The Collaborative Initial Glaucoma Treatment Study

Study Design, Methods, and Baseline Characteristics of Enrolled Patients

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Objective: The Collaborative Initial Glaucoma Treatment Study (CIGTS) is a randomized, controlled clinical trial designed to determine whether patients with newly diagnosed open-angle glaucoma (primary, pigmentary, or pseudoexfoliative) are better treated by initial treatment with medications or by immediate filtration surgery.

Design: Randomized, controlled clinical trial.

Participants: A total of 607 patients with open-angle glaucoma were enrolled.

Intervention: Patients randomized to initial medications (n=307) received a stepped regimen of medications to lower intraocular pressure. Those randomized to initial surgery (n=300) underwent trabeculectomy to lower intraocular pressure.

Main Outcome Measures: Progression in visual field loss constitutes the study's primary outcome variable. Secondary outcomes include health-related quality of life, visual acuity, and intraocular pressure.

Results: Randomized assignment resulted in a balanced distribution between treatment groups for most demographic and clinical measures assessed at enrollment. More males than females were enrolled (55% were males), and a substantial percentage (38.1%) of enrollees were blacks. Most enrollees (90.6%) were diagnosed with primary open-angle glaucoma; the remainder had either pseudoexfoliative (4.8%) or pigmentary (4.6%) forms of open-angle glaucoma.

Conclusions: Follow-up of this well-characterized group of patients should provide well-rounded guidance, based on both traditional ophthalmic measures and patients' perspectives on their health-related quality of life, on how best to initially treat open-angle glaucoma. *Ophthalmology 1999;106:653–662*

The Collaborative Initial Glaucoma Treatment Study (CIGTS) is a randomized, controlled clinical trial designed to determine whether patients with newly diagnosed open-angle glaucoma (primary, pigmentary, or pseudoexfoliative) are managed better by initial treatment with medications or by immediate filtration surgery. Patients enrolled in the study are assigned by randomization to receive either a sequence of topical medications or trabeculectomy and are being followed to evaluate the extent to which these interventions preserve their visual function, reduce their intraocular pressure (IOP), and affect their health-related quality of life. Between October 1993 and April 1997, CIGTS investigators at 14 clinical centers in the United States enrolled 607 patients, and follow-up is ongoing. This article presents the study's rationale, design, methods, and baseline findings.

Originally received: February 4, 1998.
Revision accepted: November 25, 1998. Manuscript no. 98060.

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Presented in part at the Association for Research in Vision and Ophthalmology annual meeting, Ft. Lauderdale, Florida, May 1998, and the Society for Clinical Trials annual meeting, Atlanta, Georgia, May 1998.

Supported by the National Institutes of Health, National Eye Institute, grants EY09100, EY09140, EY09141, EY09142, EY09143, EY09144, EY09145, EY09148, EY09149, EY09150, and EY09639.

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Rationale

Open-angle glaucoma, one of the major causes of impaired vision worldwide, is a condition characterized by damage to and loss of optic nerve axons, resulting most commonly in loss of peripheral aspects of the visual field, which may progress to loss of central vision. Treatment of open-angle glaucoma has been directed to lowering the IOP based on several clinical observations:

1. Many patients with open-angle glaucoma have elevated IOP.
2. Those patients who lack elevated IOP are thought to have a lower threshold for IOP-related damage.
3. IOP is amenable to measurement and reduction.
4. IOP reduction may retard or prevent further damage.

Methods to reduce IOP include use of systemic or topical medications, which lower IOP by either decreasing aqueous production or increasing aqueous outflow; use of laser energy applied to the trabecular meshwork to improve aqueous outflow; or use of filtration surgery to produce an alternate route for aqueous outflow. In the United States, medication is the most common initial approach to treating newly diagnosed open-angle glaucoma. If medications fail to prevent progression of the patient's glaucomatous damage and/or fail to maintain IOP at a level that the treating physician considers "safe," argon laser trabeculoplasty is used by some ophthalmologists as the next treatment step. Incisional surgery is performed only if medications, with or without argon laser trabeculoplasty, fail to control progression of glaucoma. The effectiveness of this treatment strategy, however, has been challenged by the findings in a number of studies of initial surgical intervention[1–15] indicating that surgical intervention may be more effective if done on an eye that had not been subjected to substantial prior treatment with topical medications. In addition, recent attention to health-related quality of life has increased clinicians' awareness of treatment side effects that can result from medications used in glaucoma treatment.[16–18]

The purpose of the CIGTS is to compare the outcomes of initial medical and surgical treatments for newly diagnosed open-angle glaucoma. Outcome measures include clinician-assessed and patient-reported visual function, IOP control, and health-related quality of life.

