Assessment of the Impact of an Endpoint Committee in the Ocular Hypertension Treatment Study

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• PURPOSE: To assess the impact of a masked Endpoint Committee on estimates of the incidence of primary open-angle glaucoma (POAG) treatment efficacy and statistical power of the Ocular Hypertension Treatment Study-Phase 1, 1994-2002 (OHTS-1).
• DESIGN: Retrospective interrater reliability analysis of endpoint attribution by the Endpoint Committee.
• METHODS: After study closeout, we recalculated estimates of endpoint incidence, treatment efficacy, and statistical power using all-cause endpoints and POAG endpoints. To avoid bias, only the first endpoint per participant is included in this report.
• RESULTS: The Endpoint Committee reviewed 267 first endpoints from 1636 participants. The Endpoint Committee attributed 58% (155 of 267) of the endpoints to POAG. The incidence of all-cause endpoints vs POAG endpoints was 19.5% and 13.2%, respectively, in the observation group and 13.1% and 5.8%, respectively, in the medication group. Treatment effect for all-cause endpoints was a 33% reduction in risk (relative risk = 0.67, 95% confidence interval [CI] of 0.54-0.84) and a 56% reduction in risk for POAG endpoints (relative risk = 0.44, 95% CI of 0.31-0.61). Post hoc statistical power for detecting treatment effect was 0.94 for all-cause endpoints and 0.99 for POAG endpoints.
• CONCLUSION: Endpoint Committee adjudication of endpoints improved POAG incidence estimates, increased statistical power, and increased calculated treatment effect by 23%. An Endpoint Committee should be considered in therapeutic trials when common ocular and systemic comorbidities, other than the target condition, could compromise study results. (Am J Ophthalmol 2019;199:193–199. © 2018 Elsevier Inc. All rights reserved.)

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CLINICALLY, THE DIAGNOSIS OF GLAUCOMA IS based on assessment of visual field abnormality and optic nerve deterioration.[1–3] However, when considering clinical trials, visual field and optic nerves may not both be evaluated. A systematic review of 13 Cochrane Reviews and 9 protocols of glaucoma intervention studies indicates no clear consensus regarding how best to assess outcomes, making it difficult to compare studies when there is significant variation. Of the glaucoma studies reviewed, only 12% used visual fields and 13% a structural assessment, 62% of which were optic nerve head change.[4] Almost all National Eye Institute–sponsored clinical trials of ocular hypertension and glaucoma have used visual fields as a primary endpoint, including the Advanced Glaucoma Intervention Study,[5] Early Manifest Glaucoma Trial[6] (EMGT), Collaborative Initial Glaucoma Treatment Study[7] (CIGTS), and The Ocular Hypertension Treatment Study[8] (OHTS). The EMGT,[6] CIGTS,[9] and OHTS[8] assessed the optic nerve as well; however, only EMGT[6] and OHTS[8] relied on the optic nerve in addition to the visual field as primary endpoints. The importance of evaluating both the visual field and the optic nerve has been noted by others, particularly when evaluating patients with ocular hypertension.[2,10] Moreover, using both functional and structural metrics is consistent with clinical practice.[1]

However, the assessment of visual field abnormality and optic nerve deterioration is complicated. It is well known that other eye conditions such as cataracts, age-related macular degeneration, and diabetic retinopathy, which may be more common than glaucoma in some groups of older adults, can cause visual field loss.[11] The task of distinguishing visual field loss attributable to glaucoma from nonglaucomatous causes can be daunting. Similarly, optic disc damage can result from nonglaucomatous causes such as ischemic optic neuropathy, demyelinating disease, and compressive optic nerve lesions. Commingling of glaucomatous and nonglaucomatous endpoints in a clinical trial can cause overestimation of the incidence or

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progression of glaucoma, underestimation of treatment effect, and/or a loss of statistical power.

The Ocular Hypertension Treatment Study–Phase 1, 1994-2002 (OHTS-1)[8] is an unmasked, randomized trial of the safety and efficacy of ocular hypotensive medication in preventing or delaying the onset of primary open-angle glaucoma (POAG). The US Food and Drug Administration and the European Medicines Agency recommend centralized adjudication when endpoints are subjective or require the application of a complex definition, and/or when treatment assignment is not masked.[12,13] Thus, to achieve greater diagnostic specificity of endpoints, the OHTS used a masked Endpoint Committee to adjudicate whether the cause of reproducible visual field abnormality and reproducible optic disc deterioration were attributable to POAG. This manuscript assesses the impact of a masked Endpoint Committee adjudication on estimates of POAG conversion, treatment effect and statistical power.

