Visual Field Quality Control in the Ocular Hypertension Treatment Study (OHTS)

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Objective: To report the impact of visual field quality control (QC) procedures on the rates of visual field unreliability, test parameter errors, and visual field defects attributed to testing artifacts in the Ocular Hypertension Treatment Study (OHTS).

Methods: OHTS technicians were certified for perimetry and were required to submit 2 sets of visual fields that met study criteria before testing study participants. The OHTS Visual Field Reading Center (VFRC) evaluated 46,777 visual fields completed by 1618 OHTS participants between February 1994 and December 2003. Visual field QC errors, rates of unreliability, and defects attributed to testing artifacts were assessed. The OHTS QC system addressed 3 areas of clinic performance: (1) test parameter errors, (2) patient data errors, and (3) shipment errors. A visual field was classified as unreliable if any of the reliability indices exceeded the 33% limit. Clinical sites were immediately contacted by the VFRC via fax, e-mail, and/or phone and instructed on how to prevent further testing errors on fields with defects attributed to testing artifacts.

Main Outcome Measures: QC errors (test parameter errors) and unreliability rates.

Results: A total of 2.4% (1136/ 46,777) of the visual fields were unreliable and 0.23% (107/46,777) had incorrect test parameters. Visual field defects attributed to testing artifacts occurred in approximately 1% (483/46,777) of the visual fields.

Conclusions: Prompt transmission of visual fields to the VFRC for ongoing and intensive QC monitoring and rapid feedback to technicians helps to reduce the frequency of unreliable visual fields and incorrect testing parameters. Visual field defects attributed to testing artifacts were infrequent in the OHTS.

Key Words: mesodermal dysplasia spectrum, oculo-auriculo-vertebral spectrum, progressive noninfectious anterior vertebral fusion, kyphosis, MRI

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Reading centers are important in clinical trials to standardize procedures, train and certify technicians, perform quality control (QC) procedures, store data, perform analyses, and assess outcomes in a masked fashion. The Visual Field Reading Center (VFRC) at the University of California, Davis has participated in 2 major multicenter clinical trials.[1–13] Procedures used by the VFRC can reduce the number of unreliable or unusable visual fields and improve the quality of visual field data.[1,3,5,9] The Ocular Hypertension Treatment Study (OHTS) used Humphrey visual fields to assess changes in visual function due to primary open angle glaucoma. Recent papers written by Kass et al[6] and Gordon et al[10] have been published regarding the outcome of the OHTS.

The purpose of this article is to report the impact of visual field quality assurance and control procedures on the rates of visual field unreliability, test parameter errors, and visual field defects attributed to testing artifacts.

METHODS

The OHTS visual field testing protocol included training, certification, and on-going feedback to technicians on each visual field test and also quarterly reports on visual field quality. Quarterly reports were distributed to OHTS clinic investigators, coordinators, Executive Committee members and Data Safety and Monitoring Committee members, reading centers (VFRC and Optic Disc Reading Center), and the National Eye Institute. The reports contained information on overall study and clinic performance from the reading centers and the data coordinating center (completed visits, number of

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participants, intraocular pressure goal, useable fields, and photographs). Clinic ranking information based on the number of goals met was also included. In addition, the OHTS Data Safety and Monitoring Committee required a more comprehensive biannual report examining the frequency of abnormal visual fields, unreliable visual fields, overall clinic QC performance, and clinic QC ranking. This information provided a direct comparison between OHTS clinical sites. The VFRC and Optic Disc Reading Center also provided more detailed quarterly performance reports with emphasis on data quality and timeliness of data transmission to the Data Coordinating Center.

Between February 1994 and December 2003, 246 technicians from 22 clinical sites were certified for OHTS. Technicians were given the VFRC perimetry protocol to review before the certification examination. To become certified for OHTS, each technician was required to successfully pass a telephone certification examination and submit 2 sets of certification visual fields on nonstudy participants to the VFRC.

