match to this filter” (this will give you all visits for this patient)

b. **To obtain a date range of visits:** click on the radio button, **Between**, and enter a range of dates. For example, enter 10/1/2002 and 12/31/2002. Make sure the box is checked next to “Show only examinations within the patients that match to this filter” at the bottom of the dialog box.

(2) Once you have your filter parameters entered, **hit OK**. The patient visits you selected should now appear on the left side of the screen.

(3) Load patient visits by **clicking** on **Record** in the main menu and then select **Load All** (or you may also use the first icon with four circles to load all patients). This will add the selected patient visits to the right side of the screen.

(4) **Go to Database** and select **Retrieve Images**.

(5) A “Retrieve Images” dialogue box will appear. **Choose Z-Scan** for series images and **click OK**.

(6) A dialogue box will appear asking “Do you want to retrieve the data for the selected patients?” **Click No**. See figure 8.1 below.

![Heidelberg Eye Explorer dialog box](FIGURE 8.1)

(7) A “Retrieve Data” dialog box will appear. You are asked to insert an optical disk with a specified number into the disk drive. Be sure to **check the box** “Keep data on hard disk after
retrieval”. Confirm by selecting Retrieve after inserting the correct disk. See figure 8.2 below.

NOTE: Your optical drive may be different (show a different letter) than the one shown in figure 8.2.

FIGURE 8.2

RETRIEVING A SINGLE IMAGE

(1) In the Main Menu, select and load the appropriate patient. On the right side of the screen, click on the desired visit date.

(2) Double click on the image to be retrieved.

(3) A dialog box titled “Retrieve Data” will appear. You are asked to insert an optical disk with a specified number into the disk drive. Confirm by selecting Retrieve after inserting the correct disk.

EXPORTING IMAGES TO THE CSLORC

On a quarterly basis, after your printlist has been approved by the CSLORC, send all OHTS images on optical disks by Federal Express, along with the corresponding HRT Image Acquisition Logs to the CSLORC.

(1) Insert a formatted optical disk into the optical drive. (It is recommended that the site have an optical disk designated only for exporting and transferring images to the CSLORC.)

(2) In the Main Menu, click on Database and Filter (or click on the funnel icon to filter).
(3) A dialog box titled “Database Filter” will appear. In the “Examination” portion, click on the radio button, Between, and enter the dates for the appropriate quarter. For example, for quarter 4, enter 10/1/2002 and 12/31/2002.

(4) Make sure the box is checked next to “Show only examinations within the patients that match to this filter” at the bottom of the dialog box (see figure 9.1). Then click OK. The patient visits you selected should now appear on the left side of the screen.

(5) Load patient visits by clicking on Record in the main menu and then select Load All (or you may also use the first icon with four circles to load all patients). This will add the selected patient visits to the right side of the screen.

(6) Check to make sure that all extra series images have been deleted from the hard drive. Only 9 series images per visit should be exported to the CSLORC.

(7) Right click on any patient on the right side of the screen. Click on HRT Batch, then Export E2E.

(8) A dialog box titled “Export HRT Data” will appear. Only check Export 3D-Images (uncheck topographies and means). Click OK.

(9) A dialog box titled “Export Options” will appear. Click on Browse and choose the optical drive. Click OK.
A dialog box titled “Patient Data Export” will appear. Click OK. After each patient has been exported a dialogue box will appear requesting, “Please insert an empty disk into drive D!” (Your site may have a different designated optical drive.) Hit OK each time this message appears.

CERTIFICATION PROCEDURES

All technicians who were certified for OHTS will only need to have a phone interview to be certified for the OHTS II HEYEX software. The phone interview will consist of questions regarding the protocol, including creating a batch printlist and exporting a batch of images to the Reading Center.

Certification of HRT imaging technicians is supervised by the coordinator and/or directors at the CSLORC. Each study site will have at least two imaging technicians certified for OHTS II 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 II HRT protocol. For a technician who has never been HRT certified, he/she must demonstrate an understanding of the correct procedures for all aspects of HRT image acquisition and processing.