METHODS

OHTS PHASE 1 (NCT0000125) WAS UNDERTAKEN IN ACCORdance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki. The institutional review board of each clinic approved the study protocol and consent form. Participants gave written informed consent to be screened and, if eligible, to be randomized.

Between February 28, 1994 and October 31, 1996, 1636 individuals with an intraocular pressure (IOP) of 24-32 mm Hg in 1 eye and 21-32 mm Hg in the fellow eye and no evidence of glaucomatous damage by standard clinical measures were randomized to either observation or to treatment with commercially available topical ocular hypotensive medications. Neither clinician nor participant was masked to the randomization assignment. Reading Centers determined the occurrence of visual field and optic disc endpoints without regard to cause, "all-cause" endpoints. The masked Endpoint Committee determined whether these endpoints were POAG endpoints. The primary hypothesis compared the incidence of POAG endpoints in the medication and observation groups. A secondary analysis compared incidence of all-cause endpoints in the randomization groups. In 2002, the OHTS primary outcome paper[13] reported that ocular hypotensive medication was safe and effective in preventing glaucoma, after which participants in the observation group were offered ocular hypotensive treatment. This report includes data to June 2002 when participants were followed according to their original randomization assignment.

The Figure illustrates the flowchart for assessment of endpoints after Reading Centers determined the occurrence of a reproducible endpoint and the Coordinating Center prepared an endpoint chart for Endpoint Committee adjudication.[14–16] Criteria for Reading Center determination of reproducible visual field abnormality and optic disc deterioration are described briefly below.

Each reproducible visual field abnormality, defined as a set of 3 consecutive, reliable visual fields with a corrected pattern standard deviation (CPSD) of $P < 5\%$ or a glaucoma hemifield test outside normal limits by STATPAC 2 criteria (Humphrey 30-2) as judged by masked readers at the Visual Field Reading Center, University of California-Davis, Sacramento, California, USA, was sent to the Coordinating Center to initiate the endpoint review process.[14,17] Eighty-six percent of the initial visual field abnormalities were not confirmed on retest and were not sent to the Endpoint Committee for review. Additional details about the process of reviewing visual fields have been previously published.[15] A reproducible disc deterioration was defined as 2 consecutive sets of optic disc photographs judged by masked certified readers at the Optic Disc Reading Center, Bascom Palmer Eye Institute, Miami, Florida, USA to show generalized or localized thinning of the optic disc neuroretinal rim compared to baseline stereoscopic optic disc photographs. About 18% of the eyes that initially showed disc deterioration from baseline were not confirmed by retake optic disc photographs and were not sent to the Endpoint Committee for review (internal report, August 2018). When 2 consecutive sets of optic disc photographs were judged to show deterioration, the case was sent to the Coordinating Center to initiate the endpoint review process. Additional details about the process of reviewing optic disc photographs have been previously published.[16]

The Coordinating Center prepared a separate masked endpoint chart for each reproducible visual field abnormality and each reproducible optic disc deterioration. Each member of the Endpoint Committee received a masked endpoint chart for review. The endpoint chart included medical and ocular history (all visual fields, all optic disc photographs, macular and red reflex photographs of both eyes) to date. The endpoint chart was masked as to randomization assignment, hypotensive medication use, IOP, and glaucoma surgery.

The masked Endpoint Committee was established to serve as an unbiased clinical surrogate to adjudicate whether reproducible changes identified by either Reading Center were attributable to POAG and to determine whether optic disc deterioration was clinically significant. Visual field abnormality was deemed a POAG endpoint based on a consistent depression in sensitivity in the pattern deviation analysis, compatible with either a nerve fiber bundle defect, paracentral scotoma, or nasal step. Defects occurring only at the margins of the visual field were typically considered artifacts unless there were optic disc changes to corroborate the clinical diagnosis of POAG.