Study Design and Methods

Organization

Fourteen clinical centers and 1 satellite center participated in the recruitment of patients and are now actively following enrolled patients (refer to Appendix for a list of study centers and personnel). The study's protocol and informed consent were approved by human studies' review boards at all participating centers. Three resource centers provide a central structure to the project (refer to Appendix). The Administrative Center provides direction to the study; the Coordinating Center provides day-to-day management of protocol questions, quality monitoring, and data activities, organizes all study meetings, and prepares information for study reports; and the Interviewing Center conducts all patient interviews by telephone for collecting health-related quality-of-life information.

Study committees include the Operations Committee, which provides for interaction of all resource center staff on the study's day-to-day management; the Steering Committee, which addresses variation in protocol interpretation, considers protocol revisions, evaluates ancillary studies, and approves any study presentations; and the Data and Safety Monitoring Committee, which reviews and approves major protocol revisions, monitors quality assurance information, evaluates collected data for indications of treatment effects and patient safety concerns, and makes recommendations to the National Eye Institute on study continuation.

Inclusion Criteria

To be eligible for the study, patients must have the following: (1) a diagnosis of primary open-angle, pseudoexfoliative, or pigmentary glaucoma in one or both eyes; (2) one of three combinations of qualifying IOP, visual field changes, and optic disc findings as follows: (a) a qualifying IOP of 20 mmHg or higher, with a Humphrey 24–2 visual field result that includes at least three contiguous points on the total deviation probability plot at the less than 2% level and a Glaucoma Hemifield Test result that is "outside normal limits," and optic discs compatible with glaucoma, or (b) a qualifying IOP of 20 to 26 mmHg, with a Humphrey 24–2 visual field result that includes at least two contiguous points in the same hemifield on the total deviation probability plot at the less than 2% level and glaucomatous optic disc damage, or (c) a qualifying IOP of 27 mmHg or higher, with glaucomatous optic disc damage (no required visual field changes); all optic disc determinations were made by a clinical center ophthalmologist; (3) a best-corrected Early Treatment Diabetic Retinopathy Study visual acuity score of 70 or greater (approximate Snellen equivalent, 20/40) in each eye; and (4) an age between 25 and 75 years.

Exclusion Criteria

Patients were ineligible to participate if they had the following: (1) a cumulative lifetime use of eyedrops for glaucoma that exceeded 14 days; (2) used any eyedrops for glaucoma in the 3 weeks before baseline I visit (washout from $\leq$14 days of use was permitted); (3) a CIGTS visual field score (see below for description) that exceeded 16.0 in either eye; (4) evidence of ocular disease other than glaucoma that might affect the measurement of IOP, assessment of visual function, visual field testing, and/or the facility of aqueous outflow; (5) proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy with more than ten microaneurysms by clinical count noted at the baseline examination; (6) undergone ophthalmic laser, refractive, conjunctival, or intraocular surgery in either eye; (7) would likely require cataract surgery within 1 year of randomization; and (8) current or expected chronic use of corticosteroids.

Enrollment and Randomization

On completion of two baseline visits in which measures of visual field and IOP were taken at each visit and other eligibility and exclusion criteria were verified, informed consent to participate was obtained from eligible patients. Their treatment assignment was determined by calling the Coordinating Center, verifying eligibility, and then having the Coordinating Center enter the stratification variables into a computer algorithm that allocated the patient to the treatment group that resulted in optimal balance across the strata. Minimization, a form of adaptive randomization,[19] was used for treatment allocation. In this approach, the two treatment groups were balanced simultaneously over five predetermined stratification variables: age (25–54, 55–64, 65–75), center (14 sites), gender (male, female), race (black, white, Asian, other), and diagnosis (primary, pigmentary, and pseudoexfoliative forms of open-angle glaucoma). Given the large number of stratum cells (792) relative to the desired sample size (600), a simple stratified randomization approach would have yielded many empty and sparse cells; therefore, the minimization approach was selected to balance treatment assignments over the marginal totals of each stratum separately.