The certification process includes a telephone session with a CSLORC coordinator. The candidate for certification should study the OHTS II Heidelberg Retina Tomograph Manual of Procedures and the HRT Operation Manual Version 3.0.4 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 needs to acquire 9 images of 2 non-study patients according to the OHTS II protocol - 6 series images of the right (3 at 15 degrees and 3 at 10 degree) and 3 of the left eye (at 10 degrees) and submit the printlist to the CSLORC. After the printlist has been approved, images and HRT Image Acquisition Logs should be transferred to the CSLORC. Certification will be awarded if the images are of satisfactory quality. All certified technicians must maintain their certification by obtaining OHTS II HRT images at least every 6 months.

To become certified for 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

Adjusting the laser target and monitoring fixation during imaging

Entering patient data

Operating the HRT; choosing the appropriate depth and focus parameters and obtaining an image

Utilizing the ‘Show Movie’ option to monitor eye movement

Saving the image data, archiving images/backing-up the database

Creating a batch printlist for transfer to the CSLORC

Exporting images for transfer to the CSLORC

Completing the OHTS HRT Image Acquisition Log

Note: .. The telephone "test" asks the technician to walk through a series of mock images, (i.e. explain each procedure and how to improve image series). Before the telephone interview, make sure your site has a certification CD (containing mock HRT image series) and the images can be viewed on a PC. If the site does not have this CD, contact the CSLORC.
INSPECTION OF IMAGE SERIES FOR QUALITY CONTROL

DARK-LIGHT-DARK PATTERN

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, images which appear slightly too bright are more acceptable than those appearing too dark.

(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:

- The first four images of the series should appear dark.
- The last four images of the series should appear dark.
- All other images should appear more or less bright.
- In the middle images, the retina should appear bright.

NOTE: The first and the last images of a series will never appear completely black under normal circumstances. A dark image means that the first/last four images appear obviously darker than the following/preceding images.

(2) If there are no images with bright colors either the adjustment of the laser scanning camera was not properly centered in the pupil, or the sensitivity of the light detector was set too low. Record the series again making sure the laser is centered in the pupil and/or the ‘Sensitivity’ knob is increased.

(3) If the series contains images with large solid white fields with read and blue dots, the sensitivity of the light detector was set too high. Turn the operation panel control knob ‘Sensitivity’ to a lower value and record the series again.
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 for the cup and/or PPA to be overexposed.

FOCUS AND SCAN DEPTH

The following steps help to judge the quality of the recorded image series with regard to the proper setting of the focal plane (which determines the axial location of the 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.

(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 too negative; 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.

(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 too positive; 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.

(3) If the image series begins with too many dark images:

The location of the first focal plane of the image series was too positive; 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.

(4) If the image series ends with too many dark images:

The location of the first focal plane of the image series was too negative; 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.

(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.

(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 again.

**NOTE:** If the quality control for an image is toggling between two scan depths, it is always best to choose the **deeper** of the two scan depths.

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 32 image series by approximately 2 images.
- 0.5 mm increase/decrease of the total scan depth compresses/expands the 32 image series by approximately 4 images 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.