To reflect clinician decision making, the Data and Safety Monitoring Committee mandated that the Endpoint Committee determine if optic disc deterioration detected by the

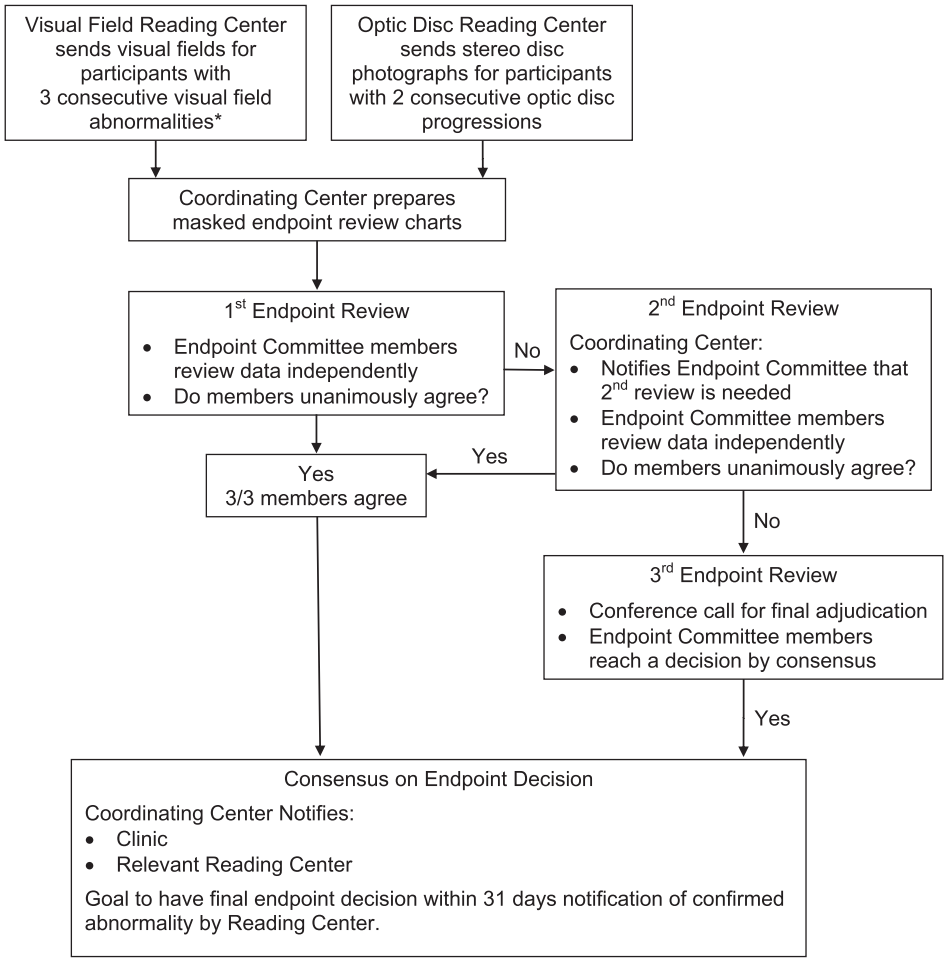

FIGURE. Flowchart of endpoint review process.

Optic Disc Reading Center met a clinical threshold of conversion to POAG to justify initiation of treatment. If the clinical threshold was not met, the Endpoint Committee did not adjudicate cause. Optic disc deterioration was deemed a POAG endpoint based on clinically significant changes in the following: optic disc rim width, the contour of the disc, or shift of the vessels across the disc rim. Disc hemorrhage alone was not considered an endpoint, unless associated with a change in contour. To mimic clinical practice, the Endpoint Committee reviewed both the disc and visual field of both eyes in their adjudication of every endpoint. If either the optic nerve or visual field endpoint did not meet these criteria, then the endpoint was rejected and additional testing was requested. Ocular media changes or other ocular diagnoses were considered in the deliberation. Examples of a visual field and optic nerve change are illustrated at https://www.vrcc.wustl.edu/ohts/disc/and https://www.vrcc.wustl.edu/ohts/fields/.

The Endpoint Committee process was consensus driven. The members of the Endpoint Committee (D.H., E.H., and R.P.), all practicing clinicians, remained active throughout the study. Each Endpoint Committee member independently determined whether an endpoint was "most probably due to POAG" or "most probably not due to POAG" and, for optic disc deterioration, whether the "change was clinically significant." The "Endpoint Form" is posted on https://ohts.wustl.edu/wp-content/uploads/2017/02/A_EN.pdf. If the first review did not achieve unanimity a second, independent review was conducted (Figure). If the second review did not achieve unanimity, a conference call was held. The target time for reaching unanimity was 31 days from notification of the Coordinating Center by the Reading Center of a reproducible change. The Endpoint Committee also determined if discontinuation of assessment was necessary when visual fields or optic disc stereo-photographs

became unascertainable for POAG (eg, after retinal vein occlusion or stroke).