Table 1. Sample Size Estimation

Outcome Variable	Meaningful Difference (%)	SD (%)	Sample Size Needed per Group for Power = 0.90
Visual field stability at 3 yrs	20	NA	106
Intraocular pressure (mmHg)	4.0	8.0	85
Symptoms—total no.	2.0	7.0	258
Symptoms—eye-related	1.0	3.7	288
Symptom impact score—total	4.0	14.7	284
Symptom impact score—eye-related	2.0	6.5	222
SIP psychosocial score (abridged)	3.0	10.8	273
SIP total score (abridged)	5.0	9.7	222

SD = standard deviation; NA = not applicable; SIP = Sickness Impact Profile.

Treatment Sequences

In the surgical arm, the patient's study eye underwent trabeculectomy within 14 days of randomization. If further treatment was required (refer to description of intervention failure), argon laser trabeculoplasty was the next treatment step, followed by a sequence of medications, repeat trabeculectomy with an antifibrotic agent, and then medication. In the medical arm, patients received a sequence of medications that usually began with a topical beta-blocker, followed by an alternate single topical therapeutic agent, dual topical therapy, triple topical therapy, an alternate combination of triple topical therapy, and an optional additional topical and/or oral medication or medications. If further treatment was required, the next treatment step was argon laser trabeculoplasty, followed by trabeculectomy, medication, trabeculectomy with an antifibrotic agent, and medication.

Criteria for intervention failure had to be met before further treatment steps were initiated. During the initial study period (until July 1996, when failure criteria were altered; see below), these criteria included failure to meet a target IOP that was established at the time of randomization or evidence of progressive visual field loss or both. Target IOP was established based on the patient's *reference IOP* (i.e., the mean of six separate IOP measurements taken in the course of the two baseline visits) and their *reference visual field score* (i.e., the mean of visual field scores from at least two Humphrey 24–2 visual fields taken during the two baseline visits). The formula for target IOP calculation is as follows: target IOP = (1-[reference IOP + visual field score]/100) × reference IOP. Therefore, if the reference IOP = 28 mmHg, and the reference visual field score = 5, then: target IOP = (1-[28 + 5]/100) × 28 = (1-0.33) × 28 = 0.67 × 28 = 19 mmHg. If, on a follow-up visit, the IOP was 1.0 mmHg or more above the target IOP, and this was confirmed on another visit, IOP-related intervention failure was declared and the next treatment step instituted. Visual field-related intervention failure required evidence of progressive visual field loss, which was declared if the overall score (see below for a description of score calculation) was increased by 3.0 or more units above the reference visual field score on three consecutive tests performed at separate clinic visits.

Because of concern that the use of the target IOP alone to arbitrate intervention failure might result in overly aggressive advancement in the treatment sequence, the criterion for IOP failure was modified after July 1996. The revision permitted greater tolerance for measured IOP relative to the target IOP depending on the extent of field loss in the central visual field region. Evidence of central field loss requires the strictest conformance to target, in that a measured IOP on a follow-up visit that is more than 15% over the target triggers consideration of intervention failure, whereas field loss that spares the central four points but involves the paracentral region allows more tolerance (20% or 25% above the target IOP depending on the extent of paracentral field loss) for a measured IOP at a follow-up visit relative to the target IOP.

Primary and Secondary Study Outcomes

One measure of visual function, sustained progression in visual field loss, constitutes the study's primary outcome variable. Progression represents an increase in the visual field score of three units or more from the patient's reference visual field score. This extent of change must be documented consistently over a 1-year period. Secondary outcomes include differences between treatment groups in health-related quality of life, visual acuity, and IOP.

Sample Size Estimation

Two prior studies provided some relevant information for sample size estimation. The study by Jay and Allan[3] found that visual fields showed no progression 3 years after treatment initiation in 55% of medically treated patients and 90% of surgically treated patients. Migdal and Hitchings[1] reported that IOP in medically treated patients averaged 19.2 mmHg, and IOP in surgically treated patients averaged 15.4 mmHg 2 years after treatment initiation, with an approximate standard deviation of 8.0 mmHg. We also conducted a pilot study (unpublished data, 1992) in which patients with glaucoma being treated medically and others who underwent glaucoma filtration surgery were interviewed to obtain estimates of variability in their health-related quality-of-life scores.