For a participant to meet OHTS visual field entry criteria, 2 out of a maximum of 3 visual field tests (Humphrey full threshold 30-2) for each eye were required to be normal and reliable at baseline. The OHTS perimetry protocol provided explicit instructions on how to configure the Humphrey Field Analyzer's (HFA)'s main menu to run the correct visual field test (30-2 full threshold). It was necessary for the technician to manually program the HFA before each test was performed. In August 2003, the OHTS perimetry protocol changed its testing parameter requirements from full threshold 30-2 to SITA Standard 30-2. Visual fields were classified as unreliable if either false-positive errors, false-negative errors, or fixation losses were greater than 33% (33% fixation losses are used as the limit for OHTS, in contrast to the HFA's default value of 20%).[1] Follow-up visits were scheduled every 6 months from the date of randomization. We recommended that visual fields be sent to the VFRC weekly but required that they be sent within 21 days of testing. The OHTS VFRC protocol required that all abnormal and/or unreliable visual fields be faxed to the VFRC within 7 days of testing. When the VFRC received a visual field that was abnormal and/or unreliable, the site was contacted via fax with instructions for the next follow-up visual field. If a visual field was rendered abnormal owing to a testing artifact (ie, trial lens rim, heavy/droopy lid), the clinical site was contacted via fax, e-mail, and/or telephone and instructed on how to prevent further testing errors. VFRC staff emphasized that during visual field testing, the lenses be moved as close as possible to the eye, heavy/droopy lids be taped, and the participant should be made as comfortable as possible. If the next follow-up visual field (second) was again abnormal due to a testing artifact, the OHTS Coordinating Center was also notified. To prevent the next follow-up visual field (third) from being abnormal due to testing artifact, the VFRC notified technicians (via faxes, e-mail, and telephone) with instructions for the next follow-up fields, emphasizing the importance of properly aligning the patient and/or taping heavy or droopy lids before testing. As a secondary, preventative measure, the VFRC also contacted the OHTS central coordinators. The coordinators were responsible for following up with the VFRC's original request regarding proper testing instructions. Previous papers described the study protocol and baseline clinical characteristics of participants enrolled in the OHTS.[2,3] Study rationale, organization, and procedures are discussed in the OHTS *Manual of Procedures*.[4]

According to OHTS criteria, a follow-up visual field was considered to be abnormal if the glaucoma hemifield test and/or the corrected pattern standard deviation global index were outside normal limits ($P < 1\%$ and $< 5\%$, respectively). Final determination as to whether the visual field abnormality was attributable to primary open angle glaucoma was made by the OHTS Endpoint Committee after review of all optic disc photographs, visual fields, and medical and ocular history of both eyes of the participant.[6]

The OHTS visual field QC system addressed 3 areas of clinic performance: (1) test parameter errors, (2) patient data errors, and (3) shipment errors (Table 1). Each visual field was graded on a 100-point scale with regard to whether the protocol was followed in each of these 3 areas. A score was assigned to each QC error, depending on the severity of the violation. On this scale, zero represented a perfect score, with increasing point scores reflecting more severe QC errors. Factors that rendered the data unusable for the study (eg, using the wrong test procedure) had higher point values, whereas those that produced minor errors (eg, incorrect data entry) had lower point totals.

RESULTS

Between February 1994 and December 2003, 246 certified technicians from 22 clinical sites performed 46,777 visual field tests (7257 eligibility and 39,520 follow-ups) on 1618 participants in the OHTS. Only 2.4% (1136/46,777) of the visual fields were unreliable and only 0.23% (107/46,777) had incorrect test parameters. Fixation loss errors were the most common reliability index outside normal limits; 76% (866/1,136) of the unreliable fields were due to excessive fixation losses. Excessive false-positive errors contributed to 17% (188/1136) of the unreliable visual fields, and excessive false-negative errors contributed to 11% (124/1136) of the unreliable fields (Table 2). Table 3 shows the comparison of OHTS reliability rates with those obtained for previous studies of ocular hypertension or glaucoma. The OHTS attained superior overall reliability (with an unreliability rate of only 2.4%) compared with other published studies.[5] Fixation losses, false-positive and false-negative errors contributed to 1.9%, 0.4%, and 0.3% of the total fields (46,777), respectively.