The first endpoint per participant was selected for inclusion in this report to avoid bias from subsequent endpoint reviews. Participants were classified as converting to POAG if 1 eye developed a POAG endpoint. If a POAG endpoint was detected by both visual fields and by optic disc deterioration on the same visit, 1 endpoint was selected randomly. Participants who developed an endpoint owing to causes other than POAG were classified as developing a non-POAG endpoint. We evaluated the Endpoint Committee's performance and impact as follows: (1) Intergrader agreement among Endpoint Committee members was reported as the proportion of endpoint reviews in which unanimity was achieved in the first and second rounds of independent review. (2) The all-cause and POAG endpoints were compared by randomization group and separately by visual field endpoints and optic disc endpoints. (3) Treatment effect was estimated using a post hoc Mantel-Haenszel test to calculate the relative risk of all-cause endpoints and POAG endpoints in the observation and medication groups. (4) Post hoc statistical power of the OHTS was estimated using all-cause endpoints and POAG endpoints, assuming a 2-sided alpha = 0.05 for 2-sample proportions test for a fixed sample of 1636 participants with no adjustment for censoring.

RESULTS

DATA WERE REANALYZED FOR THIS REPORT IN 2012. OVER A median follow-up of 7.5 years of OHTS, the Endpoint Committee reviewed 467 endpoints from 267 participants. The first endpoint per participant (n = 267) was selected for inclusion in this report to avoid bias from subsequent reviews. If both visual field and optic disc endpoints were detected on the same visit for 5.2% (14 of 267) of the participants, the endpoint was selected randomly for inclusion in this report.

• **INTERGRADER AGREEMENT:** The 3 members of the Endpoint Committee independently reached unanimity in the first round of review for 61.0% (163 of 267) of endpoints, in the second round for 32.2% (86 of 267) of endpoints, and in a consensus conference call for the remaining 6.7% (18 of 267). A slightly higher rate of optic disc endpoints required a third round of review: 9.6% (13 of 135) compared to 3.8% (5 of 132) of the visual field endpoints. Mean (±standard deviation) time to notification of clinics of Endpoint Committee decision in the first, second, and third rounds of review was 11.0 ± 7.1 days, 20.8 ± 14.3 days, and 31.4 ± 15.6 days, respectively.

• **ALL-CAUSE AND PRIMARY OPEN-ANGLE GLAUCOMA ENDPOINTS, TREATMENT EFFECT, AND STATISTICAL POWER:** Overall, 16.3% (267 of 1636) of the participants developed an endpoint and 9.5% (155 of 1636) developed a POAG endpoint. In the observation group, 19.5% (160 of 819) of the participants developed an endpoint compared to 13.1% (107 of 817) in the medication group (relative risk = 0.67, 95% confidence interval [CI] of 0.54-0.84)—a reduction of 33%. In the observation group 13.2% (108 of 819) developed a POAG endpoint compared to 5.8% (47 of 817) in the medication group (relative risk = 0.44, 95% CI of 0.31-0.61)—a reduction of 56%. Post hoc statistical power for detecting a treatment effect for all endpoints was 0.94 compared to >0.99 for detecting a treatment effect for POAG endpoints with the OHTS sample of 1636 participants (Table 1).

We found no evidence of bias in the Endpoint Committee's attribution of endpoints to "non-POAG" causes by randomization group. Non-POAG endpoints (n = 112) were approximately equally distributed in both randomization groups, 6.3% (52 of 819) in the observation group and 7.3% (60 of 817) in the medication group.

• **VISUAL FIELD PRIMARY OPEN-ANGLE GLAUCOMA ENDPOINTS:** Of the 132 visual field endpoints (VF endpoints), the Endpoint Committee classified 49% (65 of 132) as "probably due to POAG" and 51% (66 of 132) as "probably not due to POAG". One VF endpoint was classified as "no change" (Table 2). Other causes were recorded in notes by Endpoint Committee members and are reported in Table 3. In the observation group, 9.2% (75/819) of the participants developed a VF endpoint, compared to 7.0% (57/817) in the medication group (relative risk of 0.76, 95% CI of 0.55-1.06)—a risk reduction of 24%. In the observation group, 5.5% (45/819) of the participants developed a POAG VF endpoint compared to 2.4% (20/817) in the medication group (relative risk = 0.44, 95% CI of 0.26-0.75)—a risk reduction of 56%. Post hoc statistical power for detecting a treatment effect for all-cause VF endpoints was 0.37 compared to 0.88 for detecting a treatment effect for POAG VF endpoints with a fixed sample of 1636 participants (Table 1).