<table>
<thead>
<tr>
<th>Series begins with…</th>
<th>Series ends with…</th>
<th>Set focal plane to…</th>
<th>Set scan depth to…</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 4 dark images</td>
<td>= 4 dark images</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>= 4 dark images</td>
<td>&lt; 4 dark images</td>
<td>more negative</td>
<td>higher value</td>
</tr>
<tr>
<td>= 4 dark images</td>
<td>&gt; 4 dark images</td>
<td>OK</td>
<td>smaller value</td>
</tr>
<tr>
<td>&lt; 4 dark images</td>
<td>= 4 dark images</td>
<td>more positive</td>
<td>higher value</td>
</tr>
<tr>
<td>&lt; 4 dark images</td>
<td>&lt; 4 dark images</td>
<td>OK</td>
<td>higher value</td>
</tr>
<tr>
<td>&lt; 4 dark images</td>
<td>&gt; 4 dark images</td>
<td>more positive</td>
<td>OK</td>
</tr>
<tr>
<td>&gt; 4 dark images</td>
<td>= 4 dark images</td>
<td>OK</td>
<td>smaller value</td>
</tr>
<tr>
<td>&gt; 4 dark images</td>
<td>&lt; 4 dark images</td>
<td>more negative</td>
<td>OK</td>
</tr>
<tr>
<td>&gt; 4 dark images</td>
<td>&gt; 4 dark images</td>
<td>OK</td>
<td>smaller value</td>
</tr>
</tbody>
</table>
EYE MOVEMENT 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.

(1) In order to examine the images for eye movement, **right click** on the image and select **Show Movie**. Under the options menu check that **Show single images** and **Show image quality** are selected. All 32 images will be displayed on the right side and the movie will be displayed on the left. Halt the display of the images by **clicking** on the **Q** button below the movie image. Quite small eye movements of up to one quarter of the disc size are acceptable. (These will be automatically corrected during subsequent processing of the images.) If large or frequent eye movements are present or the image moved out of the frame, the image should be retaken.

(2) If a sudden change in the brightness of the images occurs; the patient blinked during the image acquisition period. The series must be recorded again.

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.

**NOTE: The HRT quality control does not assess framing. Therefore, it is important that the operator be aware of this problem. Often, images with framing cannot be used for analysis. Retake all images where framing occurs.**

Too large a distance between the HRT lens and the pupil can cause 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 prevent framing during image acquisition.

(1) Framed images should be re-taken after adjustment of the distance and/or alignment of the HRT laser within 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 patient’s 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.

(2) Framing is also a common problem when using corrective lenses (glasses or a trial lens). See “Trial Lens Memo I” for specifics on how to minimize this problem.

FLOATERS

Often it is necessary to view the movie of the image series to detect floaters. Stationary floaters are the most problematic because they introduce localized repeatable error to an image series. Moving floaters are less problematic because the error is less repeatable. If any type of floater is seen in the image series, the image should be retaken, especially if the floater is within the optic disc region. To eliminate floaters from the HRT field of view, ask the patient to blink several times and to look up, down, right and left.

VESSEL DOUBLING

(1) In HRT image series, uncorrected astigmatism or too much eye movement can result in doubling of vessels. Images with this problem cannot be used for data analysis. All patients with astigmatism > 1 diopter should be imaged using corrective lenses (glasses or contact lenses).

NOTE: If corrective lenses are used for the first visit, they should be used for ALL follow-up visits throughout the study.

(2) Another reason vessel doubling may occur is excessive eye movement. Make sure the patient is fixating on the fixation target during image acquisition. If the acquired image has more eye movement than a quarter of the disk size, it should be retaken.
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
# TABLE OF CONTENTS

I. INTRODUCTION ........................................................................................................... 16-53
II. Impact of SWAP on the OHTS Trial ........................................................................... 16-53
III. Informed Consent ...................................................................................................... 16-54
IV. Patient Visit Timetable ............................................................................................. 16-54
V. Testing Protocol ......................................................................................................... 16-55
VI. Data Shipment .......................................................................................................... 16-56
VII. Quality Control Assessment Procedures ................................................................. 16-56
VIII. Computation of SWAP Indices ............................................................................... 16-56
IX. Certification .............................................................................................................. 16-56
X. Appendix ................................................................................................................... 16-58
I. Introduction