When comparing the prior studies with the findings reported for OHTS, it should be noted that there were

TABLE 1. Technician QC Errors

Errors	Point Values
Test parameter errors (maximum of 60 points)	
Program 30-2 not used	−60
STATPAC 2 not used	−60
Stimulus size III not used	−60
Full threshold strategy not used	−60
Short-term fluctuation test turned off	−60
Foveal threshold test turned off	−10
Blind spot check turned off	−10
Inappropriate blind spot check size used	−10
Central fixation target not used	−5
Visual field data not saved on disk	−20
Patient data errors (maximum of 30 points)	
Pupil diameter less than 3 mm or not entered	−10
Visual acuity not entered	−3
Birth date incorrect	−5
Site ID not entered in ID field	−3
Site ID incorrect	−2
Technician ID not entered in ID field	−3
Technician ID incorrect	−2
Visit code not entered in ID field	−3
Visit code incorrect	−2
Dilation information incorrect	−2
Patient ID not entered in name field	−5
Patient ID incorrect	−4
Distance Rx not entered in name field	−10
Distance Rx entered incorrectly	−3
Rx used not entered	−10
Sphere error in patient's Rx	−7
A sphere of ± 0.25 D must be dropped for test	−3
Cylinder discrepancy in patient's Rx	−3
Axis discrepancy in patient's Rx	−2
A cylinder less than 1.00 D must be dropped and a spherical equivalent used	−3
A cylinder lens must be used for a cylinder of 1.00 D or greater	−3
VFRC Shipment errors (maximum of 10 points)	
Visual field printout not included in shipment	−3
Humphrey disk file shipped late (≤30 d)	−3
Humphrey disk file shipped late (>30 d)	−10
Humphrey disk directory not included in shipment	−2
Visual field not checked off on Humphrey disk directory	−1
Shipment not packaged properly	−2
Shipment not addressed properly	−2
Humphrey disk not labeled	−2
Humphrey disk not labeled correctly	−1
Prestudy form not included with visual field	−2
Prestudy form not completed correctly	−1
This field was not faxed to the VFRC as required	−3
This field was not faxed to the VFRC on time	−2

many differences. To our knowledge, QC procedures were not employed in the prior studies, inclusion/exclusion criteria were different, the other studies were from a single center, and patient selection was not as stringent. While we believe that QC procedures represent a major factor for reliable visual fields in the OHTS, other issues (patient selection, standardized protocols, technician training, and certification, etc) are also possible contributors to higher quality visual field information. In addition, we feel that practitioners who employ these techniques will find an improvement in the reliability and accuracy of their visual field test results.

TABLE 2. Unreliability and Incorrect Test Parameters in the OHTS

Visual Field Status	OHTS
Unreliable*	2.4% (1136/46,777)
Fixation loss errors	76% (866/1136)
False-positive errors	17% (188/1136)
False-negative errors	11% (124/1136)
Incorrect test parameters	0.23% (107/46,777)

*Note that more than one reliability index can be outside normal limits on a single visual field examination.

As shown in Figure 1, OHTS mean test, patient data, and shipment errors have generally decreased over time (1994 to 2003) with the exception of mean test error points which intermittently fluctuated owing to the introduction of a new perimeter (HFA II—second Qrt. 1999) and a change in the testing protocol from full threshold to SITA Standard (third Qrt 2003).