Using these findings, and estimates of what would be a meaningful difference between treatment groups (obtained from the literature[20–22] for the Sickness Impact Profile scores), Table 1 shows required sample sizes per group. A two-sample *t*-test model was used for the interval scale variables; a two-sample binomial model was used for the dichotomous variable, and two-sided testing at an alpha level of 0.05 was assumed. Approximately 300 patients per group would be necessary to have 90% power for all of the quality-of-life measures. The ophthalmic measures used to assess control of glaucoma (i.e., IOP and visual field changes) required smaller sample sizes per group to provide ample statistical power.

Outcome Assessment Methods

Visual Field. The visual field examination protocol developed for the Advanced Glaucoma Intervention Study (AGIS),[23,24] which makes use of the Humphrey Field Analyzer equipped with Statpac 2 software (Humphrey Systems, Dublin, CA) for the central 24–2

Table 2. Tests Performed at Study Visits through Month 24

Assessment	Baseline	Month 2	Month 3	Month 6	Month 12	Month 18	Month 24
Visual field	Yes	No	Yes	Yes	Yes	Yes	Yes
Refraction	Yes	No	Yes	Yes	Yes	Yes	Yes
Visual acuity	Yes	No	Yes	Yes	Yes	Yes	Yes
Slit-lamp examination	Yes	No	Yes	Yes	Yes	Yes	Yes
IOP	Yes	No	Yes	Yes	Yes	Yes	Yes
Gonioscopy	Yes	No	No	Yes	No	Yes	No
Dilated lens examination	Yes	No	Yes	No	Yes	No	Yes
Dilated fundus examination	Yes	No	Yes	No	Yes	No	Yes
QOL interview	Yes	Yes	No	Yes	Yes	Yes	Yes

IOP = intraocular pressure; QOL = quality of life.

threshold visual field test, is used in CIGTS. Examiners are not masked to the treatment status of the patients. The method of scoring visual field test printouts differs from the method used in AGIS. The overall visual field score is generated from the total deviation probability plot values on the Humphrey 24–2 printout to account for the extent and depth of visual field loss. The score is calculated as follows. Neighboring points are defined as those adjacent to the given point on a side or corner. Each of the 52 points in the field is called a point of defect if its probability value is 0.05 or less in the same hemifield. A weight is assigned depending on the minimum depth of the defect at the given point and the two most defective neighboring points. A minimum defect of 0.05 is given a weight of 1, a minimum defect of 0.02 is given a weight of 2, a minimum defect of 0.01 is given a weight of 3, and a minimum defect of 0.005 is given a weight of 4. A point without two neighboring points all depressed to at least P equal to 0.05 or less is given a weight of 0. For example, a point at P equal to 0.01 or less with only two neighboring points of defect, both at P equal to 0.05 or less, would receive a weight of 1. The weights for all 52 points in the field are summed, resulting in a value between 0 and 208. This sum is then scaled (dividing by 10.4) to a range from 0 (no defect) to 20 (all points showing a defect at the $P < 0.005$ level).

Other Outcomes. Goldmann applanation tonometry is used to measure IOP before gonioscopy or the administration of any dilating agent. An examiner and reader take part in the measurement procedure. Refraction involves use of Chart R of the Lighthouse distant visual acuity test charts (2nd edition)[25,26] to determine the best lens correction for each eye. Spherical and cylindrical components of the refraction are determined with loose lenses, according to a specified protocol. Visual acuity measurement makes use of the AGIS visual acuity examination protocol,[23] which is a minor modification of the Early Treatment Diabetic Retinopathy Study protocol.[27] Patients are tested at 4 m, before pupil dilation or IOP testing. Lighthouse test charts 1 and 2 are used in stand- or wall-mounted Lighthouse light boxes under standardized lighting conditions. Examiners are not masked to the treatment status of the patients.

Health-related Quality of Life. An instrument was developed that incorporates a number of previously designed questionnaires along with several components made specifically for this study. Patients answer 16 questions dealing with their general health perceptions, 4 questions about adaptations and social support, the 33-item Visual Activities Questionnaire,[28] a 43-item symptom and health problem list, the 8-item Center for Epidemiologic Studies-Depression questionnaire,[29] the full 136-item Sickness Impact Profile,[30] questions on a number of possible comorbidities, and questions on compliance to and satisfaction with their treatment. The instrument is administered by telephone contact with the patient in his or her home at a prearranged time and requires approximately 45 minutes to administer. Trained interviewers at a central location conduct the interview and record patients' responses. Unless the patient reveals his or her treatment status, the interviewer is masked to that information. A more comprehensive description of this instrument, including its development and application at baseline, is provided in another article in preparation.