Short Wavelength Automated Perimetry (SWAP) is a new visual field test procedure that utilizes a bright yellow background (100 cd/m²; 315 asb) and a large (size V) blue test object to isolate and measure the sensitivity of short-wavelength-sensitive 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. Printed copies of SWAP results should not be made. 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. Patient data entry, including ID code, should be done in the same manner as for standard automated perimetry testing. 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. The disks for the SWAP ancillary study must be kept separately from the rest of the patient’s OHTS information and clinical records. Do not make a hard copy printout of the SWAP results. The Principle Investigator is not allowed to view SWAP results at any time, and should not be allowed access to the disks and storage area containing SWAP results. Patients are not to be informed of their test results for SWAP, and copies of their test results should not be given to them. 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 monthly 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. Computation of SWAP Indices

Computation of Glaucoma Hemifield Test (GHT) probability of SWAP data will be performed by comparing individual test results to a normative database. The normative database consists of 348 individuals between the ages of 18 and 85. To be included in the normative database, individuals had to have an IOP of less than 22 mm Hg OU, better than 20/40 visual acuity OU, normal optic discs OU, refractive errors of less than 5 D spherical equivalent and 3 diopters cylinder, no history of ocular or neurologic disease or surgery, no history of diabetes or other systemic diseases, and were not taking any medications known to affect visual fields or color vision. Additional details of the normal control population may be found in the following publications: (Johnson CA, Sample PA, Cioffi GA, Liebmann JR and Weinreb RN: Structure and Function Evaluation (SAFE): I. Criteria for glaucomatous visual field loss. American Journal of Ophthalmology, 2002, 134: 177-185. Johnson CA, Sample PA, Zangwill LM, Vasile CG, Cioffi GA, Liebmann JR, Weinreb RN: Structure and Function Evaluation (SAFE): II. Comparison of optic disc and visual field characteristics. American Journal of Ophthalmology, 2003, 135: 148-154.).

To increase the enrollment of African American patients in the SWAP ancillary study, five additional clinical sites were added to the original group of participating clinical centers: Pennsylvania College of Optometry / MCP Hanemann University School of Medicine, Univ. of Louisville, Kresge Eye Institute, New York Eye and Ear Infirmary and Washington D.C.

IX. 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.
X. 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.

4. 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
The Ocular Hypertension Treatment Study (OHTS) is designed 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 patients judged to be at moderate risk for developing open-angle glaucoma. The OHTS has enrolled 1636 subjects at 22 clinical centers nationwide. Subjects are followed twice yearly for a minimum of five years.

An ancillary study to the OHTS is proposed in an effort to determine whether there is a familial (genetic) risk of ocular hypertension and/or glaucoma. Only genes that have been shown to play a role in ocular hypertension or glaucoma will be screened on the OHTS panel.

All OHTS clinical centers will be asked to participate in the recruitment of OHTS subjects into this voluntary ancillary study. Following consent, blood samples will be drawn at the subject’s OHTS clinical center and shipped to the University of Iowa for freezing and storage until such time as genes are identified and cloned. Collection and processing of sample and quality control work is expected to take more than a year.

This research will be conducted as a group study and participants will be notified of results in a public forum that gives the overall results with encouragement for participants to see his/her own physician for further evaluation.
Instructions to Clinics for Participating in the Genetics Ancillary Study

Revised 1/11/02

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
- Participant ID labels (1 OHTS ID, 2 random ID)
- 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 after confirmation of receipt of blood is received from laboratory in Iowa.

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: 1) Costs of mailing samples will be billed to OHTS Chairman’s Office.
2) Random ID numbers should not be retained at clinic after receipt of confirmation of blood from University of Iowa
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 random ID, 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 after confirmation of receipt of blood is received from laboratory in Iowa.

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 #: _______________________________

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<th>Genetics Random ID #</th>
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<th>Patient's Gender</th>
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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

Packing Slip Revised 4/16/01
INFORMED CONSENT FOR PARTICIPATION IN GENETIC RESEARCH INVOLVING CODED TISSUE AND/OR DATA

Participant

HSC Approval Number 01-0089

Principal Investigator

Michael A. Kass, M.D.