• **OPTIC DISC PRIMARY OPEN-ANGLE GLAUCOMA ENDPOINTS:** Of the 135 optic disc endpoints, the Endpoint Committee classified 30.4% (41 of 135) as "not clinically significant" and did not adjudicate cause, 66.7% (90 of 135) were classified as "clinically significant and due to POAG," and 3% (4 of 135) were clinically significant and not due to POAG (Table 2). In the observation group, 10.4% (85/819) of the participants developed an optic disc endpoint compared to 6.1% (50/817) in the medication group (relative risk of 0.59, 95% CI of 0.42-0.82)—a reduction of 41%. In the observation group 7.7% (63/819) of the participants developed a POAG optic disc endpoint compared to 3.3% (27/817) in the medication group (relative risk = 0.43, 95% CI of 0.28-0.67)—a reduction of 57%. Post hoc statistical power for detecting a treatment effect for all optic disc endpoints was 0.89 and 0.97 for POAG optic disc endpoints with a fixed sample of 1636 participants (Table 1).

TABLE 1. Estimated Incidence of All-Cause Endpoints and Primary Open-Angle Glaucoma Endpoints in the Ocular Hypertension Treatment Study–Phase 1, by Group,[a] and Relative Risk and Post Hoc Estimates

Reproducible Endpoints	Endpoints in Observation Group N = 819	Endpoints in Medication Group N = 817	Relative Risk of Endpoint (95% CI)	Post Hoc Statistical Power
All-cause endpoints	19.5% (160/819)	13.1% (107/817)	0.67 (0.54, 0.84)	0.941
POAG endpoints	13.2% (108/819)	5.8% (47/817)	0.44 (0.31, 0.61)	>0.99
All-cause VF endpoints	9.2% (75/819)	7.0% (57/817)	0.76 (0.55, 1.06)	0.367
POAG VF endpoints	5.5% (45/819)	2.4% (20/817)	0.44 (0.26, 0.75)	0.883
All-cause disc endpoints[b]	10.4% (85/819)	6.1% (50/817)	0.59 (0.42, 0.82)	0.886
POAG disc endpoints	7.7% (63/819)	3.3% (27/817)	0.43 (0.28, 0.67)	0.974

POAG = primary open-angle glaucoma; VF = visual field.

[a]Sample includes the first endpoint per participant. Incidence estimates are not adjusted for variable follow-up time. Median follow-up is 7.5 years.

[b]Optic disc endpoints that were judged "not clinically significant" were not adjudicated as due to POAG or not.

TABLE 2. Endpoint Committee Adjudication of Visual Field Endpoints and Optic Disc Endpoints[a]

	Type of Endpoint			
	Visual Field		Optic Disc	
Attribution of Cause of Change	N	Percent	N	Percent
Probably due to POAG	65	49.2%	90	66.7%
Probably NOT due to POAG	66	50.0%	4	3.0%
No change/not clinically significant	1	0.8%	41	30.4%
Total	132	100%	135	100%

POAG = primary open-angle glaucoma.

[a]If 2 endpoints occurred on the same date for a participant, 1 was randomly selected for inclusion in the analysis dataset.

TABLE 3. Visual Field Endpoints Attributable to Non–Primary Open-Angle Glaucoma Causes[a]

	VF	
	N	Percent
Lid abnormalities/external disease	23	24.5%
Retinal vein occlusion	14	14.9%
Cataract/other media opacity	11	11.7%
Diabetic retinopathy	6	6.4%
Age-related macular degeneration	6	6.4%
Neurologic	6	6.4%
Other[b]	28	29.7%
All	94	100%

VF = visual field.

[a]"Other" causes (including, eg, glaucoma other than POAG, optic neuropathy, dry eyes) were recorded in Endpoint Committee notes from medical histories completed at each study visit.

[b]Total number of non-POAG causes (n = 94) is greater than the number of non-POAG visual field endpoints (n = 66) because an endpoint can be attributable to more than 1 cause.