Patient Follow-up

On enrollment and initiation of treatment, patients are followed at the clinical centers at regularly scheduled visits, which commence 3 months after treatment has begun; after a 6-month visit, subsequent visits are conducted at 6-month intervals (e.g., at 12 months, 18 months). At each study visit, information is collected and tests are conducted, as described in Table 2. Patients are asked to describe their medication use, ophthalmic surgical procedures, and healthcare services use since their last visit, and they are given an ophthalmic examination. In 1997, binocular testing of visual acuity, contrast sensitivity, and visual field was initiated at all visits. Health-related quality-of-life interviews take place at 2 months, 6 months, and then at 6-month intervals after treatment initiation.

Participating Community Ophthalmologist Involvement

Although all study data emanate from standardized examinations conducted at the clinical centers and interviews conducted by telephone, the patient may be treated and followed by a participating community ophthalmologist (PCO) outside of the clinical center. These PCOs took part in recruitment by referring potentially eligible patients to the clinical centers for evaluation and then could administer the assigned treatment based on their a priori arrangement with the clinical center ophthalmologist. All PCOs were asked to attend a prestudy initiation seminar on the protocol, and each clinical center's coordinator and ophthalmologist maintains contact with them regarding the status of referred patients.

Quality Control Measures

The importance of ensuring the quality of collected data was stressed at a meeting of all clinical center coordinators and ophthalmologists before the onset of recruitment. At this meeting, all protocol requirements and testing procedures were carefully reviewed, and general agreement was reached on the approach to be followed for interventions. Site visits to the clinical center were conducted before enrollment began. All clinical center personnel

Table 3. Characteristics of Enrolled Patients, by Treatment Group

	Medicine (n = 307)		Surgery (n = 300)		
	No.	%	*No.*	%	**P***
Age (yrs)					
25–49	80	26.1	67	22.3	0.56
50–64	133	43.3	136	45.3	
65–75	94	30.6	97	32.3	
Sex					
Female	143	46.6	130	43.3	0.42
Male	164	53.4	170	56.7	
Race					
White	167	54.4	170	56.7	0.80
Black	120	39.1	111	37.0	
Asian	4	1.3	6	2.0	
Other	16	5.2	13	4.3	
Hypertension					
No	185	60.3	197	65.7	0.17
Yes	122	39.7	103	34.3	
Diabetes					
No	247	80.5	258	86.0	0.07
Yes	60	19.5	42	14.0	
Smoking history					
Never	125	40.7	109	36.3	0.59
Ex-smoker	120	39.1	126	42.0	
Current—cigarette	49	16.0	55	18.3	
Current—other	13	4.2	10	3.3	
Family history of glaucoma					
Immediate family					
No	176	57.3	168	56.0	0.90
Yes	99	32.2	102	34.0	
Uncertain	32	10.4	30	10.0	
Distant family					
No	181	59.0	168	56.0	0.31
Yes	60	19.5	52	17.3	
Uncertain	66	21.5	80	26.7	
Glaucoma type					
POAG	278	90.6	272	90.7	0.92
Pseudoexfoliative	14	4.6	15	5.0	
Pigmentary	15	4.9	13	4.3	
Eligibility criteria					
VFD + IOP ≥ 20	211	68.7	228	76.0	0.05
Disc + IOP ≥ 27	96	31.3	72	24.0	

Immediate = parents, siblings, children; Distant = aunts, uncles, grandparents, cousins; POAG = primary open-angle glaucoma; VFD = visual field defect; IOP = intraocular pressure.

* Chi-square test contrasting the proportions in the medical and surgical groups.

who were to conduct CIGTS examinations had to pass written and hands-on testing of the protocol's requirements for the testing procedure. As the study progresses, a procedure is in place for certifying new clinical center staff, and all certified staff members must conduct at least three examinations in a 1-year period to maintain their certification.