PI’s Phone Number 362-3724

Title of Project: Ocular Hypertension Treatment Study: Genetics Ancillary Testing

You are invited to participate in a research study conducted by Dr. Kass and/or colleagues.

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. PURPOSE:

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 a 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. PARTICIPATION:

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.

Your blood sample will be banked at the University of Iowa for future studies to test for differences in the DNA that can cause ocular hypertension or glaucoma. As new genes are identified, researchers may propose studies to use your blood sample. It is estimated that your blood sample will remain available to researchers for a minimum of 10 years.

Research results will not be available to you or your physician except under extraordinary circumstances. These are situations in which a life-threatening medical disorder is discovered for which medical treatment is available to prevent or alleviate long-term medical complications. If such a situation should occur, we will contact you. If you prefer the principal investigator or a member of the research team to notify your
primary care physician or specialist of any findings that may be critical to your health care, please initial here __________.

3. **COSTS TO PARTICIPANTS:**
   There will be no costs to you for participating in this research study. You will not receive any medical or financial benefit from participating in this research.

4. **RISKS:** 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.

5. **BENEFITS:**

   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.

6. **ALTERNATIVES:**
   The alternative is to decline participation in this study.
7. **PROTECTED HEALTH INFORMATION (PHI):** is any health information through which you can be identified. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). A decision to participate in this research means that you agree to let the research team use and share your PHI for the study explained above. Blood samples are sent to the University of Iowa with a random ID without names or OHTS ID numbers. The Coordinating Center receives the following variables from the University of Iowa: clinic site sending the sample, date sample received by Iowa, participant gender, and genetics random ID. The Chairman’s Office will not utilize any of your PHI. A master list linking the code number and the participant’s identity is kept in a locked cabinet at Coordinating Center located at WUMS and only designated members will have access to the master list. PHI will not be shared with anyone outside of Washington University.

WUMC will protect your information according to State and Federal laws. There is always the possibility that your information could be shared in a way that it would no longer be protected by law. Your identity will not be revealed in any publication that may result from this study.

**Officials of Federal or State government agencies or the University may look at, use, or copy information in your research file to complete Federal, State or University responsibilities. A representative of the Sponsor, (insert Sponsor’s name or delete this sentence), may also have access to your file.**

The research team will use and share your information for a minimum of 10 years after closure of the study. At that point, the investigator will remove the identifiers from your information, making it impossible to link you to the study.

Your participation is voluntary and you may choose not to participate in this research study or withdraw at any time. Your choice will not 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. If you decide to end your participation in the study, please complete the withdrawal letter, found at [http://medicine.wustl.edu/~hsc/hipaa/](http://medicine.wustl.edu/~hsc/hipaa/), or you may request that the Investigator send you a copy of the letter.

Do you already have contact restrictions in place with WUMC?  
(Example – no calls at home, no messages left for you, etc.)

[ ] Yes  [ ] No

Please specify any contact restrictions you want to request for this study only.
____________________________________________________________________________________
____________________________________________________________________________________

8. **CONTACTS:** If you have any questions or concerns regarding this study, or if any problems arise, you may call the PI, Dr. Michael Kass at 314-362-3724. You may also ask questions, state concerns regarding your rights as a research subject, or express any feelings of pressure to participate Dr. Philip Ludbrook, Chairman of the University's Human Studies Committee, at (314) 633-7400 or (800) 438-0445.

9. **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 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 8. 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.

10. 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.

Version 4.0  3/10/03
11. 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 copy of this consent form for my records. I hereby give my permission to participate in the research described above, titled:

________________________________________________   __________________________________________________

Participant’s Signature   Date   Signature of person providing Informed Consent   Date
(If designee, see guideline Who May Obtain Consent)

The Notice of Privacy Practices (a separate document) describes the procedures used by WUMC to protect your information. If you have not already received the Notice of Privacy Practices, the research team will make one available to you.

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I have been offered a copy of the WUMC Notice of Privacy Practices.

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