DISCUSSION

THE ENDPOINT COMMITTEE HAD A CLEAR IMPACT ON THE accuracy of estimates of POAG conversion and treatment effect. Overall, 16.3% of the participants developed an endpoint, but only 9.5% of the participants had an endpoint attributed to POAG by the Endpoint Committee. The impact of the Endpoint Committee's determination of POAG from non-POAG endpoints was most pronounced for VF endpoints. Eight percent of the participants developed a VF endpoint, but only 4% developed a VF endpoint attributed to POAG. Non-POAG causes of visual field abnormalities such as cataract, lid abnormalities, and neurologic disorders (Table 3) would be expected in a long-term study in older adults.

The US Food and Drug Administration and the European Medicines Agency recommend centralized adjudication when endpoints are subjective or require the application of a complex definition, and/or when treatment assignment is not masked. To our knowledge, OHTS is the only National Institutes of Health–sponsored trial in glaucoma to use a masked Endpoint Committee to adjudicate whether reproducible visual field abnormalities and/or optic disc deterioration were attributable to POAG. Beyond the field of ophthalmology, the number of therapeutic trials using Endpoint Committees has increased and best practice guidelines for their operation have been developed.[18–21]

Four key components of the Endpoint Committee are as follows: (1) masking, (2) standardization of outcome determination over time and across clinics, (3) integrating both functional and structural tests, and (4) requirement of unanimity. The benefits of the Endpoint Committee are clear, particularly when considering the removal of non-POAG causes that dilute the treatment effect. The calculated treatment effect was greater for POAG endpoints than

for all-cause endpoints because medication has little or no effect on non-POAG endpoints. Treatment reduced the estimate of all-cause endpoints by 33% (relative risk of 0.67) and the estimate of POAG endpoints by 56% (relative risk of 0.44).

In order to make OHTS results more generalizable to clinical practice, the Data and Safety Monitoring Committee instructed the Endpoint Committee to require optic disc endpoints to be "clinically significant" in magnitude to justify initiation of treatment. The Endpoint Committee classified nearly a third of all optic disc endpoints as "not clinically significant," although these endpoints had been documented as reproducible by trained readers at the Optic Disc Reading Center. Optic disc endpoints that were judged "not clinically significant" were not adjudicated as to cause. Of the "clinically significant" optic disc endpoints, 97% were attributed to POAG. This high level of specificity should not be interpreted as evidence that optic disc endpoints are generally more specific for POAG than visual field endpoints, since adjudication was performed only for the subset of clinically significant optic disc endpoints.

There are some important considerations in evaluating the benefit and limitations of an Endpoint Committee. Not all treatment trials benefit from endpoint adjudication. In a review of 10 trials with over 9000 events from more than 95 000 participants, Pogue and associates found no difference between adjudicated composite outcomes (cardiovascular death, myocardial infarction, or stroke) and nonadjudicated outcomes.[22] Adjudication may be less critical if study duration is short, patient sample is homogeneous, outcomes are quantitative, and there are few competing causes of endpoints.[2,3] The use of artificial intelligence and statistical techniques (eg, PROGRESSOR) could increase the certainty of disease presence/progression in Reading Centers and thereby could increase the certainty of causal attribution.[23] However, given the uncertainty of causal attribution of visual field abnormality and optic disc deterioration, glaucoma intervention studies can benefit from a centralized process that drives consensus. Positioning the Endpoint Committee review following the Reading Center review mitigated bias and affirmed clinically relevant endpoints.

A limitation of the OHTS Endpoint review process is related to turnover in Endpoint Committee membership, which could have, but did not, occur during this study. Thus, training and certification of Endpoint Committee members should be considered in future studies. Moreover, there was no attempt to externally validate the Endpoint Committee's attribution of endpoints to POAG in OHTS. When competing ocular or systemic conditions co-occurred with a possible POAG cause, there is a risk that the attribution process may favor diagnostic specificity and result in an undercount of POAG events.

We conclude that the masked adjudication of endpoints by the Endpoint Committee increased statistical power and increased the accuracy of estimates of POAG conversion and treatment effect. Given the strong effect of treatment in this trial, the increased power was not critical. However, in studies where the therapeutic intervention has a less robust effect, the increased power could be critical. An Endpoint Committee should be considered in therapeutic trials when common ocular and systemic comorbidities, other than the target condition, could compromise study results.

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