At each clinical center, one individual is appointed as the center's coordinator, and that person is charged with ensuring that the study protocol is followed, new personnel are adequately trained, and data forms are fully completed and promptly submitted. At the Coordinating Center, the Protocol Monitor interacts regularly with clinic coordinators on the timing of treatments and any protocol questions. All data are submitted to the Coordinating Center, where forms are visually inspected for obvious errors of omission or logical inconsistencies. After double entry of forms data, a computerized audit program is applied to evaluate form completeness, internal consistency, outliers, and entries that do not conform to coding requirements. Questionable or errant data are returned to the clinical center's coordinator for clarification or correction.

Results: Baseline Characteristics

The recruitment phase of the study was completed in 38 months, with a total of 607 patients entered. Recruitment varied from 35 to 64 patients within the 11 clinical centers involved at the study's onset, and from 11 to 18 patients within the 3 centers added in 1995.

There were no substantial imbalances evident between treatment groups on demographic factors (Table 3). More males than females have been enrolled (334 of 607 enrollees [55%] were males), and a substantial proportion of the study group (38%, 231 of 607) are blacks. Age at enrollment (Fig 1) indicates no male/female difference but does show an evident and statistically significant disparity between blacks and whites ($P = 0.0014$), which

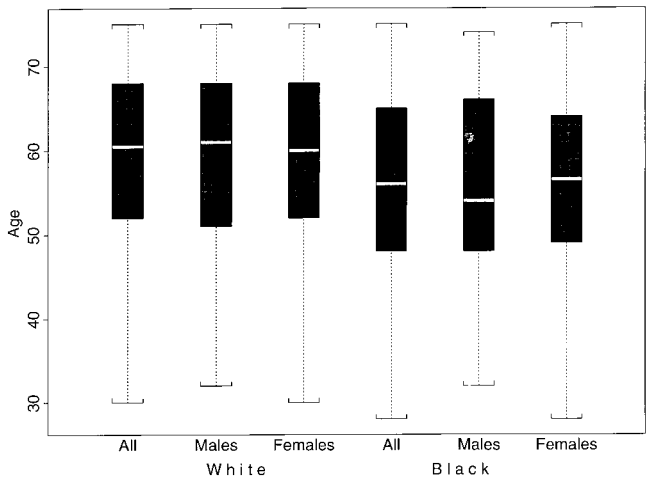

Figure 1. Age at enrollment by race and gender. A statistical comparison of the mean age at enrollment indicates that whites (mean age, 58.9 years) are significantly older than blacks (mean age, 55.9 years); $P = 0.0014$, independent Student's *t* test. Key to boxplot values: The black box spans the values from the 25th to the 75th percentiles, with the median shown as a white horizontal band across the box. The "whiskers" (dotted lines) are drawn from each end of the box to the minimum and maximum values of the data.

is consistent for both males and females. The median age of blacks at entry (56 years) is 5 years younger than whites (61 years).

One third of CIGTS patients reported a history of glaucoma in their immediate family (Table 3), and a slightly higher frequency indicated they had been diagnosed with systemic hypertension. Diabetes mellitus was reported in 102 (17%) of the 607 enrolled patients. Most patients had either never smoked or had quit smoking (39% and 41%, respectively); 127 (21%) of 607 patients were current smokers. Patients randomized to initial medicine had a greater frequency of hypertension and diabetes.

Randomization resulted in similar distributions of most ophthalmic variables in the two treatment groups. Of the multiple variables evaluated, two differences were found between treatment groups:

1. The percentage of patients who showed visual field defects at enrollment is significantly higher ($P = 0.05$) in the surgery group (76%; 228 of 300) than in the medical group (69%; 211 of 307).
2. The frequency of hemorrhage on the optic disc rim tissue or adjacent peripapillary area was significantly higher ($P = 0.02$) in the surgery group (5%; 15 of 300) than in the medical group (1.6%; 5 of 307).

The higher frequency of visual field defects at baseline in the surgery group likely contributed to a slightly, albeit insignificantly, higher reference visual field score in the surgery group (5.0 vs. 4.6), but IOP, visual acuity, and cup-to-disc ratios were very similar (Table 4).