Visual field defects attributed to testing artifacts (trial lens rim artifacts and heavy/droopy lids) occurred in approximately 1.03% (483/ 46,777) of the OHTS total visual fields. Trial lens rim artifacts typically produced visual field abnormalities such as peripheral rim, partial peripheral rim, or inferior depression defects; heavy/droopy lids typically produced abnormalities such as superior depression defects (Table 4). Although we have not reported these types of visual field testing artifacts as QC measures for the OHTS, abnormalities caused by a trial lens rim artifact or ptosis will automatically generate feedback from the VFRC to reduce the probability that they will occur in future tests.

DISCUSSION

To our knowledge, few clinical trials have used visual field testing protocols with such stringent and timely QC procedures as the OHTS. QC is of the utmost importance for maintaining good reliability rates and ensuring the validity and integrity of visual field data. In addition, QC can reduce the expense of missing data and potential for bias.

One of the key elements in QC functions is to adapt procedures to identify problems in a particular trial. The

TABLE 3. Comparison of OHTS' Reliability Rates With Other Reported Rates*

Study (Participants)	Overall Unreliability Rate (%)	Fixation Losses (%)	False-positive Rate (%)	False-negative Rate (%)
OHTS* (OH)	2.4	1.9	0.4	0.3
Bickler-Bluth (OH)[14]	15.0	—	< 7.0	< 7.0
Birt (G)[15]	25.0	—	5.0	9.0

*FLs, FPs, and FNs reflect 33% cut-off rate unless otherwise noted; n = 46,777.
G indicates glaucomatous; OH, ocular hypertensives.

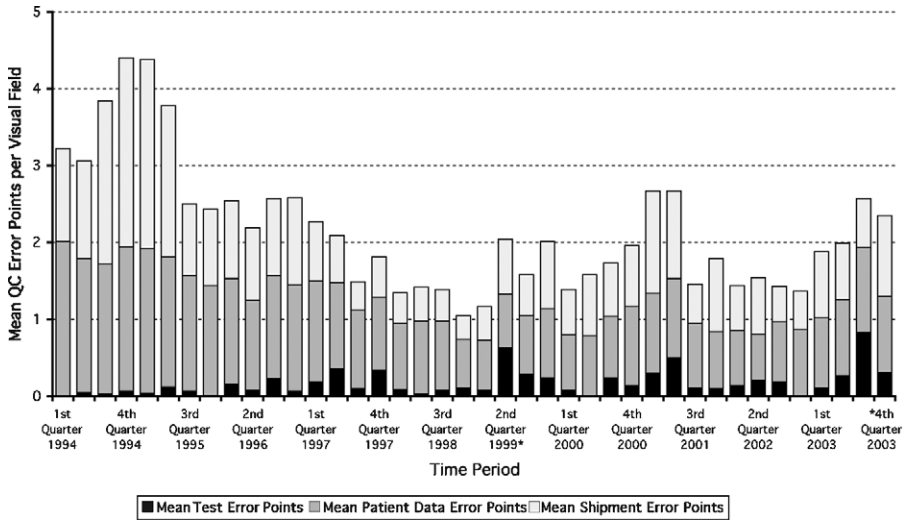

FIGURE 1. QC performance of OHTS clinics includes all processed visual fields performed on OHTS participants from January 1, 1994 to December 31, 2003.

best example for the need of a VFRC occurred with the Optic Neuritis Treatment Trial (ONTT). The UC Davis VFRC has been the reading center for the ONTT since 1988. Recent papers written by Keltner et al and Johnson et al have been published regarding the baseline, QC functions, and the 1-year follow-up of the ONTT.[8,9,13] Both the ONTT and the OHTS had similar protocols for visual field testing even though the study samples differed in disease entities, glaucoma/ocular hypertension, and optic neuritis, respectively.