Overall, patients assigned to surgery had their treatment administered by the Clinical Center's principal investigator (PI) more frequently than patients assigned to medicine; 73% (220 of 300 patients) of those randomized to surgery were treated by a Clinical Center's PI, whereas 64% (197 of 307 patients) of those assigned to medicine were treated by a Clinical Center's PI (Table 5). Centers that relied heavily on PCOs to identify eligible patients from their practices (e.g., Gainesville, Seattle, and Winston–Salem) were more likely to have the treating ophthalmologist be the PCO.

Discussion

Unlike several other clinical trials of glaucoma treatment in which the randomization unit was the eye, such as the Glaucoma Laser Trial[31] and the Advanced Glaucoma Intervention Study,[23] the CIGTS randomization unit was the patient. Even though patients might have presented with only one eye meeting the criteria for treatment, they had to consent to participate based on the foreknowledge that should their other eye eventually meet the treatment criteria, it would receive the same treatment approach used for the first eye. This decision was based on the desire to assess treatment effects in patients rather than in eyes. Because glaucoma is chronic and its treatment is not usually confined to a single eye, the CIGTS was designed specifically to encompass both eyes and to capture the effects of treatment on patients.

Clinical centers involved in this study were selected based on their ability to provide excellent care to patients with glaucoma, their ability to recruit, and, in some cases, their access to a racially diverse referral population. The 607 enrolled patients have a median age (59 years) that is similar to the 291 patients in the Glaucoma Laser Trial (median age, 61 years),[31] who were also newly diagnosed glaucoma patients. The substantial percentage of blacks in the study population (38%; 231 of 607), and the nearly equal distribution of males and females, will provide statistical power to assessments of race and gender as covariates in outcome analyses. Because most patients (91%) were diagnosed with primary open-angle glaucoma, the number available in the other two diagnostic categories (pigmentary and pseudoexfoliative forms of open-angle glaucoma) will limit separate evaluations of these patients.

Randomization was effective in producing two groups with very comparable characteristics, both in terms of demographic, general medical, and ophthalmic parameters, with two exceptions. Patients in the surgery group showed a higher frequency of visual field loss (76% vs. 69%) and disc hemorrhage (5% vs. 1.6%) at baseline. Other intergroup differences, such as the higher frequency of hypertension and diabetes in medically treated patients, were not statistically significant but will also require consideration of adjustment in outcome analyses. The mean age of blacks at

Table 4. Intraocular Pressure, Visual Field, Visual Acuity, and Cup-to-Disc Ratio, by Treatment Group, for the Primary Study Eye: Mean (SD)

Variable	Medicine (n = 307)	Surgery (n = 300)	P*
Qualifying IOP	27.6 (5.5)	27.4 (5.7)	0.71
Reference visual field score	4.6 (4.2)	5.0 (4.3)	0.15
Visual acuity score	85.6 (5.9)	85.8 (5.5)	0.62
Horizontal CDR	0.64 (0.18)	0.63 (0.17)	0.70
Vertical CDR	0.69 (0.17)	0.70 (0.17)	0.51

SD = standard deviation; IOP = intraocular pressure; CDR = cup-to-disc ratio.

* Independent, two-tailed Student's *t* tests contrasting mean values between the medical and surgical groups.

Table 5. Percent Distribution of Treating Physicians, by Treatment Group and Clinical Center

	Medicine (n = 307)			Surgery (n = 300)		
Clinical Center	*n*	*CC (%)*	*PCO (%)*	*n*	*CC (%)*	*PCO (%)*
Albany	21	76.2	23.8	20	90.0	10.0
Baltimore	31	67.7	32.3	28	75.0	25.0
Cleveland	25	84.0	16.0	25	88.0	12.0
Gainesville	28	32.1	67.9	29	79.3	20.7
Houston	20	85.0	15.0	20	90.0	10.0
Long Island	32	78.1	21.9	32	62.5	37.5
Los Angeles	17	70.6	29.4	18	88.9	11.1
Minneapolis*	10	60.0	40.0	8	75.0	25.0
New York City	21	90.5	9.5	21	100.0	0.0
Oklahoma City*	6	50.0	50.0	5	100.0	0.0
Scheie, PA*	8	87.5	12.5	8	100.0	0.0
Seattle	26	34.6	65.4	27	33.3	66.7
Wills, PA	30	70.0	30.0	28	67.9	32.1
Winston-Salem	32	34.4	65.6	31	45.2	54.8
Total†	307	64.2	35.8	300	73.3	26.7

CC = clinical center; PCO = participating community ophthalmologist.

* Center added in 1995.

† $P = 0.01$ (chi-square test) for the overall comparison of the percentage of patients being treated by CC and PCO between the medicine and surgery groups.

enrollment (55.9 years) was significantly younger than whites (58.9 years), which is consistent with reports from other studies.[32–36]

It should be recognized that "newly diagnosed" does not imply that CIGTS patients uniformly exhibited early glaucomatous change. The range of visual field loss at baseline included some patients who overlap with the AGIS population in terms of severity of loss. In most cases, however, the extent of glaucomatous damage was not yet substantial. Entry criteria allowed for enrollment of patients whose visual field did not show glaucomatous loss. Such patients had to exhibit consistently elevated IOP values (27 mmHg or higher) and optic disc changes on ophthalmoscopy that were clearly indicative of glaucoma to the examining ophthalmologist. A total of 168 patients (27.7%) were enrolled under these criteria. Whereas some might question whether these patients definitely have glaucoma, the study investigators agreed that such patients should be included because their IOP and optic nerve status would have prompted treatment outside of the study protocol. In addition, it is recognized that detectable visual field loss in glaucoma occurs well after the disease process has begun.[37–39]

Involvement of PCOs in the study goes well beyond their referral of patients to the clinical centers. Participating community ophthalmologists are permitted to administer medications, perform surgical interventions, and thereby maintain a primary care relationship with the study patient. On average across centers, 36% of medically treated patients and 27% of surgically treated patients received therapy from a PCO. To ensure that the study protocol was followed, the clinical center's ophthalmologist discussed the protocol with the PCO before its administration, and any subsequent interventions had to receive approval by the clinical center's ophthalmologist. To ensure consistency and quality of collected data, patients are required to undergo baseline examinations and scheduled follow-up examinations at their clinical center.

Outcome assessments include those commonly evaluated in previous studies of glaucoma treatment, such as the monocular testing of visual field, IOP, and visual acuity. An important addition to these measures is the thorough assessment of the patient's health-related quality of life. The instrument used represents a combination of previously validated questionnaires that assess more general health dimensions (e.g., the Sickness Impact Profile)[30] and vision-related dimensions (the Visual Activities Questionnaire[28]), and new questionnaires that address treatment-related symptoms and concerns related to vision. Pilot testing of this instrument was considered essential in determining its final content and psychometric properties. Binocular measures of visual acuity, visual field, and contrast sensitivity were added late in the recruitment phase, and so baseline information on study patients will be limited. Information on these binocular vision measures over time, however, will be available and may provide a better assessment of the patient's visual function than that gained by monocular tests alone.

As the study progresses, its protocol allows for inclusion of new medications for treating glaucoma, such as the use of topical carbonic anhydrase inhibitors and prostaglandin analogs. By providing this flexibility, along with the option of PCO involvement, it is hoped that the study will yield outcome data that are relevant to how glaucoma is being treated in the ophthalmic community and thereby provide directly applicable and germane guidance to clinicians on how best to begin treating a patient who is diagnosed with open-angle glaucoma.

Acknowledgments. In developing the protocol for this study, the CIGTS Investigators benefited greatly from access to the AGIS protocol (Advanced Glaucoma Intervention Study Manual of Op-

erations: National Technical Information Service, Accession No. PB93-220192. Springfield, VA) and thank that study's investigators for the wealth of procedural information that was available from their efforts. In particular, the authors thank Marshall H. Becker, PhD, MPH, who contributed substantially to the development and implementation of the quality-of-life measurement approach and who served as Co-Principal Investigator of the Interviewing Center before his untimely death on November 26, 1993; Douglas E. Gaasterland, MD, Study Co-Chairman of AGIS, for his assistance in developing the CIGTS protocol for visual field and visual acuity testing; Argye Hillis, PhD, and her colleagues for sharing protocol information from the Central Vein Occlusion Study; Maureen G. Maguire, PhD, consultant to the Coordinating Center, and Richard A. Deyo, MD, MPH, and Donald A. Patrick, PhD, MSPH, consultants to the Interviewing Center, for providing valuable advice during the study's planning stage and ongoing course.

Appendix

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(Abbreviations: PI, principal investigator; CI, coinvestigator; CC, clinic coordinator; T, technician; OP, ophthalmic photographer)

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