The OHTS and the ONTT 10-year follow-up study unreliability rates were both very low at 2.4% (1136/46,777) and 6% (43/722), respectively; however, the OHTS unreliability rate was lower than the ONTT. There were many differences in the OHTS and ONTT testing protocols (Table 5). An important QC error occurred in the ONTT 10-year follow-up study. A total of 19% (34/173) of the ONTT visual fields had incorrect test parameter errors, whereas only 0.23% (107/46,777) of the OHTS visual fields had incorrect test parameters. The VFRC analyzed the cause for this high rate of incorrect test parameter errors and determined that the one-time follow-up visit in the 10-year follow-up study lacked ongoing visual field feedback and clinic center ranking. Thus in the 15-year ONTT follow-up study, the VFRC developed a new strategy which included immediate fax requests and a point-value system. The VFRC reviewed each faxed visual field, and if it was determined that the wrong test parameter was used, the clinic would be immediately notified and the correct visual field was performed. In addition to immediate feedback, each visual field was graded on a 100-point scale. By adapting this similar OHTS strategy to the ONTT QC procedures, incorrect test parameter errors decreased from 19% (34/173) in the 10-year ONTT follow-up study to 1.5% (10/637) in the 15-year follow-up study. Thus it would appear that with appropriate feedback, testing errors can be reduced by analyzing QC issues and taking the appropriate corrective action.

TABLE 4. Percentage of Visual Field Testing Artifacts in OHTS Total Visual Fields

VF Abnormality	No. VFs	% of VFs (n = 46,777)
Peripheral rim	6	0.01
Partial peripheral rim	293	0.63
Superior depression	153	0.33
Inferior depression	31	0.06
Total	483	1.03

The effects of ptosis on visual field testing can be prevented by taping the participant's lid with surgical tape, whereas trial lens rim artifacts can be prevented by (1) correctly aligning the participant's eye in the center of the trial lens rim(s) during testing and (2) instructing the participant not to lose forehead contact with the perimeter's brow band. As shown in Table 4, visual field loss attributed to testing artifacts occurred in only 1.03% of the total OHTS visual fields. Interestingly, the ONTT 10-year follow-up study also reported that visual field defects attributed to testing artifact occurred in less than 1% (7/722) of its total visual fields. To our knowledge, few previous studies have reported visual field abnormalities likely due to testing artifacts. Thus, we cannot adequately compare the frequencies of these types of artifactual abnormalities with other studies.

The QC procedures used in the OHTS have likely proven very effective in producing high quality visual field data; however, there is no control group to completely validate this assumption. As seen in Table 3, the OHTS unreliability rate is superior to other glaucoma studies previously published. Unfortunately, complete details of the QC procedures used in these older articles are not well described.

While QC measures used to produce high quality visual field data are essential in clinical trials, we believe that many of the same principles can be used in routine clinical settings. In every ophthalmology practice, it would be advisable for technicians to: (1) read standard

TABLE 5. Major QC Differences Between Study Protocols Used in OHTS and ONTT

Study Parameters	OHTS	ONTT
Visual field entry criteria	2 sets of normal, reliable baseline/qualifying visual fields	1 abnormal visual field consistent with optic neuritis (not required to be reliable)
Visual field shipment criteria	Weekly	Not specified
Visual field testing frequency	Every 6 mo	Once for 180 participants; twice for 90 participants
Technician certification	Certified for perimetry by the VFRC* via: (1) Phone examination (2) Visual field testing (4 satisfactory fields from both eyes of 2 nonstudy participants)	Certified for perimetry by Jaeb† via: (1) Phone examination (2) No certification fields required
QC ranking	Clinics ranked by their QC scores and detailed quarterly reports sent to clinic PIs/coordinators/techs (Table 3)	None
Clinic error notification	Contacted within 24 h via QC reports, faxes, telephone, and e-mails	Contacted within 24 h via telephone and e-mails. However, often all visual field testing completed and sent in batches before feedback was possible

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instructions to the participant each time before testing (this has been shown to be effective in reducing variability),[16] (2) use the proper refraction,[3] (3) insure proper participant ergonomics to avoid fatigue, (4) properly align the trial lens to the eye to avoid a trial lens rim artifact, and (5) tape the lids if ptosis is present to avoid a superior visual field defect.

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